CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-108

ADMINISTRATIVE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-108 Applicant Mylan Pharmaceuticals Inc.
Drug Nifedipine Extended Release (OROS) Tablets, 30 mg Strength

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:
1. Project Manager Tim Ames
Review Support Br

DRAFT RECEIPT
Date 12/9/99
Initials JEG

FINAL ACTION
Date _____
Initials _____

Application Summary:
Original Rec'd date 08-APR-97
Date Acceptable for Filing 27-MAY-97
Patent Certification (type) P IV
Date of Office Bio Review 23-DEC-98
Methods Val. Samples Pending Yes ☐ No ☒
30 Day Clock Start _____ End _____
Commitment Rcd. from Firm Yes ☐ No ☐
First Generic Yes ☐ No ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 12-NOV-99
Date Patent/Exclus.expires [redacted]-DEC-99
Citizens Petition/Legal Case Yes ☒ No P
(If YES, attach email from PM to Pet. Coord. notifying of pending approval)
Pediatric Exclusivity Tracking System
Date checked 9-DEC-99 ☒ N 19684
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☒ Date 15-MAR-99

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

2. Div. Dir./Deputy Dir.
Chemistry Div. I or II
Date 12/14/99 Initials _____
Date 12/14/99 Initials _____
Comments: Previously T+ CMC satisfactory.

3. Office Level Chem Review (1st Generic Only)
Chemistry Div. I or II
Date _____ Initials _____
Date _____ Initials _____
Comments: Completed by F. Holcombe at the time of the tentative approval (prior to 12/1/99)

4. Pat Beers Block
Supv., Review Support Branch
Date 12/15/99 Initials _____
Date 12/15/99 Initials _____
RLD = 19-684
EER Status: Acceptable for all facilities as of Nov. 18, 1999 (none OAI)

Bioequivalence sites:
Clinical site: testing: Mylan Inc Pittsburgh PA; non-testing: Clinic's Pharmacological Research Morgantown W.V.
Inspection needed: ☐ yes ☒ no
Status: ☒ acceptable ☐ unacceptable ☐ pending
Date of status: based on inspection history
Analytical site: Mylan Pharmaceuticals Inc.
Inspection needed: ☐ yes ☒ no
Status: ☒ acceptable ☐ unacceptable ☐ pending
Date of status: based on history from OSI.

Labeling Status: Acceptable 4/28/98

Bioequivalence office level sign off: Acceptable 12/23/98 (testing and non-testing studies)
Microbiology status: N/A
Patent Certification: Para IV; filing received; 30 month expires 12/16/99
Controlled Correspondence/Cit.Pet:
Comments:

M.V. deposition found acceptable for regulatory purposes by the Philadelphia District Lab on 8/12/99.

REVIEWER: | **DRAFT RECEIPT** | **FINAL ACTION**

5. Supv., Reg. Support Branch — Date 12/16/99 Initials [illegible] — Date 12/17/99 Initials [illegible]

Contains certification: Yes ☒ No ☐ (required by the GDEA if sub after 6/1/92) — Determ. of Involvement? Yes ☐ No ☒

Patent/Exclusivity Certification: Yes ☒ No ☐ — Pediatric Exclusivity Tracking System

If Para. IV Certification- did applicant Notify patent holder/NDA holder in a Timely manner: Yes ☒ No ☐ — Date Checked N/A; Nothing Submitted ☐; Written request issued ☐; Study Submitted ☐

Was applicant sued w/in 45 days: Yes ☒ No ☐ — office level BIO 12/23/98

Has case been settled: Yes ☐ No ☒ — Date settled: 30 month period expired — EER acceptable 11/18/99

Is applicant eligible for 180 day Generic Drugs Exclusivity: Yes ☒ No ☐

Comments: 30 month period expires 12/17/99 - litigation on the '446 patent only. Mylan appears to be 1st to file w/ PIV - eligible for 180 day exclusivity. No exclusivity

6. Robert L. West, Dir. Div. Labeling & Prog. Support — Date 12/17/99 Initials [illegible] — Date 12/17/99 Initials [illegible]

Comments: Acceptable EES dated 11/15/99 (Received 12/1/99). NDHE - Director noted this NADH received tentative approval on 3/15/99 pending resolution of PIV challenge on '446 patent. Firm's 10/14/99 amendment notes that no changes made to the labeling since CHC sections since time of TH. Final CHC review completed 12/14/99. Methods validation completed. FPL & bio previously acceptable. Bio test site (clinical and analytical) have satisfactory DSI inspectional history. Refer to Kickman's patent assessment (in file). Recommend: Approval

7. Gary Buehler, Deputy Director, OGD — Date 12/17/99 Initials [illegible] — Date 12/17/99 Initials [illegible]

Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☒ No ☐

Comments: 30-month stay of approval expired 12/16/99. Pfizer C.P. 951-0421 has been requested to. Appropriate notice of approval issued by C. Rawlse 12/15/99. No response. Abbreviated exclusivity. No pediatric study submitted by Pfizer. O.K to approve.

8. Douglas L. Sporn, Director, OGD — Date 12/17/99 Initials GR3 — Date 12/17/99 Initials GR3

Comments: Tentative approval letter was signed by R. Williams, M.D. First generic approval for extended-release tablet

Roger Williams, M.D., Deputy Center Director for Pharmaceutical Science — Date _____ Initials _____ — Date _____ Initials _____

First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

9. Project Manager Tim Ames, Review Support Branch — Date _____ Initials _____ — Date 12/17/99 Initials [illegible]

NM Pediatric Exclusivity Tracking System (check just prior to notification to firm)

Applicant notification:

12/17/99 11:30a Time notified of approval by phone 1435 Time approval letter faxed

FDA Notification:

12/17/99 Date e-mail message sent to "OGD approvals" account

12/17/99 Date Approval letter copied to "//cder/drugapp" directory

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75108/000**
Stamp: **08-APR-1997** Regulatory Due:
Applicant: **MYLAN PHARMS**
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265044310

Priority: Org Code: **600**
Action Goal: District Goal: **08-JUN-1998**
Brand Name:
Established Name: **NIFEDIPINE**
Generic Name:
Dosage Form: **EXT (EXTENDED-RELEASE TABLET**
Strength: **30 MG**

FDA Contacts: **T. AMES (HFD-640) 301-827-5849 , Project Manager**
J. SIMMONS (HFD-810) 301-594-2570 , Team Leader

Overall Recommendation:

ACCEPTABLE on 18-NOV-1999 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 17-JUN-1998 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 02-SEP-1997 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 29-AUG-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1110315**
MYLAN PHARMACEUTICALS INC
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265054310

DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **16-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Patent and Exclusivity Search Results from query on 019684 001.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019684	001	4327725	NOV 25,2000	
019684	001	4612008	SEP 16,2003	
019684	001	4765989	SEP 16,2003	
019684	001	4783337	SEP 16,2003	
019684	001	5264446	NOV 23,2010	

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

Printed by Pat Beers-Block

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 01-Apr-1999 08:47am
From: DSI Bioequivalence
DSIBE
Dept: HFD-340 MPN1 115
Tel No: 301-594-1023

TO: Pat Beers-Block (BEERSBLOCKP)

CC: Elaine Hu (HUE)
CC: Robert West (WESTR)
CC: William Rickman (RICKMAN)
Subject: RE: Inspectional history for UCSF and Novum Pharm

Novum/Biodecision (clinical only)

Insp.Date	Application	Classification
01/28/94	A74342/alprazolam	OAI
02/10/94	A74149/guanabenz	VAI
04/19/94	A74408/flurbiprofen	VAI
04/29/94	A74100/cimetidine	VAI
04/20/95	A74514/diclofenac	VAI
10/30/95	A72423/megestrol acetate	VAI (citizen petition)
0/95	A70646/megestrol acetate	VAI (citizen petition)
10/30/95	A74669/carbidopa/LDOPA	NAI
02/20/96	A74654/orphenadrine/ aspirin/caffeine	VAI
06/04/96	A40114/estradiol	VAI
12/10/96	A74286/desoximetasone	VAI (PD assay)
04/17/97	A74736/pentazocine/ naloxone	VAI
12/10/97	A74935/fluocinonide	NAI (PD assay)
07/29/98	A74517/guanabenz	VAI
12/17/98	A74489/hydrocortisone valerate	VAI (PD assay)
12/17/98	A74904/desoximetasone	VAI (PD assay)

University of California San Francisco (analytical under EL Lin, Ph.D.)

01/16/96	A74145/guanfacine	NAI
05/28/96	N20267/ibuprofen	VAI

Printed by Pat Beers-Block

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 16-Apr-1999 09:37am
From: DSI Bioequivalence
DSIBE
Dept: HFD-340 MPN1 115
Tel No: 301-827-5460

TO: Pat Beers-Block (BEERSBLOCKP)

Subject: FWD: Inspectional status of Analytical/clinical BE sites

CCP/MylanCCP Mylan

Clinical Date/Class	Analytical Date/Class	Application
10/25/93-NAI	10/25/93-NAI	ANDA 74-226/glypizine
10/25/93-NAI		NDA 20-392/cysteamine
7/27/94-NAI	6/29/94-NAI	ANDA 74-452/gemfibrozil
9/10/96-VAI	9/11/96-NAI	ANDA 74-701/triamterine+hydrochlorthiazide
2/6/97-NAI	1/28/97-NAI	ANDA 74-559/nitroglycerin patch
5/21/97-NAI	5/13/97-NAI	ANDA 74-792/glyburide
5 '97-NAI	5/13/97-NAI	ANDA 74-932/etodolac
1. 98-VAI		ANDA 74-896/captopril+hydrochlorthiazide
10/26/98-NAI		ANDA 75-001/astemizole
4/16/99-?	4/12/99-(NAI)	ANDA 75-138/verapamil
4/16/99-?	4/12/99-(NAI)	ANDA 40-298/phenytoin ER

{MFS4/16/99}

Electronic Mail Message

Date: 12/15/99 4:42:00 PM
From: Cecelia Parise (PARISEC)
To: See Below
Subject: ANDA approvals related to lawsuits and petitions

This e-mail is to notify you that OGD is preparing to issue full approval to:

1. Mylan, ANDA 75-108 Nifedipine extended-release tablets, 30 mg, generic version of Procardia XL. The 30 month stay of approval expires on December 16, 1999. Mylan's application may be approved on this date.

Bert W. Rein on behalf of Pfizer submitted a citizen petition 93P-0421/CP1 on October 28, 1998. The Citizen petition requested that for generic versions of Procardia XL (1) dosage forms with varing relase mechanisms should be distinct dosage forms. (2) An ANDA suitability petition should be required before reviewing an ANDA with a different release mechanism(3) the petition should contain a "full statement" and (4) more than bioequivalence tests should be required to assure the same therapeutic effect(5) stay consideration of ANDA until a petition has been filed and approved.

Pfizer filed suit in U.S. District Court on July 28, 1997.

The petition response was issued on August 12, 1997. The agency denied the petition.

Decision was issued on March 31, 1998 in the district court that granted the motion to dismiss in part and denied in part. Because the mere receipt of Mylan's ANDA is not judicially reviewable final agency action.

The decision was appealed and determined to be unripe for review on July 16, 1999 by the court of appeals.

The Mylan application is eligible for full approval on December 16, 1999. It is possible that Pfizer will reinstitute the lawsuit after the Mylan application is approved.

(2) Purepac, ANDA 74-984, Diltiazem Hydrochloride Extended-release Capsules, Generic version of Cardizem CD eligible for approval on December 20, 1999 after the expiration of Andrx's 180-day generic drug exclusivity.

Andrx submitted a citizen petition 98P-0145/CP1 on February 26, 1998, requesting (1) clarification of requirements for demonstrating in vivo bioequivalence to a two-peak pharmacokinetic profile (2) a generic drug product should match the two-peak profile unless exceptional circumstances are shown (3) refrain from approving any ANDA for a product that does not demonstrate that the sponsonr's drug matches the two-peak profile of the RLD.
(4) refrain from approving any ANDA with a two-peak pharmacokinetic profile, unless pharmacokinetic data demonstrate that the sponsor's drug matches the two-peak profil for the RLD or that the ANDA demonstrates through clinical data that the difference in profiles is not medically significant and all of the other exceptional circumstances are shown.

October 22, 1999, FDA denied the petition in part, and granted the petition in part.

On November 5, 1999, Andrx submitted a petition for reconsideration of partial denial (1) require plasma profile matches in bioequivalence determinations for drug products with multiple-peak profiles unless the ANDA shows profile differences are medically significant, (2) refrain from approving any such ANDA that doesn't have a matching profile, (3) refrain from approving any ANDA for a generic version of Cardizem CD that does not have a matching two-peak profile.

Purepac's ANDA 74-984 Diltiazem Hydrochloride extended-release capsules, is a generic version of Cardiazem CD. The Purepac product was designed with two sets of beads that have different release rates that are designed to match the release rates of Cardizem CD.

The Purepac ANDA 74-984 is eligible for approval on December 20, 1999.

Cecelia

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CHECKLIST FOR APPROVAL/TENTATIVE APPROVAL LETTERS WHEN AN ANDA CONTAINS PARAGRAPH IV CERTIFICATION

The following information should be completed and/or answered before a final or tentati approval letter can be issued to a firm. Complete the "licensing agreement" questions applicable. **Approval of the ANDA should not be granted unless all applicable questions are answered "yes" on this checklist.**

ANDA applicant name:	MYLAN Pharm.
ANDA number:	75-108
Drug product name:	Nifedipine ER Tablets
Did the ANDA applicant give P.IV notice[1] to each PO and AH (if different)? If the PO and AH do not live or work in the U.S., was a copy provided to the U.S. designee of the PO and AH[2]? YES	
Did the ANDA applicant send the P.IV notice after it received OGD's acknowledgement letter [314.95(b)]? YES	
es OGD have copies of the signed return receipts from the PO and AH (if different) or a letter from PO and AH acknowledging receipt [314.95(e)]? YES	
In the absence of a signed return receipt or letter, did the applicant receive OGD permission to submit another form of documentation in advance? N/A	
Does OGD have a copy of the other form of documentation of receipt of notice from the PO and AH [314.95(e)]? YES	
Did the ANDA applicant submit an amendment that the notice was sent and met the content requirements under 314.95(b)&(c)? YES	
Was the ANDA applicant sued on the patent challenge? YES on '446 patent only!	
Name of person(s) that sued the applicant: Pfizer and Bayer	
Date of lawsuit: Civil Action # 97-1309 Western District of Pennsylvania July 18, 1997	

[1] .95(e) states that a "copy of the notice itself need not be submitted to the agency". Also, page 50350, #60, preamble states that gency does not have the expertise to become involved in issues concerning sufficiency of notice. Therefore, OGD will not read tne notice to determine if the notice met the content requirements.

[2] See 314.52, 314.53, 314.95(a)(2), and by implication, 314.95(a)(1).

Did ANDA applicant or the PO/AH notify OGD of the filing of legal action within 45 days receipt of P.IV notification [314.107(f)(2)]? YES
If ANDA applicant is a licensee, did it submit a statement that it has been granted a license [314.94(a)(12)(v)]? N/A
[redacted]
Name and address (state and country) of each PO: 4612008 – ALZA 4765989 - ALZA 4327725 - ALZA 4783337 – ALZA 5264446 -
Name and address of U.S. agent if PO is foreign:

Specific number and expiration date of each patent that claims the drug product:	4612008 ex 9/16/2003 4327725 ex 11/25/2000
	4783337 ex 9/16/2003
	4765989 ex 9/16/2003
	5264446 ex 11/23/2010

OGD intends to approve the ANDA within 45 days of notification, did each PO and the [illegible] send OGD a statement that it waives its right to sue within the 45 days after it received the P.IV notice[3] [314.107(f)(3)]? N/A
Does the statement (above) follow the format in the proposed rule [314.107(f)(3)]? N/A
[redacted]
Name of AH: Pfizer
Name of U.S. agent if AH is foreign:
Was the patent timely filed? Yes
If the AH is either the PO or an exclusive licensee of the PO and, if OGD intends to approve the ANDA within 45 days of notification, did the AH send OGD a statement that it waives its right to sue within the 45 days after it received the P.IV notice [314.107(f)(3)]? N/A

[3] Although a patent owner doesn't have to consent to final ANDA approval (see preamble, page 50351, #67) for a licensee, it does have to submit a waiver to OGD in the 45 day period.

