

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-108

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

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ANDA # 75-108

SPONSOR : Mylan Pharmaceuticals, Inc.

DRUG & DOSAGE FORM : Nifedipine ER Tablets

STRENGTH (s) : 30 mg

TYPE OF STUDY: X SD X SDF X MULT OTHER

STUDY SITES: Novum Pharmaceuticals Research Services, Inc.

CLINICAL : Novum Pharmaceuticals Research Services, Inc.

ANALYTICAL : Mylan Pharmaceuticals, Inc.

STUDY SUMMARY :

See Supervisory Review

PRIMARY REVIEWER :

BRANCH :

INITIAL : _____

DATE : _____

BRANCH CHIEF :

BRANCH :

INITIAL : _____

DATE : _____

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL : _____

DATE : 12/23/98

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-108

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Nifedipine Extended Release Tablets, 30 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 250 mL of SGF, with 0.25% TWEEN 80 for the first hour, then 250 ml of 0.01M phosphate buffer, pH 6.8 with 0.25% TWEEN 80 between 2 and 24 hrs, both at 37° C using USP Apparatus (III) at 20 dpm. The test product should meet the following tentative specifications:

1 hr	NMT 5%
2 hrs	NMT 15%
8 hrs	40-65%
12 hrs	65-90%
24 hrs	NLT 80%

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

Sincerely yours,

/S/

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

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Sincerely yours,

- /S/ -

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

BIOEQUIVALENCY DEFICIENCY

ANDA: 75-108

APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Nifedipine ER Tablets, 30 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

All three bioequivalence studies, fasting, non-fasting and steady-state, for the test product meet the acceptance criteria of the 90% confidence intervals of log-transformed AUCs and CMAX being within the limit of [0.80;1.25]. However, the test and reference products **can not 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 two products, especially for the steady-state study. The TMAX difference between the test and reference products of 61% for the this study (TMAX(Test)= 14.0 hrs and TMAX(Reference)= 8.7 hrs) is also considered significant.

Sincerely yours,


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

Nifedipine ER Tablets, 30 mg
ANDA # 75-108
Reviewer: Hoainhon Nguyen
WP #75108sd.o97

Mylan Pharmaceuticals
Morgantown, West Virginia
Submission Date:
October 31, 1997
December 8, 1997

Review of Study Amendments

I. Background:

The October 31, 1997 amendment consists of the firm's responses to the deficiency comments by the Division of Bioequivalence communicated in the letter dated October 15, 1997. Below under Part A, the deficiency comments are recaptured, followed by the firm's responses, and the DBE new comments.

The December 8, 1997 amendment addresses the concern the Office of Generic Drugs had as the results of the Agency's pre-approval inspection which was detailed in the July 30, 1997 EIR, specifically the finding by the inspector that *"Mylan tested the product from a bio-batch (produced using the filed process) against the innovator product (Pfizer Procardia XL tabs.) in a pivotal fasting study. Mylan's product was not bioequivalent to the innovator lot. Mylan retested without first investigating to assure that a problem did not exist with their bio-batch. Retest results were acceptable."* (Memo from Bruce W. Hartman, CSO of Investigations and Preapproval Branch, HFD-324, to Gordon R. Johnston, Office of Generic Drugs, HFD-301, September 3, 1997) The firm has provided its response to the office concern as prepared by the attorney at law David Adams of Olsson, Frank and Weeda. In addition, the firm also has submitted a summary of the bioequivalence studies which were of concern to the office. The summary was entitled "Bioequivalency Testing of Lot-to-Lot Differences of Procardia XL® Extended Release Tablets and of Mylan's Nifedipine ER Tablet with Two Lots of Procardia XL® Extended Release Tablets". According to Mylan, *"These bioequivalency studies and the summary report have been audited and reviewed by scientific experts outside of Mylan who worked under the direction of legal counsel."* Part B below is the review for the December 8, 1997 amendment.

Part A: Deficiency Comments and Responses:

Deficiency Comments:

- “1. *The single-dose, fasting and the multiple-dose bioequivalence studies have been found incomplete by the Division of Bioequivalence. Long-term stability data are insufficient.*

Long-term stability of frozen samples is required for a period equivalent to the longest time between first sample withdrawal and final sample analysis.

The frozen control samples were prepared and stored at an unspecified temperature for only 21 days and compared with the control nominal values. The actual maximum sample freezer storage length was 40 days (between November 25, 1996 and January 13, 1997) for the single-dose, fasting study, 51 days (between January 21 and March 13, 1997) for the multiple-dose study, and 38 days (between January 5 and February 12, 1997) for the non-fasting study. The duration studied is therefore not sufficient. It should be at least 51 days.

The freezer temperature used for the storage of these stability control samples also is needed.

2. *The single-dose, non-fasting bioequivalence study conducted has been found unacceptable. The ratio of CMAX geometric means of the test to reference product in the non-fasting study (for non-fasting treatments B and A) exceeded 1.25. The actual ratio was 1.36.*

3. *No further dissolution testing or data is needed. However, the Division recommends that the specifications be modified as follows:*

<i>1 hr</i>	<i>No release</i>
<i>2 hr</i>	<i>NMT 15%</i>
<i>8 hr</i>	<i>35-55%</i>
<i>12 hr</i>	<i>65-85%</i>
<i>24 hr</i>	<i>NLT 80%</i>

These limits, recommended by the Agency, are considered to reflect more closely the observed data."

Firm's Responses:

1. The firm has submitted the results of the ongoing long-term stability study which covered the freezer storage of nifedipine in plasma control samples at -70°C for 152 days. The % difference in concentrations as compared with the nominal values from Day 0 for the controls of 46.1 ng/ml and 1.95 ng/ml was less than 10% (9.2% and 2.2%, respectively).

2. *"The ratio of Cmax geometric means of the test to reference product in the non-fasting study (for non-fasting treatments B and A) was 1.06. The FDA calculated ratio of 1.36 was the ratio of Cmax geometric means of the Mylan fed to Mylan fasting treatments (treatment B vs. C)."*

3. *"With respect to the Agency's recommendation regarding modification of the dissolution specifications, Mylan does not believe that the Agency's proposed controls are representative of the data available."* Mylan's comments on the individual FDA-proposed time points are given below.

<u>Submitted Specification</u>		<u>Agency's Proposed Specification</u>		<u>Comments</u>
1 hr	NMT 15%	1 hr	No release	<i>This is not a delayed-release product.</i>
2 hr	NMT 25%	2 hr	NMT 15%	<i>Agree with Agency's proposal.</i>
8 hr	35%-65%	8 hr	35%-55%	<i>There are individual tablet results from stability samples with values at or above the upper limit of the Agency's proposed range. The average values for the stability samples are within 5% of the proposed upper</i>
12 hr	60%-90%	12 hr	60%-85%	

24 hr NLT 80% 24 hr NLT 80%

*limits.
Agree with Agency's
proposal."*

Mylan further proposes the following specifications:

DBE's Comments on Firm's Responses:

1. The long-term stability data submitted are adequate and acceptable.
1. The firm is correct in pointing out the error made by the reviewer. The summary table for nifedipine PK parameters for the non-fasting study should be revised to read as follows (See the review dated October 2, 1997 for comparison).