Does the written statement (above) follow the format in the proposed rule (p.50368) [314.107(f)(3)]? N/A

[redacted]

Names of the parties in the licensing agreement: N/A
Licensor: _____

Licensee: _____

Is the licensor the PO, AH/PO, or a designated representative of the PO [314.53(c)(1)(iv) and 314.95(a)(1)]? N/A

Do we have a copy of the signed licensing agreement? N/A

Name of the person who provided us a copy of the agreement: N/A

Date of the agreement: N/A

Has GC authorized approval if there are provisions in the agreement that appear to preclude granting immediate effective approval, such as a date before which approval could be granted, etc.? N/A

If OGD has written evidence that the PO assigned its rights or is a name other than the person originally issued the patent, has GC authorized approval? N/A

When the licensing agreement was sent to OGD, was the transmittal on the ANDA applicant's letterhead with an original signature (or if faxed, is it signed)? N/A

In the case of patent litigation, has OGD received a copy of the following? N/A

1. Stipulation signed by the parties to the agreement to dismiss the case because of the licensing agreement.

2. Stipulation free of any obstacles to final approval.

3. Signed court order dismissing the case.

[redacted]

If the ANDA refers to a listed drug that is itself a licensed generic of a patented pioneer drug, is there a P.IV certificate as to the patent on the pioneer [314.94(a)(12)(i)(B)]? N/A

Overall tentative approval letter:

Does the approval letter include:

1. All patents and their expiration dates? YES
2. References to relevant court rulings, if any, that impacted on the decision to issue a tentative or final approval. YES
3. The reason why OGD is issuing final approval, if that is the case, of the ANDA before the expiration of the patent? YES

If the ANDA applicant is a licensee, does the letter: N/A

1. Disclose the patent owner's identity*? On 1/17/96, PTO confirmed that once patent is issued, it is public information.
2. Omit the details of the licensing agreement (details are not allowed in the letter per C. A. Hooton 9/28/95)?

Regulatory Counsel (re: GC referrals) Date

Regulatory Support Branch /S/ 12/16/99 Date

V:\division\regsupp\pivappchklst

* OGD should have GC advice if it is evident that the current PO is different from the original PO. The existence of an agreement between the assignee of the PO and the ANDA holder may not mean the current PO's name is public.

ANDA APPROVAL SUMMARY

AADA OR ANDA NUMBER: 75-108

DRUG PRODUCT: Nifedipine Extended-release Tablets, 30 mg

FIRM: Mylan Pharmaceuticals, Inc.

DOSAGE FORM: Extended-release Tablets **STRENGTH:** 30 mg

CGMP STATEMENT/EER UPDATE STATUS: Satisfactory in original filing/Acceptable on Aug. 29, 1997, by M. Egas (HFD-322); Withhold on Sept. 2, 1997, by J.D. Ambrogio (HFD-324); Acceptable on June 17, 1998, by J.D. Ambrogio (HFD-324).

BIO STUDY: A Dale P. Conner Bio review (dated 12/23/98, in final) of the 4/7/97, 10/31/97, and 12/8/97, submissions recommended that "...this product must be judged to be bioequivalent and therefore approvable. The sponsor has met all established bioequivalence requirements.". Bioequivalency was ACCEPTABLE, and dissolution specs. that corresponded to those proposed by the applicant in the 10/31/97, amendment were recommended.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The ds is the subject of a compendium monograph, and for this reason, methods validation was not conducted for this material. Methods validation for the dosage form was performed at the PHI-District Laboratory, and the W. Charles Becoat MEMO dated 8/19/99, concludes that "Based upon the analytical results, the NDA methods appear to be suitable for regulatory control of this product. No problems were encountered with the analytical methods.".

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN THE CONTAINER SECTION?:

Container/closure systems: Yes, described below.

Stability Protocol: Satisfactory.
Stability Data: Satisfactory for the following lot in support of the proposed expiration dating period of 24 mos.:

	Lot #	Batch Size	Stability Conditions
Tablet Cores	2C004G	Tablet Cores	
Extended-release Tablets	2C009G[1]	Tablets	40°C/75% RH/3 mos. 27.5°C/12 mos.

[1] Packaged into 432 bottles of 100's tablets).
Packaged into 201 bottles of 500's tablets).

LABELING: The A. Vezza review dated 4/24/98, states that the FPL for the containers in the 3/12/98, submission are satisfactory. The same review declares that the FPL for the insert in the 4/21/98, submission are satisfactory.

STERILIZATION VALIDATION (IF APPLICABLE): N/A.

SIZE OF BIO BATCH (FIRM'S SOURCE OF DS O.K.?):
Bio batch is the same as the stability batch. Yes. See **STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN THE CONTAINER SECTION?**

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
The stability batch is the same as Bio batch. See **STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN THE CONTAINER SECTION?**

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:
The manufacturing process for the proposed batch size of tablet cores and Extended-release Tablets is the same as for the executed batch. Descriptions of the manufacturing processes and a comparison between the two batch sizes are located on pp. 7802 ff. of the original filing.

/S/ 12/14/99

CHEMIST: Robert C. Permisohn **DATE:** December 14, 1999
TEAM LEADER: Ubrani V. Venkataram Ph.D. **DATE:** 12/14/99

/S/

Telephone Conversation Memorandum

ANDA: 75-108

DRUG: Nifedipine Extended-release Tablets, 30 mg

FIRM: Mylan Pharmaceuticals, Inc.

PERSONS INVOLVED: Frank Sisto, Mylan
Tim Ames, FDA

PHONE NUMBER: 800-848-0461

DATE: 3/22/99

Firm called to request clarification as to the amendment dates listed on their March 15, 1999 Tentative Approval Letter. Specifically, the firm had no record of amendments being made on July 18, 1997 and December 23, 1998. In fact, these were not amendments made by Mylan, but the July 18, 1997 was a piece from Pfizer notifying the Agency of their legal action against Mylan relating to patent infringement by ANDA 75-108, and the December 23, 1998 piece was an internal OGD document. Both dates were erroneously added to the referenced amendments. Mr. Sisto was informed that these dates were in error.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Branch 6, OGD

/S/

OGD APPROVAL ROUTING SUMMARY

NDA # 75-108 Applicant Mylan Pharmaceuticals Inc.

Drug Nifedipine Extended-Release Tablets

Strength 30 mg

APPROVAL ☐ TENTATIVE APPROVAL ☒ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐

REVIEWER:	DRAFT RECEIPT	FINAL ACTION
1. Tim Ames	Date 1/19/99	Date
Review Support Br	Initials	Initials

Application Summary:

Original Rec'd date 06-APR-97

Date Acceptable for Filing 27-MAY-97

Patent Certification (type) AP IV

Date of Office Bio Review 23-DEC-98

Methods Val. Samples Pending Yes ☒ No ☐

30 Day Clock Start _____ End _____

Commitment rcd. from Firm Yes ☐ No ☒

First Generic Yes ☒ No ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐

Date of EER Status 17-JUN-98

Date Patent in effect 23-NOV-2010

Citizens Petition/Legal Case Yes ☐ No ☒

(If YES, attach email from PM to Pet. Coord. notifying of pending approval)

Pediatric Exclusivity Tracking System

Date checked 21-JAN-99

Nothing Submitted ☒

Written request issued ☐

Study Submitted ☐

ER product, diss. "interim" specs to be stated in AP [redacted] letter.

Comments:

2. Div. Dir./Deputy Dir.	Date 2/3/99	Date 2/19/99
Chemistry Div. I or II	Initials	Initials

Comments: 2/16 - firm was contacted for 1) Comparison plate 2) Blend uniformity 3) 9% moisture spec instability. 2/17/99 amendment OK. Chemistry is satisfactory

3. Office Level Chem Review (1st Generic Only)	Date 2/23/99	Date 3/12/99
Chemistry Div. I or II	Initials	Initials

Comments: SATISFACTORY

4. Pat Beers Block	Date	Date
Supv., Review Support Branch	Initials	Initials

Comments: Refer to DLB review below

3/15/99

c:\wpfile\branch7\ames\apsum.wpd

REVIEWER: | **DRAFT RECEIPT** | **FINAL ACTION**

5. Peter Rickman
Supv., Reg. Support Branch
Contains certification Yes ☒ No ☐
(required by the GDEA if sub after 6/1/92)
Paragraph 4 Certification Yes ☒ No ☐
RLD 19-684.
NO EXCLUSIVITY ISSUES
SEE CHECKLIST for PIV Patent info
Comments:
office Level Bio 12/23/98
EER acceptable 6/17/98 per EES 3/12/99

Draft Receipt: Date 3/12/99 Initials [initials]
Final Action: Date 3/12/99 Initials [initials]
Determ. of involvement? Yes ☐ No ☒
Pediatric Exclusivity Tracking System
Date Checked 3/15/99
Nothing Submitted ☒ RLL
Written request issued ☐
Study Submitted ☐

6. ~~Jerry Phillips~~
Dir. Div. Labeling & Prog. Support
Comments: Acceptable EES dated 6/17/98 (verified 3/15/99). No O.A.I. alerts noted. Bioequivalence studies (fasting, fasting - fed multidose, and fed) found acceptable 2/23/98. Office level bio endorsed D. Conner 12/23/98. Pharm/Tox consult on inactives found acceptable 3/98. H. Fanning concurred. Pharm consult (C. Ganley) - OK. Labeling acceptable for TA 4/29/98. CMC Acceptable 2/2/99. Methods validation pending. Recommend: Tentative Approval - First generic OIC audit completed.

Draft Receipt: Date 3/15/99 Initials RLL
Final Action: Date 3/15/99 Initials [signature]

7. Gordon Johnston
Deputy Director, OGD
Patent Cert - P_4 Yes ☒ No ☐
Pend. Legal Action Yes ☒ No ☐
Comments: P IV Certifications to 5 patents. Mylan sued on '446 patent only. Controlled correspondence from Pfizer (97-201). T. Sherwood notified

Draft Receipt: Date 3/15/99 Initials RLL
Petition Status Pending
Final Action: Date 3/15/99 Initials [signature] for

8. ~~Doug Sporn~~
~~Dir., OGD~~
~~Comments:~~

Date ______ Initials ______
Date ______ Initials ______

Roger Williams, M.D.
Dep.Dir., CDER
First Generic Tentative Approval ☒
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐

Date ______ Initials ______
Date 3/15/99 Initials [signature]

9. Tim Ames
Review Support Branch
RLL N/A Pediatric Exclusivity Tracking System (check just prior to notification to firm)

Date 3/15/99 Initials [signature]
Date ______ Initials ______

Applicant notification:
3:05p Time notified of approval by phone 3:08p Time approval letter faxed
3/15/99 [signature]

FDA Notification:
✓ Date e-mail message sent to "OGD approvals" account
✓ Date Approval letter copied to "//cder/drugapp" directory

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 16-Mar-1999 02:20pm EST
From: Nasser Mahmud
MAHMUDN
Dept: HFD-615 MPN2 105E
Tel No: 301-827-5862 FAX t-

TO: Eda Howard * (HOWARDE)

CC: Elaine Hu (HUE)

Subject: please hold review copies

Hello Eda,
please hold on to duplicate copies for ANDAs 75-108 and . We need to request DSI inspections for them. Thank you.

Nasser

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 75108/000**
Stamp: **08-APR-1997** Regulatory Due:
Applicant: **MYLAN PHARMS**
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265044310

Priority: Org Code: **600**
Action Goal: District Goal: **08-JUN-1998**
Brand Name:
Established Name: **NIFEDIPINE**
Generic Name:
Dosage Form: **EXT (EXTENDED-RELEASE TABLET**
Strength: **30 MG**

FDA Contacts: **T. AMES (HFD-617) 301-827-5849 , Project Manager**
J. SIMMONS (HFD-810) 301-594-2570 , Team Leader

Overall Recommendation:

ACCEPTABLE on 17-JUN-1998 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 02-SEP-1997 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 29-AUG-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment: DMF No:
FARMACEU AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **12-JUN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: **1110315** DMF No:
MYLAN PHARMACEUTICALS INC AADA No:
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265054310

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **17-JUN-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

6/20/96

CHECKLIST FOR APPROVAL/TENTATIVE APPROVAL LETTERS
WHEN ANDA HAS ¶IV CERTIFICATION

The following questions should be completed and/or answered "yes" before a tentative approval or final approval letter can be issued to a firm that made a paragraph IV certification. **Complete the "licensing agreement" questions if applicable. APPROVAL OF ANDA SHOULD NOT BE GRANTED UNLESS ALL QUESTIONS ARE ANSWERED "YES."**

ANDA APPLICANT NAME: MYLAN PHARM **ANDA #:** 75-108
DRUG PRODUCT NAME: Nifedipine ER TABLETS **Vol.#, Page#**

A.	**Patent Owner (PO)**	YES	NO
1.	Name and address (state and country) of each PO: SEE BELOW *	---	---
2.	Specific number and expiration date of each patent that claims the drug product: 4612008 ex 9/16/2003 4783337 ex 9/16/2003 4765989 ex 9/16/2003 5264446 11/23/2010 4327725 ex 11/25/2000	---	---
3.	If OGD intends to approve the ANDA, whether or not ANDA is a licensee[1], within 45 days of notification, did each PO send OGD a statement that it waives its right to sue within the 45 days after it received the ¶IV notice? [§314.107(f)(3)]. NOTE: Although, a patent owner doesn't have to "consent" to final ANDA approval (see Preamble at p. 50351, #67) for a licensee, it does have to submit a waiver to OGD in this particular 45-day scenario.		
4.	Does the written statement (item 3 above) follow the format in the proposed rule? [§314.107(f)(3); p. 50368]		
5.	Name and address of U.S. agent if PO is foreign: _____		

* 4612008 ex 9/16/2003 ALZA
4783337 ex 9/16/2003 ALZA
4765989 ex 9/16/2003 ALZA
5264446 ex 11/23/2010 BAYER (GERMANY)
4327725 ex 11/25/2000 ALZA

[1]OGD doesn't have to check whether the NDA holder agreed to the licensing agreement between the patent owner and the ANDA applicant (Preamble at p. 50351, #67).

B. NDA Applicant/Application Holder (AH) (if Different from PO)	Y	N
1. Name of AH: PFIZER	---	---
2. Name of U.S. agent if AH is foreign: N/A	---	---
3. Is the patent information timely filed? If the answer is "no," when did the AH submit patent information to FDA? YES		
4. If the AH is either the PO or an exclusive licensee of the PO and, if OGD intends to approve the ANDA (whether or not ANDA is a licensee) within 45 days of notification, did the AH send OGD a statement that it waives its right to sue within the 45 days after it received the ¶IV notice? [§314.107(f)(3)] N/A		
5. Does the written statement follow the format in the proposed rule? [§314.107(f)(3); p. 50368] N/A		

C. **ANDA APPLICANT**	Y	N
1. Name of the ANDA applicant: MYLAN	---	---
2. Did the ANDA applicant give ¶IV notice[2] to each PO and AH, or if the PO and AH do not live or work in the U.S., a copy to the U.S. designee of the PO and AH[3]? YES	YES	
3. Did the ANDA applicant send the, ¶IV notice after it received OGD's acknowledgement letter [§314.95(b)]? YES	YES	
4. Does OGD have copies of the signed return receipts from the PO and AH (if different)? [§314.95(e)] or a letter from PO and AH acknowledging receipt? YES	YES	
5. In the absence of a signed return receipt or letter, did the applicant receive OGD permission to submit another form of documentation? In addition to return receipt, letter from Pfizer	YES	
6. Does OGD have a copy of the other form of documentation of receipt of notice from the PO and AH? [§314.95(e)] Letter from Pfizer		
7. Did the ANDA applicant submit an amendment that the notice was sent and met the content requirements under §314.95(b)&(c)? YES	YES	
8. Was the ANDA applicant sued on the patent challenge? YES	YES	
9. Name of "person" that sued applicant: PFIZER		
10. Date of lawsuit: July 18, 1997		
11. Did ANDA applicant or the PO notify OGD of the filing of legal action within 45 days of receipt of ¶IV notification? [§314.107(f)(2)] YES	YES	
12. If ANDA applicant is a licensee, did it submit a statement that it has been granted a license [§314.94(a)(12)(v)]? N/A	N/A	---

[2]§314.95(e) states that a "copy of the notice itself need not be submitted to the agency." Also, p. 50350, item 60, Preamble, states that the agency does not have the expertise to become involved in issues concerning sufficiency of notice. Therefore, OGD won't read the notice to determine if the notice met the content requirements.

[3]See §314.52, §314.53, §314.95(a)(2), and by implication, §314.95(a)(1).

D. **Licensing Agreement/Licensee (Complete section if ANDA applicant is a licensee.)** N/A	Y	N
1. Names of the parties to the licensing agreement:	---	---
Licensor: _____	---	---
Licensee: _____		
2. Is the licensor the PO, or the AH/PO, or a designated representative [§314.53(c)(1)(iv) and 314.95(a)(1)] of the PO?		
3. Do we have a copy of the **signed** licensing agreement?	N/A	
4. Name of "person" that provided us a copy of the agreement:	---	---
_____	---	---
5. Date of the agreement: _____		
6. Has GC authorized approval if there are provisions in the agreement that appear to preclude granting immediate effective approval, such as a date before which approval could be granted, etc.?		
7. Has GC authorized approval if OGD does not have a signed licensing agreement between the PO and the ANDA applicant but believes that a license is implied because either: (1) the ANDA applicant has not challenged the patent, or (2) if ANDA filed a ¶IV, the licensor hasn't filed a lawsuit, or (3) it is evident by the ANDA label that the PO is manufacturing for the ANDA applicant, i.e. "manufactured for ANDA name by PO name."		
8. If OGD has written evidence that the PO assigned its rights or is a name other than the person originally issued the patent, has GC authorized approval?		
9. When the licensing agreement was sent to OGD, was the transmittal on the ANDA applicant's letterhead with an original signature (or if faxed, is it signed)?		
10. In the case of patent litigation, has OGD received a copy of the:		
(a) Stipulation signed by the parties to the agreement to dismiss the case because of the licensing agreement?		
(b) Is the Stipulation free of any obstacle to final approval?		
(c) Signed court order dismissing the case?		

	Y	N
E. Drug Product 1. If the ANDA refers to a listed drug that is itself a licensed generic of a patented pioneer drug [§314.94(a)(12)(i)(B)], is there a ¶IV certificate as to the patent on the pioneer? N/A		
F. ~~Approval~~/Tentative Approval Letter 1. Does the approval letter include: A. All patents and their expiration dates? B. References to relevant court rulings, if any, that impacted on the decision to issue a tentative or final approval C. The reason why the Office is issuing final approval, if that is the case, of the ANDA before the expiration of the patent? 2. If the ANDA applicant is a licensee, does the letter: A. Disclose the patent owner identity? On 1/17/96 PTO confirmed that once patent is issued, it is public information. NOTE: OGD should have GC advice if it is evident that the current PO is different from the original PO. The existence of an agreement between the assignee of the PO and the ANDA holder may not mean the current PO's name is public. B. Omit the details of the licensing agreement? (Details are not allowed in the letter per C.A.Hooton 9/28/95.) **Signatures:** Regulatory Counsel (re: GC referrals) Date Regulatory Support Branch 3/12/99 Date	YES	

ANDA 75-108
Mylan/Nifedipine

ANDA APPROVAL SUMMARY

AADA OR ANDA NUMBER: 75-108

DRUG PRODUCT: Nifedipine Extended-release Tablets, 30 mg

FIRM: Mylan Pharmaceuticals, Inc.

DOSAGE FORM: Extended-release Tablets **STRENGTH:** 30 mg

CGMP STATEMENT/EER UPDATE STATUS: Satisfactory in original filing/Acceptable on Aug. 29, 1997, by M. Egas (HFD-322); Withhold on Sept. 2, 1997, by J.D. Ambrogio (HFD-324); Acceptable on June 17, 1998, by J.D. Ambrogio (HFD-324).

BIO STUDY: A Dale P. Conner Bio review (dated 12/23/98, in final) of the 4/7/97, 10/31/97, and 12/8/97, submissions recommended that "...this product must be judged to be bioequivalent and therefore approvable. The sponsor has met all established bioequivalence requirements.". Bioequivalency was ACCEPTABLE, and dissolution specs. that corresponded to those proposed by the applicant in the 10/31/97, amendment were recommended.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The ds is the subject of a compendium monograph, and for this reason, methods validation was not conducted for this material. Methods validation for the dosage form is pending.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN THE CONTAINER SECTION?:

Container/closure systems: Yes, described below.

ANDA 75-108
Mylan/Nifedipine

500's -

Stability Protocol: Satisfactory.
Stability Data: Satisfactory for the following lot in support of the proposed expiration dating period of 24 mos.:

	Lot #	Batch Size	Stability Conditions
Tablet Cores	2C004G	Tablet Cores	
Extended-release Tablets	2C009G[1]	Tablets	40°C/75% RH/3 mos. 27.5°C/12 mos.

[1] Packaged into 432 bottles of 100's ablets).
Packaged into 201 bottles of 500's) tablets).

LABELING: The A. Vezza review dated 4/24/98, states that the FPL for the containers in the 3/12/98, submission are satisfactory. The same review declares that the FPL for the insert in the 4/21/98, submission are satisfactory.

STERILIZATION VALIDATION (IF APPLICABLE): N/A.

SIZE OF BIO BATCH (FIRM'S SOURCE OF DS O.K.?):
Bio batch is the same as the stability batch. Yes. See **STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN THE CONTAINER SECTION?**

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
The stability batch is the same as Bio batch. See **STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN THE CONTAINER SECTION?**

ANDA 75-108
Mylan/Nifedipine

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

The manufacturing process for the proposed batch size of ablet cores and Extended-release Tablets is the same as for the executed batch. Descriptions of the manufacturing processes and a comparison between the two batch sizes are located on pp. 7802 ff. of the original filing.

/S/ 1/27/99

CHEMIST: Robert C. Permisohn **DATE:** January 8, 1999

TEAM LEADER: Ubrani V. Venkataram Ph.D. **DATE:** January 26, 1999

/S/ 2/2/99

F/T by pah/1-26-99

Nifedipine ER Tablets, 30 mg
ANDA #75-108
Reviewer: Dale P. Conner

Mylan Pharmaceuticals
Morgantown, West Virginia
Submission Dates:
April 7, 1997
October 31, 1997
December 8, 1997

Supervisory Review of Application and Amendments

Administrative History (see Administrative Record Summary attached)

Original ANDA submitted	7 April 1997
Review completed	2 October 1997
Deficiency letter issued	15 October 1997
Amendment submitted	31 October 1997
Review of amendment completed	23 April 1998

Summary of Previous Review Comments/Conclusions

1. The *in vitro* testing conducted by Mylan on its Nifedipine ER Tablets 30 mg was found acceptable.
2. The three studies submitted by the Mylan consisted of fasting single-dose, non-fasting single-dose and multiple-dose designs. The *in vivo* bioequivalence studies comparing test (Mylan's Nifedipine ER) to reference (Procardia XL®) passed the regulatory criteria (90% confidence interval criteria (80 – 125%) for log-transformed AUC and Cmax parameters for the single and multiple-dose fasted studies, and point estimate criteria for the single-dose non-fasted study.
3. Despite 1 and 2 above, it was concluded in the review of the amendment submitted on October 31, 1997, that "the test and reference products cannot be considered bioequivalent according to the current overall acceptance criteria of the Division of Bioequivalence due to the unusual and distinct differences in the individual and mean PK profiles between the two products, especially for the steady-state study. The Tmax difference between the two products is 61% for this study."

Supervisory Comments

1. It is clear from the data submitted by the sponsor and the subsequent review by Division of Bioequivalence reviewers that the specific regulatory requirements for declaring two products bioequivalent have been met. Results from the in vivo studies submitted are as follows:

Study	Parameter	90% CI	Ratio T/R
Single-Dose Fasting	ln AUC (0-t)	0.82 – 0.97	0.89
	ln AUC (0-inf)	0.83 – 0.97	0.90
	ln Cmax	0.94 – 1.15	1.04
	tmax	---	1.12
Multiple-Dose	ln AUC (0-24hr)	0.87 – 1.09	0.97
	ln Cmax	0.87 – 1.08	0.97
	tmax	---	1.61
	Cmin	---	0.96
Single-Dose Non-Fasting	ln AUC (0-t)	---	0.95
	ln AUC (o-inf)	---	0.95
	ln Cmax	---	1.06
	tmax	---	1.82

2. Extensive discussion of these issues with many FDA personnel, including experienced reviewers and supervisors from DBE as well as managers and scientists from the Office of Generic Drugs and the Office of Pharmaceutical Sciences has occurred (see attached minutes of the Four Division Directors meeting as well as the meeting of 24 November 1998 with Dr. Roger Williams). These discussions as well as examination of publicly available FDA documents have revealed that the "acceptance criteria" for products that do not appear to have the same PK profile do not currently exist. In addition, no firm and well-articulated criteria for tmax comparisons exist.

3. In the opinion of the medical consultant, Dr. Charles Ganley, the perceived differences in the pharmacokinetic profiles should not result in any clinically relevant differences in these two products. Dr. Ray Lipicky, Director of HFD-110, expressed a contrary opinion based on theoretical grounds but did not provide any supporting information or a strong argument regarding the clinical relevance of these perceived differences on the switchability of these products.

Recommendation

In the absence of any established regulatory or scientific criteria for assessment of PK profile similarity or equivalence, this product must be judged to be bioequivalent and therefore approvable. The sponsor has met all established regulatory bioequivalence requirements.

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs, FDA

Nifedipine Extended Release Tablets, 60 mg
ANDA 75-108
Mylan Pharmaceuticals

Administrative Record

A. Summary of Review:

Mylan submitted an ANDA (75-108) for Nifedipine extended release tablets on April 7, 1997. The review was finalized by Dr. Nguyen on October 2, 1997. A deficiency letter was issued to Mylan on October 15, 1997, stating that the food study was unacceptable (Cmax did not pass the point estimate criteria), and long-term stability data was not included for both single dose fasting, and multiple dose studies.

Mylan submitted an amendment to this deficiency on October 31, 1997. This submission addressed the long-term stability data, the results of the food study, and the results of an EIR inspection on July 30, 1997. The long-term stability data, as well as the food study (calculation error by the reviewer), were found acceptable. The Investigations and Preapproval Branch, HFD-324, addressed the question of unsubmitted failed biostudies by Mylan for Procardia XL. Mylan provided the results of a study comparing two lots of the Reference product indicating that the two lots did not pass the requirements of average bioequivalence for Cmax. The information provided from this inspection (the failed studies were justified due to lot to lot variability of the RLD, and high nifedipine overage in the RLD) was also found acceptable by the reviewer. However, the reviewer felt that even though the criteria for bioequivalence was met, the PK profiles of these two products, were different, with a difference in Tmax of 61% in the multiple dose study. In addition, the dissolution specifications were revised. This review was concurred with by the team leader on 4/15/98 and Director on 4/23/98.

2. Discussion at 4-DD's meeting:

The issue of profile dissimilarity was brought up at the 4-DD's meeting held on July 8, 1998 (see attachment A), since the Division of Bioequivalence had received several ANDA's meeting standard BE criteria, but showing different profiles (differences in Tmax, lag time, multiple peaks, food effects causing changes in profiles, and combinations of these). In addition, a Citizen's Petition had been submitted by Andrx on February 28, 1998, requesting OGD not to approve any generic products equivalent to Cardizem CD, that do not match the twin peaks profiles. Andrx stated that their generic product

matched the twin peak profile observed with Cardizem CD. It was decided at the 4-DD's meeting that this issue should be referred to the Metrics Working Group, which should finalize a recommendation to the 4-DD's and BCC.

3. Medical Consults:

A consult response from the Division of Cardio-Renal Drug Products (HFD-110) was received by the OGD, on August 11, 1998, regarding the twin peak issue. This consult provided conflicting opinions from the reviewer, and Director of the Division. The reviewer's opinion is that New Drug applicants are not required to perform PD measurements for the determination of bioequivalence when comparing formulations, so if bioequivalence criteria is met, the products should be deemed bioequivalent. The two peak PK profile should not be a requirement to determine bioequivalence. However, the Medical Division Director did not agree (see attachment B).

A second consult was received from HFD-110 on September 17, 1998, regarding the differences in Tmax observed on ANDA 75-108 (Mylan's nifedipine). The Division concluded that there is no data to support the clinical relevance of differences in Tmax among anti-hypertensive and anti-angina products (see attachment C).

4. Meeting with Dr. Williams

On November 24, 1998, a meeting was held with Dr. Roger Williams, to determine how to handle all the applications pending in the Division of Bioequivalence, which meet BE criteria, but show different PK profiles. The Metrics Working Group has not finalized a recommendation for these cases. It was decided that if the BE studies for these products meet BE criteria, they should be found acceptable and approved. Bioequivalence standards must be changed in a prospective manner, and the policy change process must be followed to allow public comments. The applications will be approved (see attachment D).

Attachment B

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	594-1174
Attention:	Harvey Greenberg
Company Name:	Generics
Phone:	827-5862
Subject:	Protocol 98-067 - Diltiazem Once-a-Day CR
Date:	8/11/98
Pages including this sheet:	4

From: **Sandra Benton**
Phone: **301-594-5364**
Fax: **301-594-5494**

Original will be sent to you through ODEI.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE 4/10/95

FROM Director, Division of Cardio-Renal Drug Products, HFD-110 Lipicky

SUBJECT Bioequivalence Criterai for Cardiazem CD

TO Harvey Greenberg, HFD-615

Just a few word to amplify Dr. Ganley's consult.

I agree totally with the notion that bioequivalence should be determined by measurements of plasma concentration as a function of time. Crude bioassay, such as measurements of blood-pressure as a function of time, should not even be considered.

I do think that the basis of approval of a new formulation that is intended to be biopharmaceutically indistinguishable from a reference product should account for the plasma concentration versus time profile of the reference formulation. So, if the reference formulation has 2 (or more) peaks, the new formulation should have the same profile. Else, it is hard for me to see how one would be able to predict that one fromulation can be interchanged with the other.

The problem being addressed in the above comments is whether or not the 2 formulations are the same, and consequently interchangeable from one administration to another. That is what I think you were asking about.

Publically clarifying the requirements for demonstrating bioequivalence is addressed by neither Dr. Ganley nor myself. My opinion is that 2 peaks require 2 peaks. Whether you agree, disagree or wish to make public the considerations related to such a decision, is your call. I have no opinion in that regard.

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date 8/04/98
From HFD-110, Division of Cardio-Renal Drug Products (DCRDP)
Subject: Bioequivalence Criteria for Cardiazem CD
To HFD-615, Harvey Greenberg

Background

Andrx Pharmaceuticals submitted a Citizens Petition on 3/10/98 requesting that the Acting Commissioner should refrain from approving any ANDA for Cardiazem CD, a controlled release product that manifests a "two peak" pharmacokinetic profile.....unless pharmacokinetic data demonstrates that the ANDA sponsor's drug matches the two peak pharmacokinetic profile of the reference and/or the ANDA demonstrates, through clinical data, that the difference in profiles is not medically significant and all of the other exceptional circumstances are shown.

The Office of Generic Drugs (OGD) is currently reviewing ANDAs for generic versions of Cardiazem CD. Andrx Pharmaceuticals has submitted an ANDA whose drug product apparently follows the "2 peak" pharmacokinetic profile. Information on the Andrx application has not been included in the information provided. The material provided for review includes:

- Citizens Petition (CP) from Andrx Pharmaceuticals
- Letters in support of the CP from Dr. William White, M.D.[1], Dr. Bertram Pitt, M.D.[2] and Dr. William Jusko, Ph.D.[3]
- Response to CP from Dr. Patrick Marroum, Ph.D. and Dr. André Jackson, Ph.D.
- Biopharm review of application ANDA 75-116[4] (an extended release Diltiazem product with a single pharmacokinetic peak)
- A letter from Dr. L. Endrenyi, Ph.D.[5] contesting the CP.
- A submission from Biovail contesting the CP.
- A submission from Teva contesting the CP.

Discussion

All of the material provided by OGD has been reviewed but will not be summarized in this memorandum. The primary issue to be addressed from a medical viewpoint is whether the "two peak" pharmacokinetic profile leads to significant differences in clinical effect. The following comments are made in response to the issues raised in the information provided.

Medical Significance of the Two Peaks[6]

- During the FDA review of the Cardiazem CD NDA, the sponsor of the application did not believe that there was a significant effect on blood pressure caused by the two peak concentration profile. This is understandable in view of the potential consequences to the approval of the Cardiazem CD application. If it had been determined from the pharmacokinetic/pharmacodynamic data that the "valley" between the "two concentration peaks" lead to a clinically significant decline in blood pressure control, this could have been viewed as detrimental and could have possibly resulted in a non-approvable action.