Table V
Nifedipine Comparative Pharmacokinetic Parameters
Dose=2x30 mg; n=19
Non-Fasting Study

<u>Parameters</u>	<u>Mylan's</u> <u>Mean (CV%)</u> <u>(Fasting-C)</u>	<u>Mylan's</u> <u>Mean (CV%)</u> <u>(Non-Fasting-B)</u>	<u>Procardia XL®</u> <u>Mean (CV%)</u> <u>(Non-Fasting-A)</u>	<u>Ratio</u> <u>T/R</u> <u>(B/A)</u>
AUC (0-T) ng.hr/mL	546.8*	650.2*	686.1*	0.95
AUC (0-Inf) ng.hr/mL	560.6*	663.7*	698.4*	0.95
C _{MAX} (ng/mL)	31.18*	42.31*	39.82*	1.06
T _{MAX} (hrs)	14.0(42)	18.9(37)	10.4(72)	
K _{EL} (1/hrs)	0.150(43)	0.142(34)	0.148(43)	
T _{1/2} (hrs)	5.39(38)	5.56(41)	5.36(35)	

*Geometric LSMeans

The 90% confidence intervals for log-transformed AUCs and C_{MAX} meet the limit of [0.80;1.25]. See further comments under Deficiency section.

3. The Division of Bioequivalence agrees with the newly proposed dissolution specifications for the test product by the firm.

Part B: Submission of Biostudies That Failed:

1. Responses by Firm's Attorney:

The firm did not submit the biostudy that failed bioequivalence criteria mainly for these reasons:

- *“FDA’s longstanding policy has been that bioequivalence studies that do not demonstrate bioequivalence under FDA’s approval criteria need not be submitted in an ANDA. This policy is reflected in the wording of the statute as well as the wording of the agency’s regulations. The 1984 “Waxman-Hatch” Amendments to the Federal Food, Drug and Cosmetic Act, which established the statutory ANDA process, provided a simple requirement that an ANDA contain “information to show that the new drug is bioequivalent to the listed drug.” 21 U.S.C. 355(j)(2)(A)(iv).”*
- *“The agency’s policy on bioequivalence studies in ANDAs has long been different from its policies on information related to safety and effectiveness in NDAs. FDA’s regulations for NDAs require that NDAs contain “any information derived from clinical investigations” as well as any other possibly relevant information. 21 CFR 314.50(d)(5)(iv)(1984). This is to ensure that the agency had before it any and all information that may be relevant to a global assessment of safety and efficacy.”*
- *During bioequivalence determinations for a test product, “There are often numerous minor formulation changes that are required, as well as retesting that may be required due lot-to-lot differences in the listed drug.”*
- *“Thus, studies that fail to show bioequivalence are not themselves evidence of the generic drug’s actual bioequivalence. Indeed, it is my understanding that, due to lot-to-lot differences among listed drugs, bioequivalence studies conducted at random on marketed products can fail to show bioequivalence between certain generic and listed drug lots, as well as between different lots of the same listed drug.”*

2. Summaries of Biostudies:

In addition to three bioequivalence studies (fasting, non-fasting and multiple-dose) that were submitted previously (NIFE-9666A, NIFE-9661A and NIFE-9668, respectively) and found acceptable, the firm has provided the summaries of three other biostudies. These summaries are given in the review attachment.

According to the preliminary formulation development program, *“it was discovered that significant differences between lots existed for the Procardia XL® Extended Release Tablet, both in the laboratory setting and in human testing.”* Specifically, two lots of

the reference product were studied: Lot Nos. 57P016A (Expiration Date: April 1, 2000, with potency of 109.1% of the label claim) and 47P125A (Expiration Date: August 1, 1997, with potency of 111.4% of the label claim). Both lots contains a nifedipine overage of approximately ten percent as compared with only a three percent overage in the test product. The two lots of the reference product also showed differences as high as twenty percent during the sampling period. (See dissolution profiles in the review attachment.) The following three studies were not submitted previously for the reasons cited by the firm's attorney above.

Study NIFE-9557: The study evaluated the relative bioavailability of the above-mentioned two lots of the reference product using a replicate design, thirteen-subject study which was *"comparable to that of a two-way crossover study in twenty-six subjects."* *"The results of this study indicated that the two lots did not pass the requirements for average bioequivalence for C_{max}. Specifically, log transformed C_{max} for Lot 57P016A was 20% greater than for Lot 47P125A, and this difference was statistically significant ($p=0.0006$). In addition, the confidence interval for log transformed C_{max} (111% to 131%) was outside the acceptable range. These data were in agreement with the in vitro dissolution data which demonstrated that Lot 57P016A exhibited a faster in vitro release rate of nifedipine than Lot 47P125A"*.

Study NIFE-9666: The study evaluated the bioequivalence between the test product, Lot No. 2C009G (same lot as that used in the previously submitted bioequivalence studies), and the reference product, Lot No. 47P125A, under fasting conditions. *"Results indicated that the Test and Reference products were not different with respect to AUC_{inf} (90% confidence interval of 95% to 114%). A difference in mean C_{max} values between the products were observed (90% confidence interval of 105% to 130%)."*

It should be noted that this was the study that was brought up in the pre-approval inspection report.

Study NIFE-9661: The study evaluated the bioequivalence between the same test and reference lots as in Study NIFE-9666, under non-fasting conditions. *"Study results indicated that Mylan's Nifedipine ER product met the FDA requirements for bioequivalence in a food study."*

Mylan selected Lot No. 57P016A for the final pivotal bioequivalence studies

(NIFE-9666A, NIFE-9668 and NIFE-9661A) for comparison with its biolot No. 2C009G for these reasons:

- a. The potency difference between test Lot No. 2C009G and reference Lot No. 57P016A is closer to the required 5% (103.5% versus 109.1%). The potency of reference Lot No. 47P125A was 111.4%.
- b. The expiration date of reference Lot No. 57P016A (April 1, 2000) is later than reference Lot No. 47P125A (August 1, 1997).
- c. Reference Lot No. 57P016A also had a dissolution profile which was more similar to that of the test Lot No. 2C009G than did reference Lot No. 47P125A.

The three final pivotal studies demonstrate that the test and reference products are bioequivalent under fasting, non-fasting and steady-state conditions.

DBE's Comments on Firm's Responses:

The firm's responses and supportive information addressing the office's inspection report question of unsubmitted biostudies are considered adequate and acceptable by the Division of Bioequivalence. The information provided on the previously conducted and unsubmitted studies does not change or invalidate the results of the three pivotal bioequivalence studies, NIFE-9666A, NIFE-9668 and NIFE-9661A, which were submitted and reviewed. In addition, the firm has reasonably justified the failure of its biostudy No. NIFE-9666 as due to the lot-to-lot variations, as well as the high nifedipine overage, in the reference product.

II. Deficiency:

All three bioequivalence studies, fasting, non-fasting and steady-state, for the test product meet the acceptance criteria of the 90% confidence intervals of log-transformed AUCs and CMAX being within the limit of [0.80;1.25]. However, the test and reference products **can not 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 two products, especially for the steady-state study. The TMAX difference between the

test and reference products is 61% for this study (TMAX(Test) = 14.0 hrs and TMAX(Reference) = 8.7 hrs).

III. Overall Recommendations:

1. The **single-dose, fasting** bioequivalence study, the **mutiple-dose** bioequivalence study and the **single-dose, non-fasting** bioequivalence study conducted by Mylan Laboratories on the test product, Nifedipine ER Tablets, 30 mg, lot # 2C009G, comparing it with the reference product, Pratt 's Procardia XL® Tablets, 30 mg Tablets, lot # 57P016A, has been found **unacceptable** by the Division of Bioequivalence for the reason cited in the Deficiency section above.

2. The in-vitro dissolution testing conducted by Mylan on its Nifedipine ER Tablets, 30 mg, and Pratt 's Procardia XL Tablets, has been found acceptable.