---

[1] University of Connecticut Professor of Medicine
[2] University of Michigan Professor of Internal Medicine
[3] University of Buffalo Professor of Pharmaceutics
[4] Biovail Diltiazem Hydrochloride ER.
[5] University of Toronto Professor Emeritus of Pharmacology and Biostatistics.
[6] In this review, Dr. Marroum has noted that the two peak phenomena has not been demonstrated with the innovator product across all studies nor in all subjects.

Because the Cardiazem CD application was approved, any suggestion that the "two peak" phenomena is clinically relevant is without merit.

- There is no data that associates a specific absolute difference in blood pressure with a clinically significant difference in outcome. Clinical trials in hypertension that show a benefit on clinical outcome are based on titration to a pre-specified blood pressure and not to an absolute difference from baseline. It is difficult to imagine that a short lived fluctuation in blood pressure (if indeed it exists at steady state and is solely related to a decrease in diltiazem concentration)[7] is somehow clinically beneficial. In fact, if the reported fluctuation with Cardiazem CD was determined to be clinically meaningful, it certainly cannot be viewed as a benefit and would suggest that 1) the drug product is not an adequate controlled release product maintaining blood pressure control over 24 hours and 2) the drug product and it's generic versions should not be marketed at all.
- Cardiazem CD is not viewed as a drug with a narrow therapeutic index. Thus, concerns raised regarding safety[8] related to the "two peak" pharmacokinetic profile should not be an issue.

Request for Clinical Data in Determining Bioequivalence

- The Division of Cardio-Renal Drug Products does not require sponsors of New Drug Applications for anti hypertensive drugs to perform pharmacodynamic measurements for the determination of bioequivalence when comparing formulations. It would be very difficult to design a clinical trial that would use pharmacodynamic data (systolic and diastolic blood pressure) as the measure for the determination of bioequivalence. There is sufficient intrasubject and intersubject variability with blood pressure measurements that any bioequivalence criteria that depends on pharmacodynamic measurements would have to be fairly lax. Consequently, pharmacokinetic criteria should continue to be the standard for bioequivalence determinations for Cardiazem CD.
- New Drug Applications for the treatment of hypertension are approved based on data showing that the drug lowers blood pressure. For this indication, blood pressure is a surrogate endpoint. There is an implicit assumption that lowering blood pressure is beneficial based on data from clinical outcome trials in patients with diastolic or systolic hypertension. There is no requirement of a sponsor of an NDA to show a benefit on clinical outcome (e.g. decrease in stroke, death, MI, CHF). The suggestion by one of the advocates[9] of the Citizens Petition that a study be performed to compare the efficacy and safety of two products is unreasonable. The only meaningful study to compare the clinical efficacy and safety of two products would be a clinical outcome study and would require the enrollment of tens of thousands of patients.
- A comparison of 24 hour ambulatory blood pressure monitoring data between two products (as suggested by Dr. Pitt) would not be viewed as a reasonable method for assessing bioequivalence. The shape of the curves are very dependent on the frequency of blood pressure measurements and the type of analysis performed on the measurements.

Recommendation

Bioequivalence for Cardiazem CD should be based on pharmacokinetic criteria and not pharmacodynamic criteria. The "two peak" pharmacokinetic profile should not be a requirement for the determination of bioequivalence for Cardiazem CD.

If there are additional questions related to this issue that are not addressed in this memorandum, please contact HFD-110.

/S/

Charles J. Ganley, M.D.

DCRDP DIRECTOR

cc Division File
HFD-110/ganley; HFD-007/Virginia Beakes; Office of Generic Drugs/ Gordon Johnston

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[7] The trial from which the 24 hour ambulatory blood pressure was obtained was not reviewed again

[8] Dr. Pitt's comments

[9] Dr. White, M.D.

Attachment C

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 9/17/98
From: HFD-110. Division of Cardio-Renal Drug Products (DCRDP)
Subject: Clinical Relevance of the Difference in Tmax Between Generic and Reference Drug
To: HFD-615. Harvey Greenberg

Background Information

The Office of Generic Drugs provided the bioequivalence reviews for three ANDAs. ANDA 75-108. 75-116 and 75-269. The reference listed drugs in all three ANDAs are extended release products.

The following tables list the Tmax values from the single dose (fasted or fed) and multiple dose studies of three ANDAs.

Table 1.a. Tmax Data from ANDA 75-108 [Tmax in hours]

Study	N	Generic	Procardia XL
Fasting, Single Dose	38	14.4 (34)	12.9 (52)
Fasting, Multiple Dose	34	14.0 (46)	8.7 (62)
Non-fasting, Single Dose	19	18.9 (37)	10.4 (72)

( ) = coefficient of variation

Table 1.b. Tmax Data (hours) from ANDA 75-269 [Tmax in hours]

Study	N	Generic	Adalat CC
Fasting, Single Dose	63	6.4 (31)	6.27 (47)
Non-fasting, Single Dose	21	4.0	4.3
Fasting, Multiple Dose	48	3.57 (33)	3.97 (67)

( ) = coefficient of variation

Table 1.c. Tmax Data (hours) from ANDA 75-116 [Tmax in hours]

Study	N	Generic	Cardiazem CD
Fasting, Single Dose	41	6.96 (18)	6.78 (18)
Non-fasting, Single Dose	26	6.14 (18)	6.0 (19)
Fasting, Multiple Dose		10.19 (24)	6.57(44)

( ) = coefficient of variation

As described in the reviews of ANDAs 75-116 (10/31/97) and 75-108 (4/7/97), the Division of Bioequivalence reviewer expressed concern regarding the difference in Tmax between the reference and generic products. In both instances. Tmax differences were cited as reasons to not approve the applications[1]. There is no explanation specifying the criteria that led them to this decision. In application 75-116. the difference in Tmax at steady state is approximately 3.6 hours for the multiple dose study. The single dose fasting and single dose fed study had differences in Tmax of less than .5 hours. In application 75-108. the Tmax was consistently greater for the generic product for all studies although the variability[2] of

[1] AUC and Cmax bioequivalence criteria were met.
[2] The point estimate and the coefficient of variation.

the Tmax was greater for the reference drug. The difference between drug products ranged from 1.5 hours (single dose, fasting) to 8.5 hours (single dose, fed).

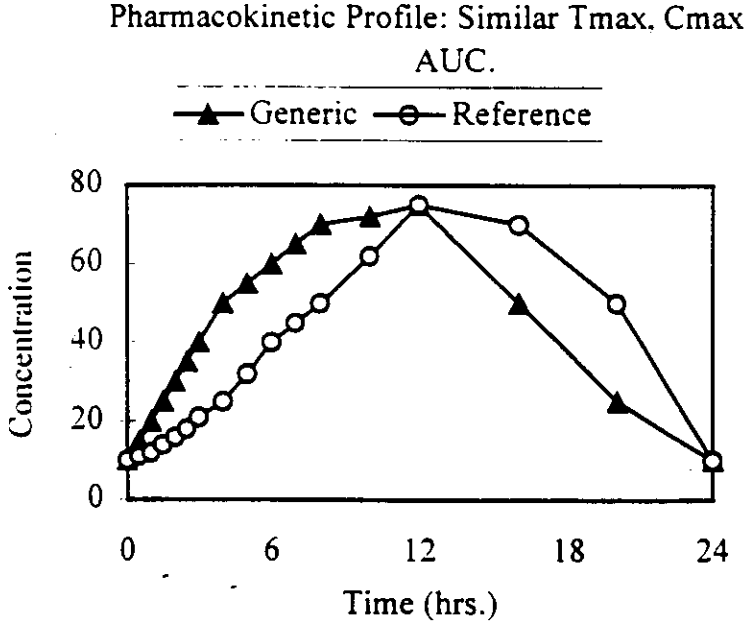
Discussion

From a clinical viewpoint, it is unlikely that the differences in Tmax observed between the generic and reference drugs will lead to a significant difference in clinical outcomes for the following reasons.

- First, anti-hypertensive agents are generally titrated by physicians to a blood pressure at trough that is less than 90 mmHg. As a consequence, blood pressures at peak are generally going to be less than 90 mm Hg. It is likely inconsequential as to when the nadir of blood pressure occurs (assuming that Cmax is related to maximum effect).
- Second, there are no studies in hypertensive patients showing that one class of drugs or drugs within a class are superior to others[3] with regard to the reduction of clinical outcomes (e.g. stroke). Because different drugs approved for the treatment of hypertension have different Tmax values (and presumably different times of maximum effect), the time of Tmax has little bearing on clinical efficacy. The decision to approve a drug for hypertension is not based on the time of Tmax.

The DCRDP does not wish to provide specific comments on the approval of any of the applications provided. As a general rule, however, Tmax alone is an inadequate measure of the rate of absorption or as a descriptor of the pharmacokinetic profile. This is illustrated by the figures 1 and 2. In figure 1, the Cmax, Tmax and AUC are similar between drug products. In figure 2, the Cmax and AUC are similar while the Tmax differs by 4 hours between drug products. A visual inspection of the profiles for each figure suggest that the drug products are more alike in figure 2 than figure 1 even though the difference in Tmax between the drug products is greater in figure 2. Thus, additional methods for comparing the profiles of the curves should be utilized. The comparison should not depend solely on the Tmax.

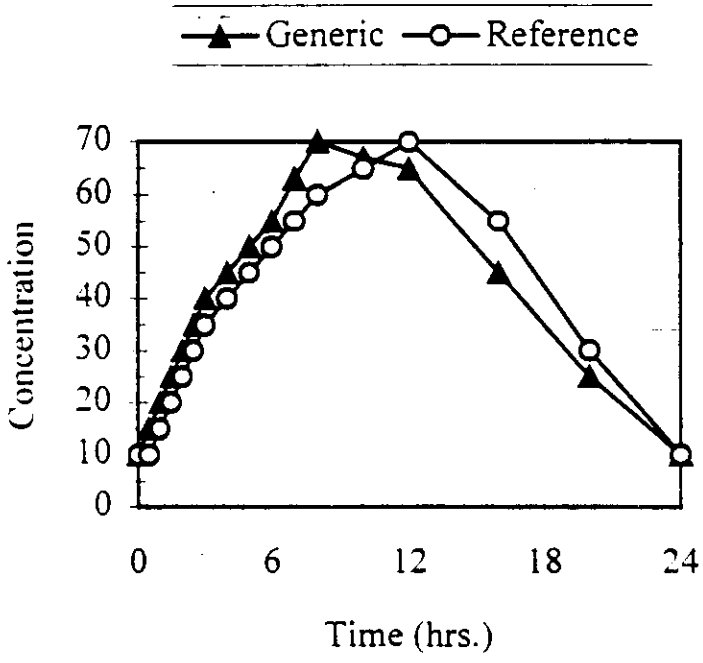
Figure 1.



[3] There are at least two ongoing studies to answer this question.

Figure 2.

Pharmacokinetic Profile:Similar Cmax and Auc but Tmax Differs by 4 Hours.



Conclusions

1. There is no data to support the clinical relevance of differences in Tmax among anti-hypertensive and anti-angina drug products.
2. Tmax alone is a poor method to compare the concentration versus time profile between drug products. Tmax alone is not a good predictor of the shape of the concentration response curve. It is more appropriate to perform analysis that compare the entire curves.
3. There is no absolute difference in Tmax for anti-hypertensive and anti-angina drug products that can be identified as being clinically relevant.

/S/

Charles J. Ganley, M.D.

Attachment D

DATE: November 24, 1998 Time: 10:30am Dr. Williams' Office
Woodmont II

Subject: Calcium Channel Blockers, Profile differences

Meeting Type: Internal

Meeting Chair: Roger Williams

FDA Participants:
Dale Conner, Director, Division of Bioequivalence
Rabindra Patnaik, Deputy Director, DBE
Yi-Chain Huang, Team Leader, Branch I, DBE
Barbara Davit, Team Leader, Branch III, DBE
Lizzie Sanchez, Special Assistant to Director, DBE

Meeting Objective:

To discuss the findings of pending ANDA's for Calcium Channel Blockers, specifically nifedipine extended-release tablets compared to Procardia XL. Even though the studies pass 90% CI, the pharmacokinetic profile looks different (Different Tmax and lag time).

Discussions:

1. The Division has received several ANDA's for Calcium Channel Blockers, especially nifedipine, which meet the 90% CI criteria for AUC and Cmax, however, there are differences in the pharmacokinetic profile.

2. Dr. Davit summarized the findings from Lek's ANDA 75-334 for nifedipine extended-release compared to Procardia XL. The generic product meets the criteria, but the Tmax is reduced by food for the reference product (RLD) compared to the generic product. The Tmax is 10 hrs for the RLD and 22 hrs for the generic product. The apparent Cmax for the mean curves look different. Dr. Williams suggested that individual curves be evaluated.

3. Alza, the manufacturer of the release mechanism used for Procardia XL, (OROS system) claim that their product is not affected by physiological factors. The labeling for Procardia XL states that food may slightly affect the rate of absorption of the drug. However, the data presented to the agency in this ANDA does not support that. Food seems to increase the rate of absorption of Procardia XL, compared to the generic product. Since the hemodynamic effects of Procardia may change depending on the rate of administration, there could be a

greater risk to patients with the Procardia XL product than with the generic products, which show a slower rate of absorption than Procardia XL when administered with food. Data from the generic products study may be redacted, and presented at the Alza meeting to be held on December 2nd, 1998. Alza would like the agency to require generic products, 90% CI for Tmax or any other criteria to show a comparable rate of absorption to Procardia XL, when administered with food.

4. Since the Division has received several applications showing this problem, should the agency change the standards for bioequivalence. If the standards need to be changed, they must be changed in a prospective manner. The Metrics Working Group is evaluating early and total exposure metrics, which may be helpful in the future. For the present time, if the bioequivalence standards are met, we should not fail the generic products.

5. Another example of dissimilar profiles is ANDA 75-125, verapamil capsules by Biovail. All studies (fasting, fed, and multiple dose) showed a lag time for the test product compared to the reference product. AUC and Cmax meet the current bioequivalence criteria. The application should be found acceptable.

6. Mylan's ANDA for Nifedipine compared to Procardia XL (ANDA 75-108), shows the same food effect discussed above for the Lek's ANDA. The ANDA should also be approved.

Action Items:

1. The ANDA's should be finalized and found acceptable if the current BE criteria is met. The Metrics Working Group is deliberating the issue to deal with profile differences.

2. Data from the generic ANDA's may be redacted and presented at the Alza meeting.

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Calcium Channel Blockers 11/10/98
Pending ANDA's

A. Nifedipine

ANDA #	Firm	Problem
75-289	Biovail	Fasting study- AC, Fed study incomplete, MD unacceptable because they deleted subjects who did not have bowel movements. Dissolution is also unacceptable. RLD=Procardia XL Reviewer: Andre Jackson
75-108	Mylan	Fasting, fed and MD studies meet BE criteria. However, Tmax is 61% different (Test =14 hrs; RLD = 8.7hrs). Clinical consult from Dr. Ganley received. Review sent to Dr. Williams. RLD=Procardia XL. Reviewer: Hoi Nguyen
75-269	Biovail	Amendment reviewed and found acceptable. Review with team leader. No problems with profile similarity. RLD=Adalat CC. Reviewer: Sikta Pradhan
75-128	Elan	Fasting, fed, and MD studies acceptable. Dissolution unacceptable. Amendment in que. RLD-Adalat CC. Reviewer: Jahnavi Kharidia.
75-334	Lek	Fasting and fed studies meet BE criteria. MD study under review. Fed study shows differences in Tmax. RLD 10 hrs, test 21 hrs. RLD=Procardia XL. Reviewer: Moheb Makary.

B. Diltiazem:

ANDA #	Firm	Problem
75-116	Biovail	RLD shows twin peaks, which test product do not mimic. Tmax for diltiazem is also 55% different at steady state (test 10.9 hr; RLD 6.57 hr). OPS decision is not to require additional criteria for twin peaks. Standard BE criteria will be applied. RLD: Cardizem CD. Reviewer: Hoi Nguyen
75-401	Andrx	All studies acceptable. RLD: Tiazac. Reviewer: Kuldeep Dhariwal.
74-984	Purepac	All studies acceptable. Mimics twin peaks observed with Cardizem CD. RLD: Cardizem CD. Reviewer: Park and Nouravarsani.
74-845	Biovail	All studies acceptable. RLD: Cardizem SR. Reviewer: Lin Chuang

C. Verapamil

ANDA #	Firm	Problem
75-138	Mylan	All studies meet BE criteria, including sprinkling study. RLD:Verelan SR. Reviewer: Moheb Makary.
75-072	Duramed	All studies meet BE criteria except for the 180 mg strength (fails Cmax). The fed study for the 240mg strength also fails, since one subject that the firm claims is an outlier, was not removed by the reviewer from the analysis. The firm plans to contest this. RLD: Isoptin SR. Reviewer: Moheb Makary
75-125	Biovail	All studies meet BE criteria except for the 120 mg strength (fails Cmax). However, the firm employed 2 hours as the first sampling time, instead of 1 hr. Most of the subjects dosed with the test product showed no measurable levels of verapamil and norverapamil at two hours compared to the RLD. Sprinkling study was requested according to labeling. RLD: Verelan SR. Reviewer: Moheb Makary

Tuesday, November 10, 1998
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APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-108** Date of Submission: **April 21, 1998**

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

Established Name: **Nifedipine Extended-release Tablets 30 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 100s and 500s
Satisfactory as of March 12, 1998 submission.

Professional Package Insert Labeling:
Satisfactory as of April 21, 1998 submission.

Revisions needed post-approval: NONE

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Procardia XL®

NDA Number: 19-684

NDA Drug Name: Procardia XL® (Nifedipine extended-release) Tablet

NDA Firm: Pratt Pharmaceuticals

Date of Approval of NDA Insert and supplement #: 8/12/97 (S-014)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? FOR UD Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	

	Yes	No	N.A.
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement? HOWEVER - see FTR and NOTE TO CHEMIST		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. The RLD has "Store below 86°F (30°C)." while the ANDA has "Store at CRT 15°-30°C (59°-86°F)." Is this acceptable. The answer is "YES" by reviewing chemist N. Gregory.

2. The firm has included the ingredients of "Timerx N" in their listing of inactives in the DESCRIPTION section as we asked.

3. The firm has stated in the HOW SUPPLIED section that their tablet is unscored as we requested.

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the most recently approved labeling of Procardia XL® ([S-014] Approved 8/12/97; Revised 4/97).

2. Storage/Dispensing recommendations

RLD - Store below 86°F (30°C); PROTECT FROM MOISTURE AND HUMIDITY; Dispense in tight containers (USP).

ANDA - Store at CRT 15°-30°C (59°-86°F); PROTECT FROM MOISTURE AND HUMIDITY; Dispense in a tight container as defined in the USP using a child-resistant closure; Keep container tightly closed.

3. The inactives are accurately listed in the description section.

4. Mylan Pharmaceuticals Inc is the sole manufacturer (v 1.16 p 7798).

5. The tablet description is accurate as seen in the HOW SUPPLIED section.

6. Container Sizes

RLD	30 mg - 100s, 300s, 5000s, UD 100s
	60 mg - 100s, 300s, 5000s, UD 100s
	90 mg - UD 100s
ANDA	30 mg - 100s, 500s

7. The containers are made of the 100s size has a CRC while the 500s size does not (v 1.17 p 8118).

8. There are 5 patents for this drug product:

5264446	11/23/10
4783337	9/16/03
4765989	9/16/03
4612008	9/16/03
4327725	11/25/00

Mylan has stated that they will market this drug product upon approval of this application and resolution of the validity, enforcement, or infringement of the above patents. This ANDA was submitted under Paragraph IV.

Date of Review: 4/24/98 Date of Submission: April 21, 1998

Primary Reviewer: Adolph Vezza /S/ Date: 4/29/98

Team Leader: Charlie Hoppes /S/ Date: 4/29/98

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

ANDA Number: **75-108** Date of Submission: **March 12, 1998**

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

Established Name: **Nifedipine Extended-release Tablets 30 mg**

Labeling Deficiencies:

INSERT - PRECAUTIONS section - Please include the "Pediatric Use" subsection with the following text as the last subsection:

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Revise your package insert labeling as described above, then prepare and submit final printed (or printers proof) package insert labeling. 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 revise your insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at

least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) In final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 100s and 500s
Satisfactory as of March 12, 1998 submission.

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Procardia XL®

NDA Number: 19-684

NDA Drug Name: Procardia XL® (Nifedipine extended-release) Tablet

NDA Firm: Pratt Pharmaceuticals

Date of Approval of NDA Insert and supplement #: 8/12/97 (S-014)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			

	Yes	No	N.A.
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? FOR UD Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement? HOWEVER - see FTR and NOTE TO CHEMIST		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			

	Yes	No	N.A.
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. The RLD has "Store below 86°F (30°C)." while the ANDA has "Store at CRT 15°-30°C (59°-86°F)." Is this acceptable. The answer is "YES" by reviewing chemist N. Gregory.

2. The firm has included the ingredients of "Timerx N" in their listing of inactives in the DESCRIPTION section as we asked.

3. The firm has stated in the HOW SUPPLIED section that their tablet is unscored as we requested.

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the most recently approved labeling of Procardia XL® ([S-014] Approved 8/12/97; Revised 4/97).

2. Storage/Dispensing recommendations

   RLD - Store below 86°F (30°C); PROTECT FROM MOISTURE AND HUMIDITY; Dispense in tight containers (USP).

   ANDA - Store at CRT 15°-30°C (59°-86°F); PROTECT FROM MOISTURE AND HUMIDITY; Dispense in a tight container as defined in the USP using a child-resistant closure; Keep container tightly closed.

3. The inactives are accurately listed in the description section.

4. Mylan Pharmaceuticals Inc is the sole manufacturer (v 1.16 p 7798).

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

ANDA Number: **75-108** Date of Submission: **March 12, 1998**

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

Established Name: **Nifedipine Extended-release Tablets 30 mg**

Labeling Deficiencies:

INSERT - PRECAUTIONS section - Please include the "Pediatric Use" subsection with the following text as the last subsection:

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Revise your package insert labeling as described above, then prepare and submit final printed (or printers proof) package insert labeling. 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 revise your insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at

least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) In final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

/S/

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

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

ANDA Number: **75-108** Dates of Submission: **May 19, 21 and 27, 1997**

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

Established Name: **Nifedipine Extended-release Tablets 30 mg**

Labeling Deficiencies:

1. CONTAINER 100s and 500s

   Satisfactory in draft.

2. INSERT

   a. DESCRIPTION

      i. Improve the legibility of the C=O double bonds in the structural formula.

      ii. Decrease the print size of the subscripts in the molecular formula.

      iii. Second paragraph

         A). Revise the molecular weight to read 346.34.

         B). Last sentence - The nifedipine ... 30 mg of ...

      iv. Last paragraph

         A). Combine the last paragraph with the second paragraph.

         B). Revise the first sentence to read "Each tablet also contains the following inactive ingredients: ...".

      v. Please list the ingredients of "Timerx N" in your listing of inactive ingredients.

b. CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism, first paragraph, third sentence -

... the 24-hour dosing ... (add hyphen).

c. INDICATIONS AND USAGE

i. First paragraph, first sentence -

Nifedipine extended-release tablets are indicated ...

ii. Chronic Stable Angina

A). First sentence - Nifedipine extended-release tablets are indicated ...

B). Third paragraph, first sentence - ... and beta-blocking agents ... (add hyphen).

iii. Hypertension

First sentence - Nifedipine extended-release tablets are indicated ...

d. PRECAUTIONS

i. Drug Interactions

First sentence - ... (See INDICATIONS AND USAGE and WARNINGS) ...

ii. Pregnancy: Pregnancy Category C

A). Revise this subsection as follows:

Nifedipine has been shown to produce teratogenic findings in rats and rabbits, including digital anomalies similar to those reported for phenytoin. Digital anomalies have been reported to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Nifedipine administration was associated with a variety of embryotoxic, placentotoxic, and

fetotoxic events, including stunted fetuses (rats, mice, rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice, rabbits), and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). On a mg/kg basis, all of the doses associated with the teratogenic embryotoxic or fetotoxic effects in animals were higher (3.5 to 42 times) than the maximum recommended human dose of 120 mg/day. On a mg/m^2 basis, some doses were higher and some were lower than the maximum recommended human dose but all are within an order of magnitude of it. The doses associated with placentotoxic effects in monkeys were equivalent to or lower than the maximum recommended human dose on a mg/m^2 basis.

There are no adequate ... fetus.

(Please note that the sentence beginning "There are no ..." begins another paragraph.)

e. ADVERSE EXPERIENCES

i. Revise the section heading to read "ADVERSE REACTIONS".

ii. First table - ... Extended-release Tablets (add "Tablets").

iii. Paragraph beginning "The following adverse experiences ..."

... gastrointestinal bleeding, gynecomastia.

iv. Paragraph beginning "In a subgroup of over 1000 patients ...

... immediate-release ... (add hyphen).

v. Last paragraph

... caused by nifedipine. There have been rare reports of exfoliative or bullous skin

adverse events (such as erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis) and photosensitivity reactions.

f. HOW SUPPLIED

i. Delete "USP" from the established name.

ii. State that your tablet is unscored in this section.

Revise your container labels and package insert labeling as described above, then prepare and submit final printed package insert labeling and final printed container labels.

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.

/S/

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

CC:

097

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang
HFD-617/ L. Sanchez or N. Chamberlin
HFD-65 / D. Conner 4/23/98

BIOEQUIVALENCY - UNACCEPTABLE

1. **STUDY AMENDMENT** (STA) 31-OCT-97 — Strengths: 30 mg — **Outcome: UN**

2. ~~STUDY Amendment (STA)~~ **OTHER ~~(OTH)~~** OTH 08-Dec-97 — Strengths: 30 mg — **Outcome: AC**

Outcome Decisions:
AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete

WINBIO COMMENTS:

File 75-108

DATE: November 24, 1998 Time: 10:30am

Dr. Williams' Office
Woodmont II

Subject: Calcium Channel Blockers, Profile differences

Meeting Type: Internal

Meeting Chair: Roger Williams

FDA Participants:
Dale Conner, Director, Division of Bioequivalence
Rabindra Patnaik, Deputy Director, DBE
Yi-Chain Huang, Team Leader, Branch I, DBE
Barbara Davit, Team Leader, Branch III, DBE
Lizzie Sanchez, Special Assistant to Director, DBE

Meeting Objective:

To discuss the findings of pending ANDA's for Calcium Channel Blockers, specifically nifedipine extended-release tablets compared to Procardia XL. Even though the studies pass 90% CI, the pharmacokinetic profile looks different (Different Tmax and lag time).

Discussions:

1. The Division has received several ANDA's for Calcium Chanel Blockers, especially nifedipine, which meet the 90% CI criteria for AUC and Cmax, however, there are differences in the pharmacokinetic profile.

2. Dr. Davit summarized the findings from Lek's ANDA 75-334 for nifedipine extended-release compared to Procardia XL. The generic product meets the criteria, but the Tmax is reduced by food for the reference product (RLD) compared to the generic product. The Tmax is 10 hrs for the RLD and 22 hrs for the generic product. The apparent Cmax for the mean curves look different. Dr. Williams suggested that individual curves be evaluated.

3.

affected by physiological factors. The labeling for Procardia XL states that food may slightly affect the rate of absorption of the drug. However, the data presented to the agency in this ANDA does not support that. Food seems to increase the rate of absorption of Procardia XL, compared to the generic product. Since the hemodynamic effects of Procardia may change depending on the rate of administration, there could be a

greater risk to patients with the Procardia XL product than with the generic products, which show a slower rate of absorption than Procardia XL when administered with food. Data from the generic products study may be redacted, and presented at the meeting to be held on December 2nd, 1998. would like the agency to require generic products, 90% CI for Tmax or any other criteria to show a comparable rate of absorption to Procardia XL, when administered with food.

4. Since the Division has received several applications with this problem, should the agency change the standards for bioequivalence. If the standards need to be changed, they must be changed in a prospective manner. The Metrics Working Group is evaluating early and total exposure metrics, which may be helpful in the future. For the present time, if the bioequivalence standards are met, we should not fail the generic products.

5. Another example of dissimilar profiles is ANDA 75-125, verapamil capsules by Biovail. All studies (fasting, fed, and multiple dose) showed a lag time for the test product compared to the reference product. AUC and Cmax meet the current bioequivalence criteria. The application should be found acceptable.

6. Mylan's ANDA for Nifedipine compared to Procardia XL (ANDA 75-108), shows the same food effect discussed above for the Lek's ANDA. The ANDA should also be approved.

Action Items:

1. The ANDA's should be finalized and found acceptable if the current BE criteria is met. The Metrics Working Group is deliberating the issue to deal with profile differences.

2. Data from the generic ANDA's may be redacted and presented at the Alza meeting.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation
and Research
Office of Drug Evaluation I
Division of Cardio-Renal Drug Products

Memorandum

Date: 9/29/97

From: Thomas Papoian, Ph.D.

Subject: Consult Request for Nifedipine Extended Release 30 mg
ANDA #75-108 (Mylan Pharmaceuticals, Inc.)
Safety Levels of PEG 3350, Xanthum Gum, and Locust Bean Gum

To: Director,
and Dr. Harvey Greenberg
Office of Generic Drugs (HFD-600)
Document Control Room E-150
Metro Park North 2

The amount (of the inactive ingredient, polyethylene glycol in the proposed ANDA #75-108 (Nifedipine Extended-Release 30 mg, an antianginal drug belonging to a class of pharmacological agents, the calcium channel blockers) exceeds the maximum concentration previously approved by the FDA in a solid oral dosage drug product (27.2 mg; Inactive Ingredient Guide, January 1996). Also, it is not clear whether the amounts of the inactive components, xanthum gum and locust bean gum, in the ingredient, . have been used in previously approved drug products (no established levels in the Inactive Ingredient Guide, Januarv 1996). This consult will attempt to determine whether the amounts of the inactive ingredients, , xanthum gum, and locust bean gum, in Nifedipine Extended Release 30 mg present a safety issue.

1. Polyethylene Glycol

PEG's are condensation polymers of ethylene oxide and have been approved by the FDA as direct food additives in amounts not greater than that required to produce the intended physical or intended effect. They are also employed in various pharmacological preparations including parenteral, topical, ophthalmic, oral, and rectal preparations. l represents the average molecular weight in a the range of 3000-3700. PEG 4000 is a slightly less homogenous preparation with an average molecular weight of 4000 in the molecular weight range of 3000-4800. Thus, PEG ' is contained within the molecular weight distribution of PEG 4000.

The amount of PEG n Nifedipine Extended Release is slightly more than that used in previously FDA approved products containing PEG (27.2 mg per oral capsule). Products containing PEG 4000, however, have been previously approved by the FDA

in amounts up to 449.6 mg per oral capsule. Regardless of the approved levels, studies from two reports have examined the toxicity of PEG 4000 in rats: (1) "Two Years of Repeated Oral Feeding of Polyethylene Glycol to Rats" conducted by the University of Pittsburgh for Carbide and Carbon Chemistry Co. on 5/7/54, and (2) "Summary of Evaluations Performed by the Joint FAO/WHO Export Committee on Food Additives," 1980.

1.1. Two years of repeated oral feeding of polyethylene glycol to rats (Report No. 17-60):

This study was conducted by the Mellon Institute of Industrial Research, University of Pittsburgh for Carbide and Carbon Chemistry Co., and was dated 5/7/54. A photocopy was obtained from Dr. John O'Donnell of Mylan Pharmaceuticals, Inc.

Male and female CF Wistar albino rats (20/sex/group; 183-190 gms for males and 138-142 gms for females) were given fixed concentrations of PEG in their diets at 0.5, 1.0, 2.0, 4.0, and 8.0% for two years. Controls received food without PEG. Rats were examined for diet consumption, body weights, rate of mortality, number of infections, and life span . After one year, some of the rats of each sex (no numbers given) were killed for an interim analysis which consisted of histological examination (adrenal, heart, small intestine, kidney, liver, lung, pancreas, spleen, and testis) and determination of liver and kidney weights. After two years, the remaining animals were sacrificed for examination of: hematology (RBC counts, differential WBC counts, hemoglobin), liver and kidney weights, and histologic examination of the same tissues examined in the interim sacrifice.

Results showed that the approximate consumption of PEG 4000 was: 250 mg/kg/day (0.5% diet), 500 mg/kg/day (1.0% diet), 1000 mg/kg/day (2% diet), 2000 mg/kg/day (4% diet), and 4000 mg/kg/day (8% diet). There were no apparent PEG-related effects of mortality or life span. Liver and kidney weights were not affected. Body weights in both males and females were significantly decreased (5-8%) in only the 8% PEG groups. No changes in hematology parameters were found. Histologic examination revealed no pathological changes that were not found with similar frequency in the controls.