The dissolution testing should be conducted, in 250 mL of SGF with 0.25% TWEEN 80 for the first hour, then in 250 ml of 0.01 M phosphate buffer pH 6.8 with 0.25% TWEEN 80 between 2 and 24 hours, both at 37C using USP XXIII apparatus III at 20 dpm. The test product should meet the following tentative specifications:

1 hr	NMT 5%
2 hr	NMT 15%
8 hr	40-65%
12 hr	65-90%
24 hr	NLT 80%

3. The information provided by the firm to address the question of unsubmitted bioequivalence studies of the test and reference products is considered adequate.

/S/
Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

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Concur: _____

Date: 4/23/98

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

Attachments: 4 pages

TABLE A

MEAN (%CV) NIFEDIPINE PHARMACOKINETIC PARAMETERS IN THIRTEEN HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 60 MG (2 X 30 MG) DOSE OF NIFEDIPINE EXTENDED-RELEASE TABLETS UNDER FASTING CONDITIONS (PROTOCOL NIFE-9557)					
Parameter	Arithmetic Mean A = Procardia XL® (Lot #47P125A)	Arithmetic Mean B = Procardia XL® (Lot #57P016A)	LSMEANS Ratio (B/A)*	90% Confidence Interval**	P-value**
AUCL (ng x hr/mL)	577 (33.7)	649 (43.7)	1.08	95% - 123%	0.3096
AUCI (ng x hr/mL)	598 (33.3)	664 (42.3)	1.08	94% - 124%	0.3321
CPEAK (ng/mL)	27.1 (31.8)	33.4 (39.8)	1.20	111% - 131%	0.0006
KEL (hr ⁻¹)	0.1619 (43.8)	0.1670 (37.0)	-----	-----	-----
HALF (hr)	5.00 (36.6)	4.79 (45.1)	-----	-----	-----
TPEAK (hr)	19.3 (43.1)	12.8 (56.2)	-----	-----	-----

*Ratio (B/A) = e^[LSMEAN of LNB - LSMEAN of LNA]

**Used Natural Log Transformed Parameter

WP# 75108 a, 097 Attachments 1 of 4

TABLE A

MEAN (%CV) NIFEDIPINE PHARMACOKINETIC PARAMETERS IN FORTY-ONE HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 60 MG (2 X 30 MG) DOSE OF NIFEDIPINE EXTENDED-RELEASE TABLETS UNDER FASTING CONDITIONS (PROTOCOL NIFE-9666)				
Parameter	Arithmetic Mean A = Mylan (Lot 2C009G)	Arithmetic Mean B = Procardia XL® (Lot #47P125A)	LSMEANS Ratio (A/B)*	90% Confidence Interval**
AUCL (ng x hr/mL)	825 (56.8)	790 (51.6)	1.05	96% - 116%
AUCI (ng x hr/mL)	842 (57.5)	803 (52.0)	1.04	95% - 114%
CPEAK (ng/mL)	45.7 (51.1)	38.3 (48.5)	1.17	105% - 130%
KEL (hr ⁻¹)	0.1357(37.7)	0.1236 (33.4)	-----	---
HALF (hr)	5.82 (38.1)	6.41 (40.7)	-----	---
TPEAK (hr)	16.1 (37.5)	19.1 (37.8)	-----	---

*Ratio (A/B) = e^[LSMEAN of LNA - LSMEAN of LNB]

**Used Natural Log Transformed Parameter

WP # 75108a.0177 A Handwritten 2 of 4

TABLE A

MEAN (%CV) NIFEDIPINE PHARMACOKINETIC PARAMETERS IN NINETEEN HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 60 MG (2 X 30 MG) DOSE OF NIFEDIPINE EXTENDED-RELEASE TABLETS UNDER FED CONDITIONS (Protocol NIFE-9661)				
Parameter	Arithmetic Mean A = Procardia XL® (Fed) (Lot #47P125A)	Arithmetic Mean B = Mylan (Fed) (Lot 2C009G)	Arithmetic Mean C = Mylan (Fasting) (Lot 2C009G)	LSMEANS Ratio (B/A)*
AUCL (ng x hr/mL)	949 (47.3)	1040 (51.5)	1042 (59.5)	1.01
AUCI (ng x hr/mL)	1013 (43.2)	1082 (51.4)	1082 (58.2)	0.953
CPEAK (ng/mL)	46.2 (46.5)	65.4 (60.4)	54.1 (52.7)	1.19
KEL (hr ⁻¹)	0.1425 (39.5)	0.1349 (31.8)	0.1240 (34.7)	---
HALF (hr)	5.70 (43.4)	5.59 (28.1)	6.03 (25.7)	---
TPEAK (hr)	13.4 (64.2)	18.4 (44.7)	16.5 (35.1)	---

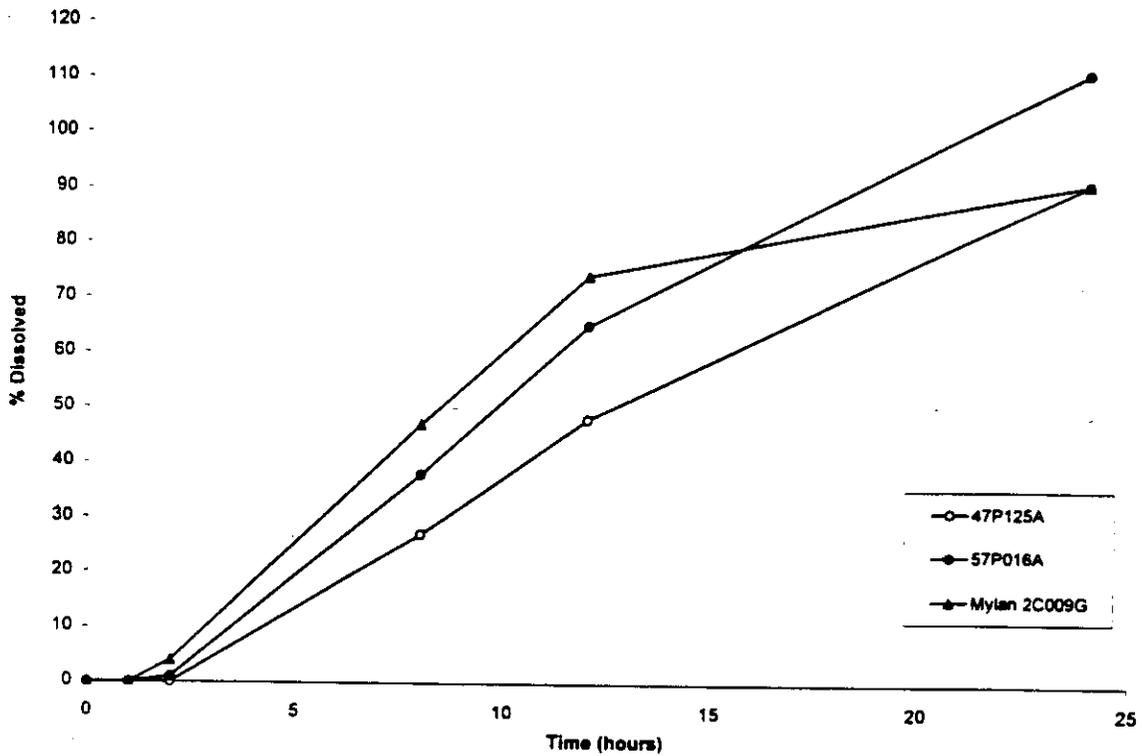
*Ratio (B/A) = e^(LSMEAN of LNB - LSMEAN of LNA)

WP# 751089.097 Attachments 3 of 4

WP# 75108a. 097 Attachments 4 of 4

Procardia XL® Extended Release Tablet and Mylan Nifedipine ER Tablet
Dissolution Profiles - Type III at 20 dpm
(Regulatory Dissolution Method)

1 Hr: Simulated gastric fluid with 0.25% TWEEN 80, 250 mL at $37.0 \pm 0.5^\circ\text{C}$.
Later Times: 0.01 M Phosphate buffer pH 6.8 ± 0.5 with 0.25% TWEEN 80, 250 mL at $37.0 \pm 0.5^\circ\text{C}$



File 75-108

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)

Lipichy

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 applications¹. 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 variability² of

¹ AUC and Cmax bioequivalence criteria were met.

² The point estimate and the coefficient of variation.

the T_{max} 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

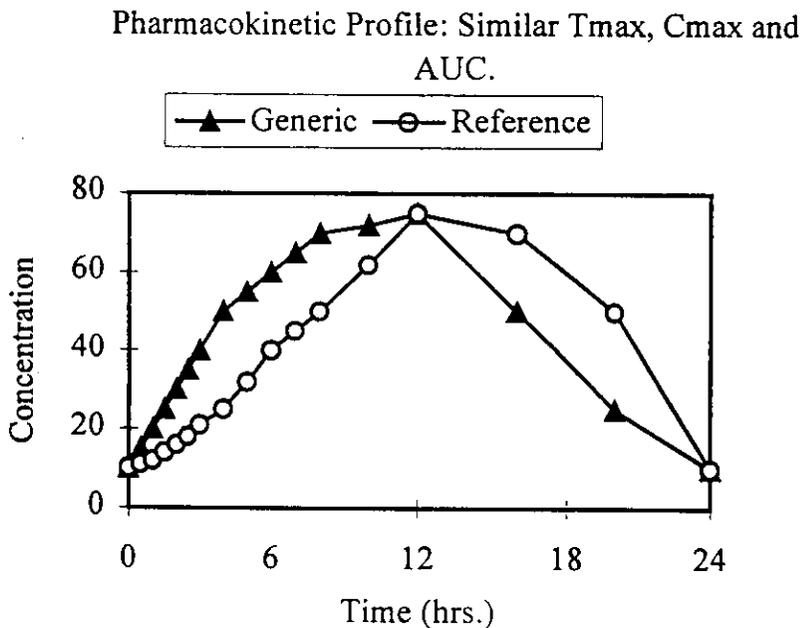
From a clinical viewpoint, it is unlikely that the differences in T_{max} observed between the generic and reference drugs will lead to a significant difference in clinical outcomes for the following reasons.

- 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 C_{max} 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 others³ with regard to the reduction of clinical outcomes (e.g. stroke). Because different drugs approved for the treatment of hypertension have different T_{max} values (and presumably different times of maximum effect), the time of T_{max} has little bearing on clinical efficacy. The decision to approve a drug for hypertension is not based on the time of T_{max}.

The DCRDP does not wish to provide specific comments on the approval of any of the applications provided. As a general rule, however, T_{max} 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 C_{max}, T_{max} and AUC are similar between drug products. In figure 2, the C_{max} and AUC are similar while the T_{max} 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 T_{max} 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 T_{max}.

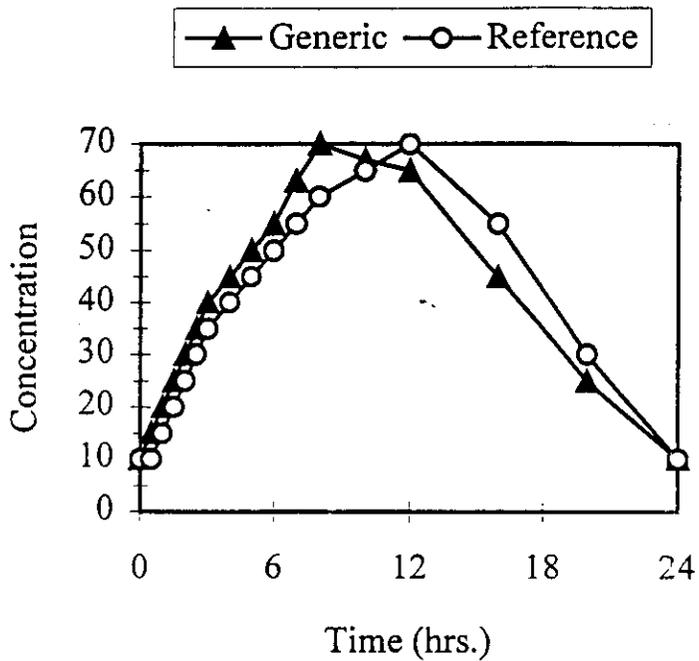
Figure 1.



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

Figure 2.

Pharmacokinetic Profile: Similar C_{max} and A_{uc} but
T_{max} Differs by 4 Hours.



Conclusions

1. There is no data to support the clinical relevance of differences in T_{max} among anti-hypertensive and anti-angina drug products.
2. T_{max} alone is a poor method to compare the concentration versus time profile between drug products. T_{max} 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 T_{max} for anti-hypertensive and anti-angina drug products that can be identified as being clinically relevant.

CS/
Charles J. Ganley, M.D.



MYLAN PHARMACEUTICALS INC

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

OCT 31 1997

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AMENDMENT

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GENERIC DRUGS

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

BIOEQUIVALENCE DATA ENCLOSED CHEMISTRY DATA ENCLOSED

RE: NIFEDIPINE ER TABLETS, 30 MG
ANDA 75-108
RESPONSE TO AGENCY LETTER DATED OCTOBER 15, 1997

Reference is made to the pending ANDA identified above and to the Agency's October 15, 1997 letter which provided comments resulting from the Bioequivalence Division's review of the bioequivalence and dissolution data submitted in the application. In response to the Agency's October 15, 1997 letter, Mylan wishes to amend this application as follows:

FDA COMMENT 1. The **single-dose, fasting** and the **multiple-dose** bioequivalence studies have been found **incomplete** by the Division of Bioequivalence. Long-term stability data are insufficient.

Long-term stability of frozen samples is required for a period equivalent to the longest time between first sample withdrawal and final sample analysis.

The frozen control samples were prepared and stored at an **unspecified temperature for only 21 days** and compared with the control nominal values. The actual maximum sample freezer storage length was **49 days** (between November 25, 1996 and January 13, 1997) for the single-dose, fasting study, **51 days** (between January 21 and March 13, 1997) for the multiple-dose study, and **38 days** (between January 5 and February 12, 1997) for the non-fasting study. The duration studied is therefore not sufficient. It should be **at least 51 days**.

The freezer temperature used for the storage of these stability control samples also is needed.

MYLAN RESPONSE: Long-term frozen stability was initiated on February 21, 1997. At the time of submission for the referenced biostudies long-term frozen stability was an active ongoing project with 21 days of frozen stability accumulated and reported in the analytical report. The analysis of long-term frozen stability

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was complete July 23, 1997 when 152 days of frozen stability had been accumulated. Attachment 1 contains the amended validation table which demonstrates the frozen stability of nifedipine for a period of 152 days.

With regard to the temperature of the freezer used for the storage of the stability control samples, the long-term frozen stability samples were stored at a nominal temperature of -70°C.

FDA COMMENT 2. The **single-dose, non-fasting** bioequivalence study conducted has been found unacceptable. The ratio of Cmax geometric means of the test to reference product in the non-fasting study (for non-fasting treatments B and A) exceeded 1.25. The actual ratio was 1.36.