It was concluded that PEG 4000 in amounts up to 8% of the diet produced no effects on diet consumption, rate of mortality, number of infections, life span, liver and kidneys weights, and histopathology of several organs, blood count data, and incidences of neoplasms. However, a slight decrease in body weight was observed with 8% PEG. Therefore, the no-observable-adverse-effect-level (NOAEL) was determined to be 4% PEG 4000 in the diet or approximately 2000 mg/kg/day. [Note: A contaminated lot of yeast was used in the diet during one week of the study which was noticed to cause a decrease in body weight gain.]

1.2. Summary of evaluations performed by the joint FAO/WHO export committee on food additives, polyethylene glycols, evaluation of certain food additives, 23rd JECFA, 1980.

This report summarizes several toxicological studies using PEG of various molecular weight ranges in several species, including humans.

When PEG 4000 was fed to rats at up to 24% of the diet for 90 days, decreases in body weights were found at the ≥8% doses which were similar to the two year studies above. No changes were found in mortality, liver and kidney weights, and histopathology of liver and kidney. The no-effect-level was 4% PEG 4000 (2000 mg/kg/day for 90 days) (Smyth *et al.* 1955). When PEG 4000 was fed to rats for two years, a 4% level showed no adverse effects, while higher levels resulted in small, nonspecific effects on growth and minor cloudy swelling of the liver (Smyth *et al.* 1955).

In dogs, PEG 4000 caused no adverse effects when fed at 2% in the diet for one year (Smyth *et al.* 1955).

Absorption from the diet decreases with increasing molecular weight. PEG 4000 was not absorbed from the rat intestine over a 5-hour period.

When 10 gms of PEG 6000 was given orally to humans, none of the PEG 6000 was found in the urine in the following 24 hours.

It was determined that the no-toxicologic-effect-level in rats was 2% of the diet (20,000 ppm) which was equivalent to 1000 mg/kg. Assuming a safety margin of 100, the estimate of the acceptable daily intake for man was extrapolated to be ≤ 10 mg/kg.

1.3. Conclusions regarding PEG

Although the studies described above were not conducted with PEG)ut rather with PEG 4000, the toxicities, however, would be very similar, since the molecular weight range of PEG is contained within PEG 4000. The NOAEL in rats was found to be 2000 mg/kg. When extrapolating doses used in animals to humans, it has been shown that conversion of dose in relation to surface area (mg/m^2) minimizes differences between species. When expressed as mg/m^2, the NOAEL of 2000 mg/kg in rats equals 17,600 mg/m^2.

Proposed formulations of Nifedipine Extended Release include 30, 60, and 90 mg which contain 30, 60, and 90 mg PEG respectively. When based on the rat NOAEL of 17,600 mg/m^2, the safety margins of the 30, 60, and 90 mg formulations are 859X, 430X, and 287X, respectively (Table 1). These values are well above the standard safety margin of 100 which is used to extrapolate from animals to humans.

Therefore, the proposed dose of 30 mg PEG ιppears to be well within a safe dose.

Table 1

Safety Margins of PEG 4000 in Man
Based on Rat NOAEL

Human Dose		Multiple of Rat NOAEL	
mg/kg	**mg/m^2**	**mg/kg**	**mg/m^2**
0.6 (30 mg/50 kg)	20.5	3333	859
1.2 (60 mg/50 kg)	40.9	1667	430
1.8 (90 mg/50 kg)	61.4	1111	287

2.

is a system containing the ingredients: locust bean gum, xanthum gum, dextrose, calcium sulfate, and ethyl cellulose. According to the Inactive Ingredient Guide of January 1996, there are no established levels for locust bean gum and xanthum gum. Of concern, therefore, are the levels of locust bean gum and xanthum gum in Nifedipine Extended Release tablets for the 30 mg, 60 mg, and 90 mg formulations:

2.1. Xanthum Gum

Xanthum gum, a high molecular weight polysaccharide gum, has been approved by the FDA as a food additive for direct use in human food (21CFR Part 172.695). In 1986, the joint FAO/WHO Expert Committee on Food Additives established an acceptable daily intake (ADI) of "not specified" which was based on a lack of observed toxicities in several short- and long-term studies in animals ("Evaluation of certain food additives and contaminants," Thirtieth Report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 751, 1987). However, since there may be a potential for high exposure to xanthum gum and the fact that it is prepared from a microbial source not normally used in food, the Committee considered

that another long-term carcinogenicity study in a second rodent species was desirable. Results of chronic toxicity studies of two years duration conducted in rats and dogs are summarized below.

2.1.1. Xanthum gum: Safety evaluation by oral administration to rats for 104-105 weeks:

This study was conducted by for the and was submitted on 7/7/68. A photocopy was obtained from Dr. John O'Donnell of Mylan Pharmaceuticals, Inc.

Male and female weanling albino rats (30/sex/group) were given xanthum gum in the diet at 250, 500, and 1000 mg/kg/day for 105 weeks. Rats were weighed weekly, and concentrations were adjusted to maintain a constant level of compound intake. Animals were observed daily for clinical signs. Body weights and food consumption were recorded weekly. Ophthalmic exams were performed every 3 months. Clinical chemistry and hematology analyses were performed periodically (7-8X) throughout the study. After 105 weeks, rats were sacrificed and subjected to a gross examination. Selected organs were weighed, and a histopathological examination performed on 23 tissues.

Results showed that there were no compound-related deaths. Soft stools were noted more frequently for the high (1000 mg/kg) and middle (500 mg/kg) doses than for the control and low (250 mg/kg) doses. This may be due to the feeding of large amounts of a high molecular weight polysaccharide. Low hemoglobin and hematocrit levels were found in 3 high dose (1000 mg/kg) males. No dose-related effects were reported on body weights, food consumption, clinical chemistry, gross necropsy, or incidences of neoplastic or nonneoplastic lesions.

It can be concluded that the observations of soft stools and low hematocrit and hemoglobin levels in a few of the high dose males were not of toxicological significance. Therefore, the no-observable-adverse effect level (NOAEL) was >1000 mg/kg/day, while the no-observable-effect level (NOEL) was 500 mg/kg/day.

2.1.2. Xanthum gum: Safety evaluation by oral administration to dogs for 107 weeks:

This study was conducted by for the and was submitted in 1968. A photocopy was obtained from Dr. John O'Donnell of Mylan Pharmaceuticals, Inc.

Male and female beagle dogs (4/sex/group; approx. 7-12 kg; 4-8 months of age) were given xanthum gum in the diet at 250, 500, and 1000 mg/kg/day for 107 weeks. Dosage adjustments were made at 3 month intervals to account for body weight changes. Dogs were weighed weekly. Daily observations included clinical signs, food consumption, behavior, stool consistency, urinary secretions, and indications of emesis. Blood pressures, ECGs, and heart rates were recorded periodically. Ophthalmologic exams, hematology, clinical chemistry, and urinalysis were conducted periodically. After 107 weeks, dogs were sacrificed and subjected to gross necropsy. Histopathologic examination was performed on 30 tissues.

No deaths were reported. Urinalysis at Week 104 found a dose-related increase in urinary specific gravity (1.031 vs 1.019 for high dose and control, respectively), but the values were within the normal range reported in the literature (1.016-1.060). Urinary albumin was observed more frequently for dogs in the high dose (1000 mg/kg) group than in the other groups. Soft stools were noted in treated dogs, but a dose effect was difficult to establish. No effects on body weights, ophthalmology, blood pressure, ECG, heart rate, hematology, or clinical chemistry were found. Gross and histopathological exams did not reveal any changes that could be attributed to treatment with xanthum gum.

It can be concluded that the increased incidence in urinary albumin at 1000 mg/kg was an adverse effect. Therefore, the NOAEL was 500 mg/kg/day.

2.1.3. Conclusions regarding xanthum gum:

The presence of soft stools in rats and dogs is probably not of toxicological significance, since studies in rats fed radiolabled xanthum gum have shown that <1% of the compound is absorbed after oral administration with >97% found in the feces. As noted above, this may be due to the feeding of large amounts of a high molecular weight polysaccharide that is not readily absorbed.

The NOAEL in rats was >1000 mg/kg/day based on a lack of any adverse effects. The NOAEL in dogs was 500 mg/kg/day based on the increase incidence in urinary albumin at 1000 mg/kg. The safety margins for humans taking the maximum proposed dose of 90 mg Nifedipine (=135 mg xanthum gum per tablet = 1.8 mg/kg based on a 50 kg individual = 61.4 mg/m^2), are 112X when based on the dog NOAEL and ≥76X when based on the rat NOAEL (Table 2). These values are very near the 100-fold safety margin used to extrapolate from animals to humans.

Therefore, the proposed doses of 75, 120, or 135 mg of xanthum gum appear to be well within a safe dose.

Table 2

Safety Margins of Xanthum Gum in Man
Based on Rat and Dog NOAELs

	Dose		Safety Margins	
Species	**mg/kg**	**mg/m^2**	**mg/kg**	**mg/m^2**
Human	2.7 (135 mg/50 kg)	92.1	--	
Dog	500	10,300	185	112
Rat	>1000	>7,000	>370	>76

2.2. *Locust Bean Gum*

Locust bean gum, another high molecular weight polysaccharide gum, has been affirmed as GRAS (generally recognized as safe) by the FDA for direct use in human food (21CFR Part 184.1343). It is used as a stabilizer and thickener in foods, and is found in various orally administered pharmaceutical preparations.

Results of two-year carcinogenicity studies in mice and rats have shown no toxicity when given at up to 7500 mg/kg (mice) or 5000 mg/kg (rats). In dogs given locust bean gum for up to 30 weeks, some reduction in body weight occurred at 4000 mg/kg. However, the most sensitive species appeared to be mice and rabbits which were used to assess the compound's teratogenicity. The NOAEL levels were 280 mg/kg for mice and 196 mg/kg for rabbits. The mouse and rabbit teratology studies are summarized below. A photocopy was obtained from Dr. John O'Donnell of Mylan Pharmaceuticals, Inc.

2.2.2. Teratologic evaluation of FDA 71-14 (carob bean or locust gum) in mice:

These studies were performed by the [illegible]
not associated with the FDA), and were submitted on 8/11/72.

Pregnant mice (approx. 40 gms; unknown gestation day) were given locust bean gum (by oral gavage?) at up to 1300 mg/kg as a suspension in corn oil for 10 consecutive days. At termination, mice were sacrificed and the uterine contents examined for evidence of teratogenicity.

Results showed that administration of 280 mg/kg had no discernible effect on nidation (implantation) or on maternal or fetal survival. The number and type of abnormalities were similar

to that found in controls. However, administration of 1300 mg/kg resulted in the deaths of a majority of the dams. Does which survived this dose, bore normal offspring.

It was concluded that the locust bean gum was not a teratogen, and that the NOAEL was 280 mg/kg.

2.2.2. Teratologic evaluation of FDA 71-14 (carob bean or locust gum) in rabbits:

These studies were performed by the
(not associated with the FDA), and were submitted on 8/11/72.

Pregnant rabbits (approx. 2.5 kg; unknown gestation day) were given locust bean gum (by oral gavage?) at up to 910 mg/kg as a suspension in corn oil for 13 consecutive days. At termination, rabbits were sacrificed and the uterine contents examined for evidence of teratogenicity.

Results showed that administration of 196 mg/kg had no discernible effect on nidation (implantation) or on maternal of fetal survival. The number and type of abnormalities were similar to that found in controls. However, administration of 910 mg/kg resulted in the deaths of a majority of the dams. Death was preceded by bloody diarrhea and urinary incontinence with anorexia for 2-3 days terminally. Does which survived this dose, bore normal offspring.

It was concluded that the locust bean gum was not a teratogen, and that the NOAEL was 196 mg/kg.

2.2.2. Conclusions regarding locust bean gum:

The most sensitive species to locust bean gum toxicity were pregnant mice and rabbits. The NOAEL in pregnant mice was 280 mg/kg, and in pregnant rabbits the NOAEL was 196 mg/kg. Higher doses resulted in death due to unknown causes.

The safety margins for humans taking the maximum proposed dose of 90 mg Nifedipine (=135 mg locust bean gum per tablet = 1.8 mg/kg based on a 50 kg individual = 61.4 mg/m^2), are 12X when based on the mouse NOAEL and 29X when based on the rabbit NOAEL (Table 3). Although these values using mg/m^2 are well below the 100-fold safety margin used to extrapolate from animals to humans, the values using mg/kg are near the 100-fold safety margin.

Therefore, the proposed doses of 75, 120, or 135 mg of locust bean gum appear to be within a safe dose.

Table 3

Safety Margins of Locust Bean Gum in Man
Based on Mouse and Rabbit NOAELs

	Dose		Safety Margins	
Species	**mg/kg**	**mg/m^2**	**mg/kg**	**mg/m^2**
Human	2.7 (135 mg/50 kg)	92.1	--	
Mouse	280	1064	104	12
Rabbit	196	2666	73	29

3. Summary

This consult reviewed animal toxicity studies to determine whether the amounts of the inactive ingredients, PEG xanthum gum, and locust bean gum, in Nifedipine Extended-Release 30 mg present a safety issue. The sponsor proposes to use higher amounts of these inactive ingredients in future Nifedipine Extended-release 60 and 90 mg tablets.

Many studies have been performed in animals over the years to examine potential toxicities of these compounds. Some were performed over 40 years ago, and lack the quality of current standards. However, sufficient information can be obtained to make an assessment of the potential safety issues with regards to their pharmaceutical use in humans. It should be noted that conversion of mg/kg to mg/m2 may reduce the safety margin, but this measure is a better extrapolation from animals to humans.

The use of PEG at the proposed levels appears to be safe. For this compound, there is a large margin of safety (287X the maximum proposed dose). For xanthum gum, the safety margin is again large for the maximum proposed dose (76-112X). The safety margins for locust bean gum were somewhat lower based on sensitivities (death) of pregnant mice and rabbits to high oral doses (12-29X). Non-pregnant mice, rats, and dogs showed no adverse effects at very high (4000-7500 mg/kg) doses. It is the opinion of this reviewer that this should not result in a safety concern, since locust bean gum is commonly found in a wide variety of foods, is generally recognized as safe by the FDA, and has not been associated with any adverse effects from its historical use. It may be worthwhile to perform a short-term toxicity study using pregnant mice and rabbits to determine the cause of death at the higher doses.

Therefore, the levels of the inactive ingredients, PEG and xanthum gum, proposed for use in Nifedipine Extended-Release 30, 60, and 90 mg, appear to be well within safe limits, and should not pose a safety issue. A remaining issue for locust bean gum is to determine the reason for the increased mortality in pregnant mice and rabbits when given high (910-1300 mg/kg) doses. However, the proposed levels of locust bean gum appear to be within a reasonable margin of safety.

Thomas Papoian, Ph.D.
Pharmacologist

Concur: Albert P. DeFelice, Ph.D.
Pharmacology Team Leader

9/22/97

Concur: Raymond J. Lipicky, M.D.
Division Director

1.1

P.C

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

ANDA Number: **75-108** Dates of Submission: **May 19, 21 and 27, 1997**

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

Established Name: **Nifedipine Extended-release Tablets 30 mg**

Labeling Deficiencies:

1. CONTAINER 100s and 500s

   Satisfactory in draft.

2. INSERT

   a. DESCRIPTION

      i. Improve the legibility of the C=O double bonds in the structural formula.

      ii. Decrease the print size of the subscripts in the molecular formula.

      iii. Second paragraph

         A). Revise the molecular weight to read 346.34.

         B). Last sentence - The nifedipine ... 30 mg of ...

      iv. Last paragraph

         A). Combine the last paragraph with the second paragraph.

         B). Revise the first sentence to read "Each tablet also contains the following inactive ingredients: ...".

      v. Please list the ingredients of "Timerx N" in your listing of inactive ingredients.

b. CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism, first paragraph, third sentence -

... the 24-hour dosing ... (add hyphen).

c. INDICATIONS AND USAGE

i. First paragraph, first sentence -

Nifedipine extended-release tablets are indicated ...

ii. Chronic Stable Angina

A). First sentence - Nifedipine extended-release tablets are indicated ...