MYLAN RESPONSE: The ratio of Cmax geometric means of the test to reference product in the non-fasting study (for non-fasting treatments B and A) was 1.06. The FDA calculated ratio of 1.36 was the ratio of Cmax geometric means of the Mylan fed to Mylan fasting treatments (treatment B vs. C).

FDA COMMENT 3. No further dissolution testing or data is needed. **However, the Division recommends that the specifications be modified as follows:**

1 hr	No release
2 hr	NMT 15%
8 hr	35-55%
12 hr	65-85%
24 hr	NLT 80%

These limits, recommended by the Agency, are considered to reflect more closely the observed data.

MYLAN RESPONSE: Mylan acknowledges the Agency's comment that no further dissolution testing or data are needed. With respect to the Agency's recommendation regarding modification of the dissolution specifications, Mylan does not believe that the Agency's proposed controls are representative of the data available. In support of Mylan's belief please refer to the room temperature stability data provided in Attachment 2 and the comments provided below.

<u>Submitted Specification</u>	<u>Agency's Proposed Specification</u>	<u>Comments</u>
1 hr NMT 15%	1 hr No release	This is not a delayed-release product.
2 hr NMT 25%	2 hr NMT 15%	Agree with Agency's proposal.
8 hr 35% - 65% 12 hr 60% - 90%	8 hr 35% - 55% 12 hr 60% - 85%	There are individual tablet results from stability samples with values at or above the upper limit of the Agency's proposed range. The average values for the stability samples are within 5% of the proposed upper limits.
24 hr NLT 80%	24 hr NLT 80%	Agree with Agency's proposal.

Therefore, based on the data currently available, Mylan proposes the following specifications which more tightly control the release profile at the early profile points and more accurately represent the stability data at the middle of the release profile:

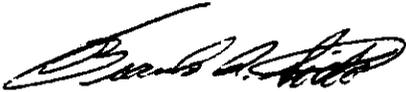
The revised finished product specifications and post-approval stability protocol, providing for the amended dissolution specifications as proposed by Mylan, can be found in Attachments 3 and 4, respectively.

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

For your reference, a copy of the agency letter dated October 15, 1997, is provided in Attachment 5.

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

Sincerely,



Frank Sisto
Executive Director
Regulatory Affairs

FRS/bad

enclosures

OCT 15 1997

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

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on April 7, 1997, for Nifedipine ER Tablets, 30 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The single-dose, fasting and the multiple-dose bioequivalence studies have been found incomplete by the Division of Bioequivalence. Long-term stability data are insufficient.

Long-term stability of frozen samples is required for a period equivalent to the longest time between first sample withdrawal and final sample analysis.

The frozen control samples were prepared and stored at an unspecified temperature for only 21 days and compared with the control nominal values. The actual maximum sample freezer storage length was 49 days (between November 25, 1996 and January 13, 1997) for the single-dose, fasting study, 51 days (between January 21 and March 13, 1997) for the multiple-dose study, and 38 days (between January 5 and February 12, 1997) for the non-fasting study. The duration studied is therefore not sufficient. It should be at least 51 days.

The freezer temperature used for the storage of these stability control samples also is needed.

2. The single-dose, non-fasting bioequivalence study conducted has been found unacceptable. The ratio of C_{MAX} geometric means of the test to reference product in the non-fasting study (for non-fasting treatments B and A) exceeded 1.25. The actual ratio was 1.36.

3. No further dissolution testing or data is needed. However, the Division recommends that the specifications be modified as follows:

1 hr	No release
2 hr	NMT 15%
8 hr	35-55%
12 hr	65-85%
24 hr	NLT 80%

These limits, recommended by the Agency, are considered to reflect more closely the observed data.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT - 2 1997

Nifedipine ER Tablets, 30 mg
ANDA # 75-108
Reviewer: Hoainhon Nguyen
WP #75108sd.497

Mylan Pharmaceuticals
Morgantown, West Virginia
Submission Date:
April 7, 1997

Review of Three Bioequivalence Studies, Disolution Data
and Waiver Requests

I. Background:

Nifedipine is a calcium-channel blocking agent, used in the treatment of vasospastic angina, chronic stable angina and hypertension. Nifedipine is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Nifedipine selectively inhibits calcium ion influx across the cell membrane or cardiac muscle and vascular smooth muscle without altering serum calcium concentrations. Nifedipine is water-insoluble.

Innovator's nifedipine extended-release tablet, Procardia XL®, also called Nifedipine GI~~TS~~TS (Gastrointestinal Therapeutic System), consists of a semipermeable membrane surrounding an osmotically active drug core. The core itself is divided into two layers: an "active" layer containing the drug, and a "push" layer containing pharmacologically inert (but osmotically active) components. As water from the GI tract enters the tablet, pressure increases in the osmotic layer and "pushes" against the drug layer, releasing drug through the precision laser-drilled tablet orifice in the active layer. The product is designed to provide nifedipine at an approximately constant rate over 24 hours. This controlled rate of drug delivery into the gastrointestinal lumen is independent of pH or gastrointestinal motility. The product depends for its action on the existence of an osmotic gradient between the contents of the bi-layer core and fluid in the GI tract. Drug delivery is essentially constant, and then gradually falls to zero. Upon swallowing, the biologically inert components of the tablets remain intact during the GI transit and are eliminated in the feces as an insoluble shell.

Nifedipine is completely absorbed after oral administration. Following oral administration of a single dose of the drug as extended-release tablets, plasma nifedipine concentrations increase gradually, reaching a peak at approximately 6 hours, and bioavailability is approximately 55-65% of that achieved with the same doses administered orally as conventional capsules. Following multiple doses, oral bioavailability from the extended-release tablets increases to approximately 75-86% of that achieved with the same doses administered as conventional capsules. Administration of nifedipine extended-release tablets with food can increase the early rate of GI absorption but reportedly does not affect overall bioavailability. With another extended-release tablet formulation (Adalat L[®], not commercially available in the US), both the rate and extent (over 12 hours) of absorption of a single dose of nifedipine were increased by administration with food. Pharmacokinetics of the innovator's ER tablets are linear over the dose range of 30 to 180 mg in that plasma drug concentrations are proportional to dose administered. There was no evidence of dose dumping either in the presence or absence of food for over 150 subjects in pharmacokinetic studies.

Nifedipine is extensively metabolized on first pass through the liver to highly water-soluble inactive metabolites accounting for 60 to 80% of the dose excreted in the urine. The elimination half-life of nifedipine is approximately 2 hours. Only traces (less than 0.1% of the dose) of unchanged form can be detected in the urine. The remainder is excreted in the feces in metabolized form, most likely as a result of biliary excretion. Binding of nifedipine to plasma proteins is concentration dependent and ranges from 92-98%.

Therapy for either hypertension or angina should be initiated with 30 or 60 mg once daily, and the tablets should be taken whole, and not bitten or divided.

Most common adverse effects associated with nifedipine ER tablets include dizziness, lightheadedness, giddiness, flushing or heat sensation, and headache, reportedly occurring in up to 25% of patients.

The firm has submitted the results of one fasting single-dose, one fasting multiple-dose and one non-fasting single-dose bioequivalence study for its Nifedipine ER Tablets, 30 mg, comparing it with Procardia XL[®] CD, 30 mg Tablets, manufactured by Pratt Pharmaceutical (a division of Pfizer). Comparative

dissolution data for the products were also submitted.

II. Bioequivalence Studies:

A. Fasting, Single-Dose Bioequivalence Study: (Study No. NIFE-9666A)

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Mylan's Nifedipine ER Tablets, 30 mg, and Pratt's Procardia XL® 30 mg Tablets under fasting conditions.

Study Investigators and Facilities:

The study was conducted at _____ between November 25 and December 10, 1996. The principal investigator was _____ Plasma samples were assayed by Mylan, Morgantown, WV, under the supervision of Michael Adams, between December 11, 1996 and January 13, 1997.

Demographics:

Thirty-eight normal, healthy non-smoking male volunteers between 19-44 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two-treatment, two-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 132 - 200 lbs and 65 - 75 in, respectively. Twenty-one subjects were caucasians and 17 blacks.

Inclusion/exclusion criteria:

Subjects did not have any history of: hypersensitivity to nifedipine or related drugs; significant chronic disease and/or hepatitis; drug and/or alcohol abuse; any acute illness at the time of the prestudy medical evaluation or dosing; use of any tobacco products; use of any medication known to alter hepatic enzyme activity within 28

days prior to the initial dose of study medication.

Restrictions:

They were free of all medications for 14 days prior to the study. No alcohol or xanthine- and caffeine-containing beverages and foods for at least 48 hours prior to each study period and throughout the study sessions. The subjects fasted overnight prior to and 5 hours after each drug administration. The washout duration between the phases was 7 days. Duration of confinement was approximately two days pre-dose to approximately 24 hours post-dose.

Treatments and Sampling:

The two treatments consisted of a single 2x30 mg dose of either the test product or reference product taken orally with 240 ml of water.

Test Product: Mylan's Nifedipine ER Tablets, 30 mg, Lot No. 2C009G (Batch size of units, potency of 103.8%).

Reference product: Pratt's Procardia XL® 30 mg tablets, lot # 57P016A (Potency of 109.1%).

NOTE 1: Potency of the test product differs from that of the reference product by approximately 5% (exactly 5.3%).

NOTE 2: Subjects were dosed in two groups, Group A numbered 1 through 29, and Group B numbered 30 through 38. Group A Period 1 was dosed on November 25, 1996 and Period 2 was dosed on December 2, 1996. Group B Period 1 was dosed on December 3, 1996 and Period 2 was dosed on December 10, 1996.

Blood samples were collected under golden light at predose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54 and 60 hours following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -70°C until assayed.

Assay Methodology:

The analytical method was developed and validated by Mylan. Nifedipine was extracted from plasma samples with a spiked internal standard using liquid-liquid extraction, and H^+ with electrochemical detection.

Assay Specificity:

The assay was specific for nifedipine with no significant interferences seen at the retention time of the drug and internal standard in the chromatograms of the predose subject samples and blank plasma standards.

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of 1.00 to 150 ng/mL for nifedipine.

Reproducibility:

(Interday CV's of actual study quality controls)

7.3% at 50.0 ng/mL, 7.57% at 10.0 ng/mL and 8.26% at 2.00 ng/mL.

The concentrations were approximately within the range of observed study subject concentrations.

Sensitivity:

(Based on actual study back-calculated standard data)

Sensitivity limit for nifedipine was 1.00 ng/mL (CV% = 4.01). Any level below this limit was reported as zero.

Prestudy assay validation data: CV% for LOQ of 1.00 ng/mL nifedipine was 9.56(n=18).

Accuracy:

(Percent recovery of actual study quality controls)

104.4% at 50.0 ng/mL, 101.8% at 10.0 ng/mL and 99.9% at 2.00 ng/mL.

Stability:

Long-term stability of frozen samples was demonstrated using frozen control samples which were prepared and stored at unspecified temperature for 21 days and compared with the control nominal values. The difference for Controls of 50.0 and 2.0 ng/mL of nifedipine was -3.56 and 2.2%, respectively. The actual maximum sample freezer storage length was 49 days (between November 25, 1996 and January 13, 1997). The long-term stability study is therefore insufficient.

Short-term stability (4 hours at room temperature for unextracted plasma samples, 96 hours at room temperature for extracted samples), freeze-thaw stability (3 cycles) and stock solution stability (30 days at 0-5°C) were evaluated and acceptable.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : $AUC(0-\infty) = AUC(0-T) + [\text{last measured concentration} / \text{KEL}]$. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

An analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters. An analysis of variance was performed to assess the group effect and determine the poolability of the two groups. A model with terms for groups, sequences, group by sequence interaction, subjects within group by sequence

interaction, treatments and periods were performed. ANOVA was also performed on the vital signs (diastolic blood pressure, systolic blood pressure, heart rate and PR intervals). The ANOVA model included terms for subject and treatment.

Results:

All thirty-eight enrolled volunteers completed the clinical portion of the study. Statistical analyses were performed using 38 data sets. According to the firm, since no statistically significant group effects were observed for lnAUCs and lnC_{MAX}, the group effect was dropped and the standard two-way crossover model was employed.

However, as a result of a consultation with Don Schuirmann (a copy of the consultation attached), the firm should have used the following model: CLASS SEQ SUBJ PER TRT GROUP; MODEL Y=SEQ SUBJ(SEQ) PER(GROUP) TRT;

The reviewer re-analyzed the data using the model recommended by Don Schuirmann, for lnAUCs and lnC_{MAX}. The 90% confidence intervals for lnAUCs and lnC_{MAX} based on this model are given below with the summary of the firm's statistical results. In addition, according to Mr. Schuirmann, the ANOVA model used for vital sign data should be the same as that used for the pharmacokinetic data. However, currently there is no clear criteria or requirement for analyzing the vital sign data, the data were omitted from reviewing.

For the firm's ANOVA model, there was significant difference ($\alpha=0.05$) between treatments for AUC(0-T) ($p=0.0094$), AUC(0-Inf) ($p=0.0149$), lnAUC(0-T) ($p=0.0204$) and lnAUC(0-Inf) ($p=0.0276$). For Schuirmann's model, there was significant difference between treatment for lnAUC(0-T) ($p=0.0212$) and lnAUC(0-Inf) ($p=0.0287$). The results for the statistical analysis are summarized in the tables below:

Table I
Nifedipine Comparative Pharmacokinetic Parameters
Dose=2x30 mg; n=38
Fasting/Single-Dose Study

<u>Parameters</u>	<u>Mylan's</u> <u>Mean (CV%)</u>	<u>Procardia XL's</u> <u>Mean (CV%)</u>	<u>90%</u> <u>C.I.</u>	<u>Ratio</u> <u>T/R</u>
AUC (0-T) ng.hr/mL	665.8*	745.2	[0.83;0.97] [0.82;0.97]**	0.89
AUC (0-Inf) ng.hr/mL, n=37	680.4*	755.9*	[0.83;0.97] [0.83;0.97]**	0.90
C _{MAX} (ng/mL)	37.84*	36.39*	[0.94;1.15] [0.94;1.15]**	1.04
T _{MAX} (hrs)	14.4(34)	12.9(52)		
K _{EL} (1/hrs) n=37	0.136(34)	0.124(35)		
T _{1/2} (hrs) n=37	5.70(36)	6.69(58)		

*Geometric LSMeans

**By re-analysis using Schuirmann's model

Table II
Comparative Mean Plasma Levels of Nifedipine
Dose=2x30 mg; n=38
ng/mL(CV%)
Fasting/Single-Dose Study