B). Third paragraph, first sentence - ... and beta-blocking agents ... (add hyphen).

iii. Hypertension

First sentence - Nifedipine extended-release tablets are indicated ...

d. PRECAUTIONS

i. Drug Interactions

First sentence - ... (See INDICATIONS AND USAGE and WARNINGS) ...

ii. Pregnancy: Pregnancy Category C

A). Revise this subsection as follows:

Nifedipine has been shown to produce teratogenic findings in rats and rabbits, including digital anomalies similar to those reported for phenytoin. Digital anomalies have been reported to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Nifedipine administration was associated with a variety of embryotoxic, placentotoxic, and

fetotoxic events, including stunted fetuses (rats, mice, rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice, rabbits), and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). On a mg/kg basis, all of the doses associated with the teratogenic embryotoxic or fetotoxic effects in animals were higher (3.5 to 42 times) than the maximum recommended human dose of 120 mg/day. On a mg/m^2 basis, some doses were higher and some were lower than the maximum recommended human dose but all are within an order of magnitude of it. The doses associated with placentotoxic effects in monkeys were equivalent to or lower than the maximum recommended human dose on a mg/m^2 basis.

There are no adequate ... fetus.

(Please note that the sentence beginning "There are no ..." begins another paragraph.)

e. ADVERSE EXPERIENCES

i. Revise the section heading to read "ADVERSE REACTIONS".

ii. First table - ... Extended-release Tablets (add "Tablets").

iii. Paragraph beginning "The following adverse experiences ..."

... gastrointestinal bleeding, gynecomastia.

iv. Paragraph beginning "In a subgroup of over 1000 patients ...

... immediate-release ... (add hyphen).

v. Last paragraph

... caused by nifedipine. There have been rare reports of exfoliative or bullous skin

adverse events (such as erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis) and photosensitivity reactions.

f. HOW SUPPLIED

i. Delete "USP" from the established name.

ii. State that your tablet is unscored in this section.

Revise your container labels and package insert labeling as described above, then prepare and submit final printed package insert labeling and final printed container labels.

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: 100s and 500s

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Procardia XL®

NDA Number: 19-684

NDA Drug Name: Procardia XL®(Nifedipine extended-release) Tablets

NDA Firm: Pratt Pharmaceuticals

Date of Approval of NDA Insert and supplement #: 8/12/97 (S-014)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			

	Yes	No	N.A.
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? FOR UD Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement? HOWEVER - see FTR and NOTE TO CHEMIST		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			

	Yes	No	N.A.
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. The RLD has "Store below 86°F (30°C)." while the ANDA has "Store at CRT 15°-30°C (59°-86°F)." Is this acceptable.

2. I have asked the firm to include the ingredients of "Timerx N" in their listing of inactives in the DESCRIPTION section. Do you concur? I was not able to find any information in the jackets as to this ingredient's composition.

3. I have asked the firm to state that their tablet is unscored.

FOR THE RECORD:

1. This review was based on the most recently approved labeling of Procardia XL® ([S-014] Approved 8/12/97; Revised 4/97).

2. Storage/Dispensing recommendations

   RLD - Store below 86°F (30°C); PROTECT FROM MOISTURE AND HUMIDITY; Dispense in tight containers (USP).

   ANDA - Store at CRT 15°-30°C (59°-86°F); PROTECT FROM MOISTURE AND HUMIDITY; Dispense in a tight container as defined in the USP using a child-resistant closure; Keep container tightly closed.

3. The inactives are accurately listed in the description section, however see NOTE TO CHEMIST # 2 (v 1.16 multiple pages).

4. Mylan Pharmaceuticals Inc is the sole manufacturer (v 1.16 p 7798).

5. The tablet description is accurate as seen in the HOW SUPPLIED section except for the fact that the firm failed to mention that the tablet is unscored (v 1.17 p 8306).

6. Container Sizes

RLD	30 mg - 100s, 300s, 5000s, UD 100s 60 mg - 100s, 300s, 5000s, UD 100s 90 mg - UD 100s
ANDA	30 mg - 100s, 500s

7. The containers are made of HDPE; the 100s size has a CRC while the 500s size does not (v 1.17 p 8118).

8. There are 5 patents for this drug product:

5264446	11/23/10
4783337	9/16/03
4765989	9/16/03
4612008	9/16/03
4327725	11/25/00

Mylan has stated that they will market this drug product upon approval of this application and resolution of the validity, enforcement, or infringement of the above patents.

Date of Review 11/26/97 Dates of Submission: May 19, 21, 27, 1997

Primary Reviewer: Adolph Vezza /S/ Date: 12/5/97

Team Leader: Charlie Hoppes /S/ Date: 12/5/97

cc:

NA1.L

5. The tablet description is accurate as seen in the HOW SUPPLIED section.

6. Container Sizes

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Date of Review: 4/6/98 Date of Submission: March 12, 1998

Primary Reviewer: Adolph Vezza /S/ Date: 4/8/98

Team Leader: Charlie Hoppes /S/ Date: 4/8/98

MYLAN PHARMACEUTICALS INC.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office)
HFD 101 Linda Carter - Forward to HFD-110

FROM:
Office of Generic Drugs, HFD-600

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
6/28/97	—	75-108	ANDA	5/19/97, 5/21/97 & 5/27

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Fenoldipine Extended Release Tablets, 30 mg	High	Calcium Channel Blocker	6/28/97

NAME OF FIRM
Mylan Pharmaceuticals, Inc

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER (Specify below)

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW	☐ CHEMISTRY
END OF PHASE II MEETING	☐ PHARMACOLOGY
CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
PROTOCOL REVIEW	☐ OTHER
OTHER	

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL – BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary)

Please evaluate whether the amount of the inactive ingredients, polyethylene glycol and Locust Bean gum present a safety issue. The amount of the inactive ingredients in the proposed ANDA exceed the maximum concentration previously approved by the Agency in a solid oral dosage drug products.

Thank you,
Harvey Greenberg

Please return the completed consult to: Office of Generic Drugs, Document Control Room E-150, Metro Park North II

NAME OF REQUESTER	METHOD OF DELIVERY (Check one)
Harvey Greenberg 827-5862	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

Printed by Mary Fanning

Electronic Mail Message

Date: 19-Dec-1997 02:05pm
From: Thomas Papoian
PAPOIANT
Dept:
Tel No: 301-594-5300 FAX 301-594-5495

TO: Mary Fanning (FANNINGM)

Subject: Nifedipine

Hi Mary,

Yes, I think that you, me, and Mylan Labs can all agree that this additional study in mice should be viewed as confirmatory, especially since the original studies in question were performed in 1972 by a totally different lab. This is your call, but I would support the path of least resistance for regulatory review on this matter.

My only question from the beginning was the reason for the deaths in pregnant mice fed locust bean gum by gavage when non-pregnant mice fed the gum in their diets survived after receiving much higher doses. It was subsequently suggested by Mylan Labs that the gavage method may have been responsible for the mortality since a large dose of xanthum gum administered all at once, rather than in their diets, may cause gastrointestinal obstruction in an animal already enlarged with pregnancy. The proposed study would only confirm this explanation and demonstrate that it was the gavage method of administration and not the pregnancy status that was responsible for the increase in mortality, an issue important for human use.

Let me know what you decide.

Tom

Printed by Mary Fanning

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 19-Dec-1997 10:58am
From: Mary Fanning
FANNINGM
Dept: HFD-600 MPN2 288
Tel No: 301-594-6740

TO: Thomas Papoian (PAPOIANT)

CC: Gordon Johnston (JOHNSTONG)
Subject: Nifedipine ANDA

Tom,

Sorry to take so long getting back to you about this review. I have discussed the study to clarify the cause of death of the pregnant animals you have asked the company to do and the regulatory process, internally. The study is fine but in writing your review there are regulatory issues to consider. If this is considered a new study which is essential to the approval, the application becomes an NDA, essentially, and likely will require considerable additional work on the part of the company to be successful. However, if this can be seen as a confirmatory study, then the application can stand as an ANDA. This study seems to be more confirmatory in nature to me since the company can try to prove their explanation for unusual and unexpected findings in their previous study in pregnant mice. I would welcome your thoughts on this topic.

Mary

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

TO (Division/Office)			FROM:	
Dr Mary Fenning HFD-600			CDR-615 / Program Support Branch	
D. 12219F	IND NO.	NDA NO. 75-108	TYPE OF DOCUMENT Safety Consult	DATE OF DOCUMENT
NAME OF DRUG N. Ferr. phe Extended Release		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE

NAME OF FIRM
Mylan Pharmaceutical

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
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- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

Pharm/Tox review completed for evaluation of inactive ingredients – please review and comment.
Does the firm get a letter??

Harvey

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)* ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

Printed by Mary Fanning

Electronic Mail Message

Date: 10-Nov-1997 03:01pm
From: Thomas Papoian
PAPOIANT
Dept:
Tel No: 301-594-5300 FAX 301-594-5495

TO: Mary Fanning (FANNINGM)

Subject: Nifedipine

Mary,

I just had a telephone conversation with Mylan Labs regarding an additional mouse toxicity study (described below) that they want to perform for their nifedipine extended release ANDA. They requested that this study be treated as "additional information" to the drug master file for rather than as a submission to the nifedipine ANDA. They would like to avoid a non-approvable letter from you pending completion of this study. In other words, they do not want to hear from you until all the data has been submitted and reviewed.

I agreed to delay my review of their latest submission (the desk copy that arrived today dated 11/7/97) until the mouse study is completed, then review the entire package as an amendment to the first consult. It is anticipated that the study will show that pregnant mice are no more sensitive than non-pregnant mice at a very large multiple of the maximum recommended human dose (MRHD). This would provide evidence that the mortality found in the previous teratology study in mice was due to the dosing method (gavage), and not to the pregnancy status of the animals.

The study to which we agreed is as follows. Two groups of mice, one pregnant and the other non-pregnant (20/group), will be given locust bean gum in their diets at 500, 1500, or 4500 mg/kg (= 185, 556, or 1667X the MRHD of 2.7 mg/kg). For the pregnant group, dosing will be from the time of mating (Day 0) to gestation Day 18 (approximately one day before parturition). The non-pregnant group will be dosed for the same duration. Mice will be monitored for clinical signs, and body weights will be taken before and after dosing. At sacrifice, mice will undergo a gross necropsy. Abnormal tissues will be fixed in formalin for further examination, if necessary. The dose at which a no-observable-adverse-effect-level (NOAEL) is observed will be used to calculate the safety margin for humans. The protocol, in writing, will be sent to me shortly. They anticipate completion of the study by the end of December 1997, with a final report completed by the end of January 1998.

If you have any questions or concerns, particularly with regards to the regulatory issues involved, please let me know.

Tom
HFD-110
x45336

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office) HFD-110/ Dr Mary Fanning			FROM: DGD/RSB HFD-615	
DATE: 3/3/98	IND NO. —	NDA NO. 75-108	TYPE OF DOCUMENT Study	DATE OF DOCUMENT 3/30/98
OF DRUG Nifedipine Extended Release		PRIORITY CONSIDERATION HFS 7	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
NAME OF FIRM Mylan				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE NDA MEETING
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- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICPENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER (specify below)

II.BIOMETRICS

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- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINtCAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (*Attach additional sheets if necessary*)

HFD-110 has completed their review of the additional safety study with the Locust Bean Gum. Please review and provide a memo with a summary of the consult.

Thanks

Henry

SIGNATURE OF REQUESTER /S/ 3/3	METHOD OF DE LIVERY (Check one) ☐ MAIL ☐ HAND
\TURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation
and Research
Office of Drug Evaluation I
Division of Cardio-Renal Drug Products

Memorandum

Date: 3/30/98

From: Thomas Papoian, Ph.D., Pharmacologist
Division of Cardio-Renal Drug Products (HFD-110)

To: Director,
and Mr. Harvey Greenberg
Office of Generic Drugs (HFD-600)
Document Control Room E-150
Metro Park North 2

Subject: Consult Request for Nifedipine Extended Release 30 mg
ANDA #75-108 (Mylan Pharmaceuticals, Inc.)
Safety Levels of PEG Xanthum Gum, and Locust Bean Gum
Document Dated 2/16/98

In a previous Consult Request dated 9/29/97, I addressed the issue of whether the amounts of the inactive ingredients, PEG xanthum gum, and locust bean gum, in Nifedipine Extended Release 30 mg presented a safety issue. In addition to the 30 mg formulation, the sponsor, Mylan Pharmaceuticals, Inc., intends to develop in the future 60 and 90 mg strengths of Nifedipine Extended Release.

Several chronic toxicology studies were reviewed in which animals were administered either PEG 4000 (Report No. 17-60, Mellon Institute of Industrial Research, University of Pittsburgh for Carbide and Carbon Chemistry Co., 5/7/54), xanthum gum (Woodard Research Corp. for the Kelco Co., 1968), or locust bean gum (National Toxicology Program, 1981; Food and Drug Research Laboratories, Inc., 8/11/72) in relatively high multiples of the proposed human exposure. The no-observable-adverse-effect levels (NOAEL) and appropriate safety margins were determined for amounts of each component in the highest (90 mg) strength tablet. The results are summarized below in Tables 1 to 3. [Please note that the human safety margins use multiples of the dose based on body weight rather than surface area. Surface area calculations are better for extrapolation between species for absorbed compounds when systemic exposures (AUCs) are unavailable because critical species differences exist between organ volumes relative to body weights, organ perfusion rates, and enzyme activities associated with metabolism. However, the use of surface area in this case was not appropriate because each of the inactive ingredients are not absorbed from the gastrointestinal tract.]

Table 1

Safety Margins of PEG 4000 in Man
Based on Rat NOAEL
(Mellon Institute Report No. 17-60)
(Nifedipine Extended Release 90 mg Contains 90 mg PEG 3350)

Human Dose (mg/kg)	Multiple of Rat NOAEL (mg/kg)
1.8 (90 mg/50 kg)	1111

Table 2

Safety Margins of Xanthum Gum in Man
Based on Rat and Dog NOAELs
(Woodard Research Corp.)
(Nifedipine Extended Release 90 mg Contains 135 mg Xanthum Gum)

Species	Dose (mg/kg)	Safety Margins (mg/kg)
Human	2.7 (135 mg/50 kg)	--
Dog	500	185
Rat	>1000	>370

Table 3

Safety Margins of Locust Bean Gum in Man
Based on Mouse (Pregnant and Non-Pregnant) and Rabbit (Pregnant) NOAELs
(National Toxicology Program; Food and Drug Research Laboratories)
(Nifedipine Extended Release 90 mg Contains 135 mg Locust Bean Gum)

Species	Dose (mg/kg)	Safety Margins (mg/kg)
Human	2.7 (135 mg/50 kg)	--
Mouse (Pregnant)	280	104
Mouse (Non-Pregnant)	4000	1481
Rabbit (Pregnant)	196	73

As can be seen, the human safety margins are large for PEG 1111X), xanthum gum (185X), and locust bean gum (73X) in Nifedipine Extended Release 90 mg. The only remaining issue was the increased mortality observed in pregnant mice given locust bean gum when compared to non-pregnant mice (104X vs 1481X safety margins, respectively; Table 3).

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Study of the effect of locust bean gum on pregnancy and delivery in mice (unaudited report):

Testing Fac
Study Number: 6482-114
Study Date(s): 12/5/97 to 1/12/98
GLP Compliance: Yes

Methods: Pregnant and non-pregnant female CD-1 mice (20/group; 11 wks old; 28 gms) were administered locust bean gum (lot no. 571111) at 500, 1500, or 4500 mg/kg/day in the diet (Certified Rodent Diet ® #8728C; Harlan Teklad) *ad libitum* from Days 0-19 for the non-pregnant females and beginning on gestation Day 0 through lactation Day 1 to the pregnant (mated) females. Controls received diet without locust bean gum.

Feed samples were taken from the Week 4 mix for analysis of test article concentration. Mice were observed twice daily for signs of mortality and moribundity. Body weights and food consumption were recorded at frequent intervals (~every 2-3 days). Pregnant females were allowed to deliver normally. Live pups were weighed, examined externally, and preserved in formalin. Mated females that delivered naturally by Day 20 and those mated females that did not deliver were sacrificed and examined grossly. Unmated female controls were also sacrificed on Day 20.

Results: All mice survived until the scheduled sacrifice. No treatment-related clinical signs were reported. Mean body weights and mean food consumption were unaffected by treatment. There were no treatment-related gross necropsy observations. Fetal growth and survival were unaffected by treatment. Pregnancy rates from the mated groups averaged about 75% (Table 4), and was this considered by Covance to be relatively low. However, the rate of pregnancy was unrelated to treatment with test article since mating occurred before administration of locust bean gum in the diet.

Table 4

Pregnancy Rates in the Mated Groups

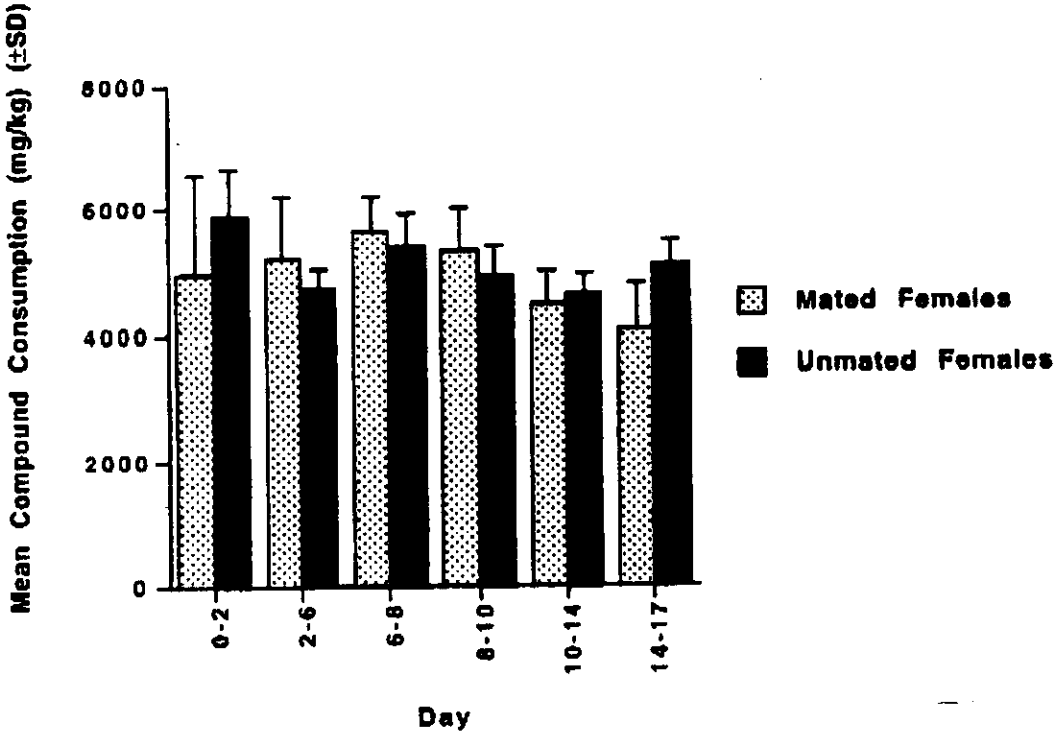
Dose (mg/kg/day)	Number Pregnant	Percent Pregnant
0	18/20	90
500	13/20	65
1500	14/10	70
4500	16/20	80
Mean	**15/20**	**75**

The amount of locust bean gum consumed (mg/kg/day) in the high dose groups is shown in Figure 1. It was calculated according to the formula below: [Note: The dietary compound concentration was based on an analytical analysis of the diet.]

$$\text{Individual compound consumption (mg/kg)} = \frac{\text{Dietary compound concentration (ppm)}}{\text{Individual body weight on last day of interval (gms)}} \times \text{Ave. daily consumption for the interval (gms)}$$

Figure 1

Actual Daily Mean Consumption of Locust Bean Gum in High Dose (4500 mg/kg/day) Mated and Unmated Female Mice



Conclusions: The results of this study showed that the increased mortality observed in a previous mouse study (Food and Drug Research Laboratories, Inc., 8/11/72) was most likely due to the gavage mode of administration, and not due to the pregnancy status of the mice in that study. This is based on the results of the present study in which no mortality or any other adverse effect was found in either pregnant or non-pregnant mice when locust bean gum was administered in their diets at up to 4500 mg/kg/day for 20 days.

Human safety margins for locust bean gum were recalculated and are shown in Table 5. When based on the results of this study, the safety margin for humans taking the maximum proposed dose of ng Nifedipine containing mg locust bean gum is 1667X. Therefore, the amount of locust bean gum proposed for use in Nifedipine Extended-release 90 mg tablets appears to be safe.

Table 5

Recalculated Safety Margins of Locust Bean Gum in Man
Based on Mouse (Pregnant and Non-Pregnant) NOAELs

(Nifedipine Extended Release 90 mg Contains 135 mg Locust Bean Gum)

Species	Dose (mg/kg)	Safety Margins (mg/kg)
Human	2.7 (135 mg/50 kg)	--
Mouse (Pregnant)	4500	1667
Mouse (Non-Pregnant)	4500	1667

5/30/98

Thomas Papoian, Ph.D.
Pharmacologist

4/4/98

Concur: Albert F. DeFelice, Ph.D.
Pharmacology Team Leader

9/3/98

Concur: Raymond J. Lipicky, M.D.
Division Director

Printed by Mary Fanning

Electronic Mail Message

Date: 26-Mar-1998 10:41am
From: Thomas Papoian
PAPOIANT
Dept:
Tel No: 301-594-5300 FAX 301-594-5495

TO: Harvey Greenberg (GREENBERG)

CC: Mary Fanning (FANNINGM)
CC: Sandy Benton (BENTONS)
Subject: Nifedipine Consult

Harvey,

I received your e-mail that you sent to Sandy Benton in our division. But you still need to send another consult request for the issues raised in my last e-mail to you. The consult request you sent about a month ago was canceled because it restated the original instructions (dated 5/28/97) which were addressed and completed in my first consult dated 9/29/97.

In the "comments/special instructions" section of your new request, please request evaluation of: (1) the safety issues raised in my previous consult dated 9/29/97, (2) Mylan's response dated 11/7/97, and (3) the results of the mouse study (unaudited report dated 2/9/98) performed in pregnant and non-pregnant mice. Also please state that the consult should be directed to me (Dr. Thomas Papoian).

The consult has now been completed, and I can begin the process of supervisory concurrence while waiting for your request. So when I receive your new request, you should be receiving the consult shortly after that. Thanks in.

Tom

PARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation
and Research
Office of Drug Evaluation I
Division of Cardio-Renal Drug Products

Memorandum

Date: 3/30/98

From: Thomas Papoian, Ph.D., Pharmacologist
Division of Cardio-Renal Drug Products (HFD-110)

To: Director,
and Mr. Harvey Greenberg
Office of Generic Drugs (HFD-600)
Document Control Room E-150
Metro Park North 2

Subject: Consult Request for Nifedipine Extended Release 30 mg
ANDA #75-108 (Mylan Pharmaceuticals, Inc.)
Safety Levels of PEG Xanthum Gum, and Locust Bean Gum
Document Dated 2/16/98

In a previous Consult Request dated 9/29/97, I addressed the issue of whether the amounts of the inactive ingredients, PEG xanthum gum, and locust bean gum, in Nifedipine Extended Release 30 mg presented a safety issue. In addition to the 30 mg formulation, the sponsor, Mylan Pharmaceuticals, Inc., intends to develop in the future 60 and 90 mg strengths of Nifedipine Extended Release.

Several chronic toxicology studies were reviewed in which animals were administered either PEG 4000 (Report No. 17-60, Mellon Institute of Industrial Research, University of Pittsburgh for Carbide and Carbon Chemistry Co., 5/7/54), xanthum gum (Woodard Research Corp. for the Kelco Co., 1968), or locust bean gum (National Toxicology Program, 1981; Food and Drug Research Laboratories, Inc., 8/11/72) in relatively high multiples of the proposed human exposure. The no-observable-adverse-effect levels (NOAEL) and appropriate safety margins were determined for amounts of each component in the highest (90 mg) strength tablet. The results are summarized below in Tables 1 to 3. [Please note that the human safety margins use multiples of the dose based on body weight rather than surface area. Surface area calculations are better for extrapolation between species for absorbed compounds when systemic exposures (AUCs) are unavailable because critical species differences exist between organ volumes relative to body weights, organ perfusion rates, and enzyme activities associated with metabolism. However, the use of surface area in this case was not appropriate because each of the inactive ingredients are not absorbed from the gastrointestinal tract.]

Table 1

Safety Margins of PEG 4000 in Man
Based on Rat NOAEL
(Mellon Institute Report No. 17-60)
(Nifedipine Extended Release 90 mg Contains

Human Dose (mg/kg)	Multiple of Rat NOAEL (mg/kg)
1.8 (90 mg/50 kg)	1111

Table 2

Safety Margins of Xanthum Gum in Man
Based on Rat and Dog NOAELs
(Woodard Research Corp.)
(Nifedipine Extended Release 90 mg Contains ng Xanthum Gum)

Species	Dose (mg/kg)	Safety Margins (mg/kg)
Human	2.7 (135 mg/50 kg)	--
Dog	500	185
Rat	>1000	>370

Table 3

Safety Margins of Locust Bean Gum in Man
Based on Mouse (Pregnant and Non-Pregnant) and Rabbit (Pregnant) NOAELs
(National Toxicology Program; Food and Drug Research Laboratories)
(Nifedipine Extended Release 90 mg Contains ; Locust Bean Gum)

Species	Dose (mg/kg)	Safety Margins (mg/kg)
Human	2.7 (135 mg/50 kg)	--
Mouse (Pregnant)	280	104
Mouse (Non-Pregnant)	4000	1481
Rabbit (Pregnant)	196	73

As can be seen, the human safety margins are large for PEG 1111X), xanthum gum (185X), and locust bean gum (73X) in Nifedipine Extended Release 90 mg. The only remaining issue was the increased mortality observed in pregnant mice given locust bean gum when compared to non-pregnant mice (104X vs 1481X safety margins, respectively; Table 3).

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Testing Facility:
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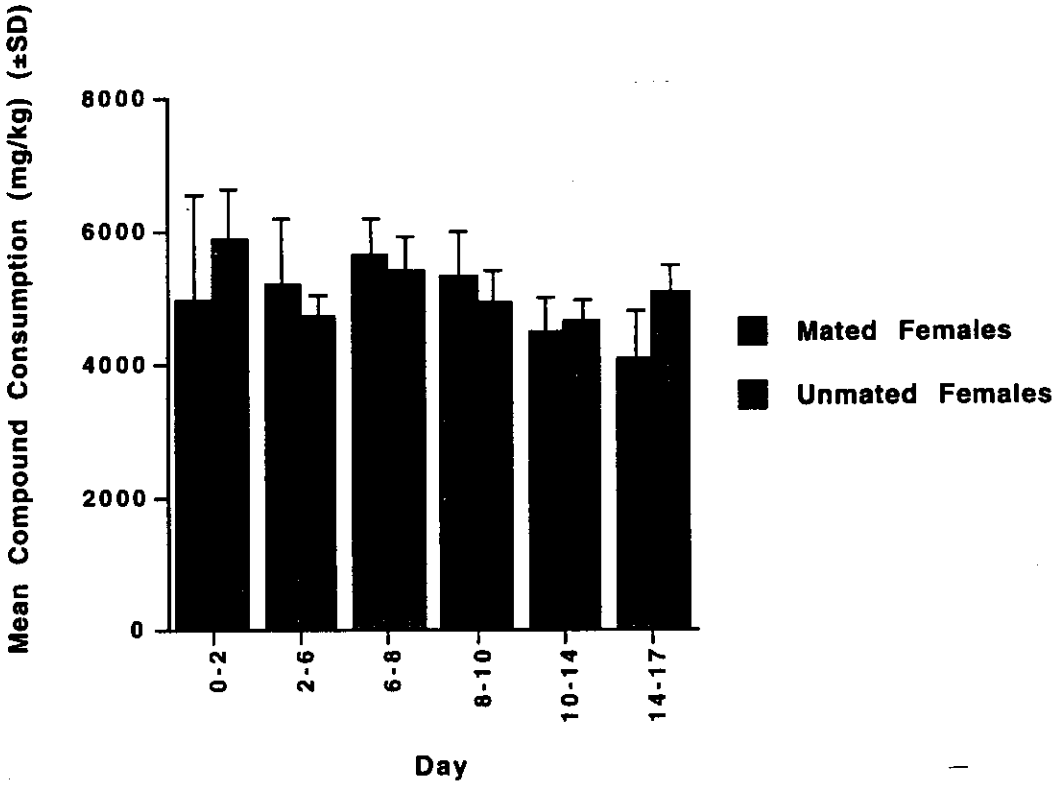

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Pharmacologist

Concur: Albert F. DeFelice, Ph.D.
Pharmacology Team Leader

Concur: Raymond J. Lipicky, M.D.
Division Director

First Generic

ANDA CHECKLIST FOR COMPLETENESS and ACCEPTABILITY of the APPLICATION

AADA / ANDA # 75-108 FIRM NAME Mylan

DRUG NAME: Nifedapine

DOSAGE FORM: Extended-release Tablets, 30mg

Supervisory Chemist (Summers) Labeling Reviewer (Adolph Vazquez)

Random Assignment (Review III) AEV

	YES	NO
Comments EC1 ✓ On Cards ✓		
Therapeutic Code 1010300 ✓ Calcium Channel Blockers	4/7/97 4/9/97	
Methods Validation Package (3 copies) (✓) Required for Non-USP drugs	✓	
Cover Letter	✓	
Letter of Authorization	✓	
U.S. Agent (If needed, Countersignature on 356h)		
DMF Referral(s)		
356 Form - Completed /Original Signature	✓	
Table of Contents	✓	
Listed Drug/Firm PROCARDIA XL Pratt Pharm Div. Pfizer	✓	
AADA Monograph	N/A	
Information to show proposed product is the same as the listed product: (i) (a) indications (ii) active ingredients(s) iii (a) route (b) dosage form (c) strength (iv) labeling -- side by side comparison - insert:	✓	
Container:	✓	
Same Formulation?		
Ophthalmics/Otics/Externals Parenterals		
Parenteral: Same Size Container / (strength/volume)		
Petition Required		
Debarment Certification pg 4	✓	
List of Convictions pg 4	✓	
Third Copy Certification	✓	
Patent Certification 11/23/2010; 9/16/2003 (2) 11/25/2000	✓ 4	
Use Patent Statement? Exclude Use in labeling / indications?	✓	
Exclusivity Addressed	✓	

Drop all Nifedipine

Five year exclusivity? If yes, cannot be filed until expiration of exclusivity or after 4 years if patent challenged.		
Labeling: 4 copies of draft (✓) or 12 copies of FPL ( )		
Statement re Rx/OTC Status	✓	
Components & Composition (Unit Composition)	V356h	
Specifications and Tests for Active Ingredients and Dosage Form	✓	
Source of Active Ingredient(s)	✓	
COA from Manufacturer of Active Ingredient(s)	✓	
Applicant COA	✓	
COA for finished product	✓	
Specifications and Tests for Inactive Ingredients		
Source of Inactive Ingredients Identified NTF need to provide	✓	Thor-Rx 72
Applicant COA for inactive ingredient	✓	on Excipients Glycerin
COA from Manufacturer of Inactive Ingredients	✓	
Manufacturing Controls		
Batch Formulation	✓	
Master Production Batch Record for largest batch size intended for production (No more than 10x pilot batch)	✓	
Certification of GMP	✓	
Description of Facilities	✓	
Address of Manufacturing Site for Production Batches	✓	
Manufacturing Procedures (Batch Records)	✓	
Package entire test batch	✓	
Batch Number(s)	✓	
Mfg. Facility	✓	
If Sterile product: Aseptic Fill _____ Terminal Sterilization _____	✓	
Stability Profile Including stability Data (Use of Stability Indication Method)	N/A	
3 months Accelerated Stability Data	✓	
Batch Number(s) Listed on Stability Records (Batch number(s) the same as the test batch	✓	
Sample Statement Plus Data	✓	
Bioavailability/Bioequivalence	✓	
Study		
In Vivo Study/Waiver Request DISK in range 1.2		
Comparative Dissolution Data Vol 1.2 attachment 7		

CDER Establishment Evaluation Report
for May 02, 1997

Application: **ANDA 75108/000**
Stamp: **08-APR-1997** Regulatory Due:
Applicant: **MYLAN PHARMS**
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265052730

Priority:
Org Code: **600**
Action Goal:
District Goal:
Brand Name:
Established Name: **NIFEDIPINE**
Generic Name:
Dosage Form: **EXT (EXTENDED-RELEASE TABLET**
Strength: **30 MG**

FDA Contacts: **T. AMES** **(HFD-617)** **301-594-0305 , Project Manager**
J. SIMMONS **(HFD-647)** **301-594-0305 , Team Leader**

Overall Recommendation:

Establishment:
DMF No: **6860**

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

Establishment: **1110315**
MYLAN PHARMACEUTICALS INC
781 CHESTNUT RIDGE RD
MORGANTOWN, WV 265054310
DMF No:

Responsibilities:
FINISHED DOSAGE MANUFACTURER