<u>Hour</u>	<u>Test</u>	<u>Reference</u>
0	0	0
1	0.110(348)	0
2	3.17(103)	0.701(127)
3	7.58(78)	9.40(57)
4	10.1(65)	17.0(49)
5	11.9(65)	19.6(54)
6	16.5(67)	26.5(58)
7	16.4(56)	24.8(52)
8	17.4(50)	24.4(65)
10	24.6(53)	26.9(74)
12	34.5(48)	28.6(67)
14	34.0(53)	29.1(66)
16	30.2(60)	28.3(61)
20	25.0(73)	24.5(67)
24	23.9(74)	29.2(69)
28	18.7(86)	22.0(65)
32	13.3(115)	15.9(66)
36	8.86(126)	10.7(76)
40	5.91(162)	6.73(96)
44	3.61(186)	4.33(103)
48	2.56(237)	3.26(133)
54	1.24(336)	1.71(199)
60	0.551(425)	0.997(256)
AUC(0-T) _{ng.hr/mL}	784(65)	868(60)
AUC(0-Inf) _{ng.hr/mL}	802(66)	879(62)
C _{MAX}	41.8(47)	41.5(56)

Adverse Effects:

There was no serious adverse effect. There were 39 possibly or probably drug related adverse events reported by 22 subjects. The events included headache (17 by Test product and 16 by Reference), ECG: bradycardia (1 by Test), neckache (1 by Test), sleepiness (1 by Test), ECG: 1° AV block (2 by Test) and nausea (1 by Reference).

B. Fasting/Multiple-Dose Bioequivalence Study: (Protocol No. NIFE-9668)

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Mylan's Nifedipine ER 30 mg Tablets and Pratt's Procardia XL® 30 mg Tablets under fasting, steady-state conditions using a crossover design.

Study Investigators and Facilities:

The study was conducted at _____ between January 20 and February 24, 1997. The principal investigators were _____ samples were assayed by Pharmacokinetics Laboratory of Mylan Pharmaceuticals, Morgantown, WV, between February 18 and March 13, 1997.

Demographics:

Forty-one normal, healthy non-smoking male volunteers between 19-45 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two-treatment, two-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 132-236 lb and 64-78 in, respectively. Eight subjects were black, and 33 caucasians.

Inclusion/exclusion criteria:

See Protocol for Fasting/Single-Dose Study above.

Restrictions:

They were free of any medications for 14 days prior to the study and during the study. No alcohol or xanthine-and caffeine-containing beverages and foods for at least 48 hours prior to each study period and throughout the study sessions. The subjects fasted for 10 hours prior to and 2 hours after each drug administration except for Day 6, when a standard meal was served at 5 hours post-dose instead of 2 hours. The washout duration between the sixth and last dose of Phase I and the first dose of Phase II was 7 days. Duration of confinement was approximately 11 hours prior to Dose 1 and until approximately 24 hours after Dose 6 each period.

Treatments and Sampling:

Each of the two treatments consisted of a single 2x30 mg dose of either the test product or reference product taken orally with 240 ml of water, once daily for a total of 6 days.

Test Product: Mylan's Nifedipine ER Tablets, 30 mg, Lot No. 2C009G (Batch size of _____ units, potency of 103.8%).

Reference product: Pratt's Procardia XL® 30 mg tablets, lot # 57P016A (Potency of 109.1%).

Blood samples were collected at pre-Dose 1, pre-Dose 4, pre-Dose 5, pre-Dose 6, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, and 24 hours following Dose 6 administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -70°C until assayed.

NOTE: Subjects were dosed in two groups, Group A numbered 1 through 35, and Group B numbered 36 through 41. Group A Period 1 was dosed from January 21 to 26, 1997, and Period 2 was dosed from February 11 to 16, 1997. Group B Period 1 was dosed from January 28 to February 2, 1997, and Period 2 was dosed from February 18 to 23, 1997.

Assay Methodology:

The analytical method was developed and validated by Mylan. Nifedipine was extracted from plasma samples with a spiked internal standard using liquid-liquid extraction, and with electrochemical detection.

Assay Specificity:

The assay was specific for nifedipine with no significant interferences seen at the retention time of the drug and internal standard in the chromatograms of the predose subject samples and blank plasma standards.

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of 1.00 to 150 ng/mL for nifedipine.

Reproducibility:

(Interday CV's of actual study quality controls)

5.8% at 50.0 ng/mL, 6.16% at 10.0 ng/mL and 8.76% at 2.00 ng/mL.

The concentrations were approximately within the range of observed study subject concentrations.

Sensitivity:

(Based on actual study back-calculated standard data)

Sensitivity limit for nifedipine was 1.00 ng/mL (CV% = 7.47). Any level below this limit was reported as zero.

Prestudy assay validation data: CV% for LOQ of 1.00 ng/mL nifedipine was 9.56(n=18).

Accuracy:

(Percent recovery of actual study quality controls)

101.6% at 50.0 ng/mL, 99.7% at 10.0 ng/mL and 98.7% at 2.00 ng/mL.

Stability:

Long-term stability of frozen samples was demonstrated using frozen control samples which were prepared and stored at **unspecified temperature** for 21 days and compared with the control nominal values. The difference for Controls of 50.0 and 2.0 ng/mL of nifedipine was -3.56 and 2.2%, respectively. The actual maximum sample freezer storage length was 51 days (between January 21 and March 13, 1997). The long-term stability study is therefore insufficient.

Short-term stability (4 hours at room temperature for unextracted plasma samples, 96 hours at room temperature for extracted samples), freeze-thaw stability (3 cycles) and stock solution stability (30 days at 0-5°C) were evaluated and acceptable.

Pharmacokinetic Results:

Steady-state pharmacokinetic parameters for nifedipine were calculated. C_{MAX} and T_{MAX} were determined from the observed plasma concentration-time profile over the sampling interval (Day 6). AUC₀₋₂₄ at steady-state was the sum of the linear trapezoidal estimation of the areas from the time of the 6th dose to 24 hours post 6th dose. CSS was AUC₀₋₂₄ divided by the dosing interval (24 hours). FLUCT1 was the percent fluctuation calculated as the difference between C_{MAX} and C_{MIN} divided by CSS, FLUCT2 was the percent fluctuation calculated as the difference between C_{MAX} and C_{MIN} divided by C_{MIN}.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects

within sequence, and days of administration for the above pharmacokinetic parameters as well as $LNAUC_{0-24}$ and $LNCMAX$. The 90% confidence intervals for AUC_{0-24} , C_{MAX} , $\ln AUC_{0-24}$ and $\ln C_{MAX}$ were calculated, based on least squares means, using the two, one-sided t-test.

Trough samples were taken prior to the morning dose on Days 4,5 and 6. An analysis of steady-state attainment was performed using concentration data from the 72, 96 and 120 hour trough plasma samples. A regression analysis of these data by subject and treatment was performed. Also, an ANOVA with terms for treatment was employed to compare for the mean slope differences between treatments.

ANOVA was also performed to assess the group effect and determine the poolability of the two groups. A model with terms for groups, sequences, group by sequence interaction, subjects within the group by sequence interaction, treatments and periods were performed.

ANOVA was performed on the vital signs (diastolic blood pressure, systolic blood pressure and heart rate). The ANOVA model included terms for subject and treatment.

Results:

Thirty-four of 41 enrolled volunteers completed the clinical portion of the study. Two subjects were discontinued due to adverse events that were possibly drug related. One subject was discontinued due to an adverse event that was not study related. Three subjects withdrew for personal reasons that were not study related and one subject was withdrawn due to a protocol violation (smoking). Data for 34 subjects were analyzed.

Steady-state attainment within 6 days could be confirmed, by regression analysis, in all subjects except for Subjects # 3(Period I, Trt A, with negative slope, $p=0.0221$), 6(Period II, TrtB, with negative slope, $p=0.0394$), 11(Period II, Trt A, positive slope, $p=0.0303$), 13(Period II, Trt B, positive slope, $p=0.0448$) and 40(Period I, Trt A, positive slope, $p=0.0379$). Data were re-analyzed by the reviewer excluding these data sets. ANOVA showed no difference in slopes between treatments.

According to the firm's analysis, no statistically significant group effects were observed for the natural log transformed pharmacokinetic parameters lnAUC, lnC_{MAX} and lnC_{SS}. Therefore, the group effect was dropped and the standard two way crossover model was employed. However, as a result of a consultation with Don Schuirmann (a copy of the consultation attached), the firm should have used the following model: CLASS SEQ SUBJ PER TRT GROUP; MODEL Y=SEQ SUBJ(SEQ) PER(GROUP) TRT;

The reviewer re-analyzed the data using the model recommended by Don Schuirmann, for lnAUCs and lnC_{MAX}. The 90% confidence intervals for lnAUCs and lnC_{MAX} based on this model are given below with the summary of the firm's statistical results. In addition, according to Mr. Schuirmann, the ANOVA model used for vital sign data should be the same as that used for the pharmacokinetic data. However, currently there is no clear criteria or requirement for analyzing the vital sign data, the data were omitted from reviewing.

For the firm's standard ANOVA model, there was significant difference ($\alpha=0.05$) between treatments for T_{MAX}($p=0.0030$). The results are summarized in the tables below:

Table III
Nifedipine Comparative Pharmacokinetic Parameters
Multiple-Dose Study; Dose = 6x2x30 mg; n = 34

<u>Parameters</u>	<u>Mylan</u>	<u>Procardia XL^R</u>	<u>90%</u>	<u>Ratio</u>
	<u>Mean (CV)</u>	<u>Mean (CV)</u>	<u>C.I.</u>	<u>T/R</u>
AUC ₀₋₂₄ ng.hr/ml	825.6*	872.4*	[0.86;1.05]	0.95
C _{MAX} (ng/ml)	52.38*	53.81*	[0.87;1.08]	0.97
AUC ₀₋₂₄ ** ng.hr/ml	879.7*	903.2*	[0.87;1.09]	0.97
C _{MAX} ** (ng/ml)	56.72*	57.11*	[0.87;1.13]	0.99
C _{SS} (ng/ml)	34.40*	36.35*		
T _{MAX} (hrs)	14.0(46)	8.71(62)		
FLUCT1(%)	104(49)	98.5(34)		
FLUCT2(%)	408(175)	342(159)		
C _{MIN} (ng/mL)	20.6(78)	21.5(71)		

*Geometric, LS Means

**Recalculated, excluding Subjects #3(Per I), 6(Per II), 11(Per II), 13(Per II) and 40(Per I) and using Don Schuirmann's ANOVA model

Table IV
Comparative Mean Plasma Levels of Nifedipine
Multiple-Dose Study; Dose = 6x2x30 mg; n = 34
ng/ml(CV)

<u>Hour</u>	<u>Test</u>	<u>Reference</u>
-120	0	0
-48	23.2(75)	26.5(58)
-24	26.5(61)	26.6(50)
0	26.3(69)	26.6(63)
0.5	25.8(71)	25.9(61)
1.0	25.3(71)	25.8(63)
1.5	26.6(66)	25.7(63)
2.0	28.5(62)	26.2(64)
2.5	30.3(61)	29.5(56)
3.0	30.2(62)	35.5(50)
4.0	32.4(63)	45.1(46)
5.0	31.1(64)	47.2(48)
6.0	37.5(61)	50.1(45)
7.0	37.4(61)	45.5(41)
8.0	39.6(64)	43.7(40)
10	41.8(59)	41.0(45)
12	45.0(57)	46.0(43)
16	45.6(48)	41.7(44)
20	36.5(50)	33.5(50)
24	35.0(61)	37.6(52)
AUC ₀₋₂₄ (ng.hr/ml)	912(48)	949(41)
C _{MAX} ng/ml	57.3(46)	58.3(38)
C _{SS} _{ng/ml}	38.0(48)	39.5(41)

Adverse Effects:

There was no serious adverse effect. There were 37 possibly or probably drug related adverse events reported by 22 subjects. The events included headache (11 by Test product and 16 by Reference), lightheadedness (1 by Test), nausea (2 by

Reference), vomiting (1 by Test, 1 by Reference), rash (3 by Test, 3 by Reference).

C. Non-Fasting/Single-Dose Bioequivalence Study: (Study # NIFE-9661A)

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Mylan's Nifedipine ER 30 mg Tablets and Pratt's Procardia XL® 30 mg Tablets under non-fasting conditions using a crossover design.

Study Investigators and Facilities:

The study was conducted at Mylan, Morgantown, West Virginia, between January 5 and 19, 1997. The principal investigators were _____ and _____ .. Plasma samples were assayed by the same facility, between January 28 and February 12, 1997.

Demographics:

Nineteen normal, healthy male volunteers between 18-38 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a three-treatment, three-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 146-232 lbs and 66-78 in, respectively. Seventeen subjects were caucasians and 2 asians.

Inclusion/exclusion criteria: See Fasting/Single-Dose Study above.

Restrictions:

They were free of all medications for 14 days prior to the study. No alcohol or xanthine-and caffeine-containing beverages and foods for at least 48 hours prior to each study period and throughout the study sessions. The subjects fasted overnight prior to and 5 hours after each drug administration for the fasting leg of the study. For the non-fasting legs, the subjects fasted overnight until 30 minutes prior to drug administration at which time each subject started ingesting a standard high-fat

content breakfast. The breakfast consisted of 1 egg, 1 buttered English muffin, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, 8 fluid ounces of whole milk, and 6 fluid ounces of orange juice. The washout duration between the phases was 7 days. Duration of confinement was approximately 48 hours pre-dose to approximately 24 hours post-dose.

Treatments and Sampling:

The three treatments consisted of a single 2x30 mg dose of either the test product or reference product taken orally with 240 ml of water, under fasting or non-fasting conditions.

Test Product: Mylan's Nifedipine ER Tablets, 30 mg, Lot No. 2C009G (Batch size of units, potency of 103.5%), for fasting treatment (Treatment C), and non-fasting treatment (Treatment B).

Reference product: Pratt's Procardia XL® 30 mg tablets, lot # 57P016A (Potency of 109.3%) for non-fasting treatment (Treatment A).

Blood samples were collected under golden lighting at predose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54 and 60 hours following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -70°C until assayed.

Assay Methodology:

The analytical method was developed and validated by Mylan. Nifedipine, and were extracted from plasma samples with a spiked internal standard using liquid-
and with

Assay Specificity:

The assay was specific for nifedipine, and with no significant interferences seen at the retention time of the drug and internal standard in the chromatograms of the predose subject samples and blank plasma standards.

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of 1.00 to 150 ng/mL for nifedipine.

Reproducibility:

(Interday CV's of actual study quality controls)

3.5% at 50.0 ng/mL, 4.75% at 10.0 ng/mL and 5.65% at 2.00 ng/mL.

The concentrations were approximately within the range of observed study subject concentrations.

Sensitivity:

(Based on actual study back-calculated standard data)

Sensitivity limit for nifedipine was 1.00 ng/mL (CV% = 3.77). Any level below this limit was reported as zero.

Prestudy assay validation data: CV% for LOQ of 1.00 ng/mL nifedipine was 9.56(n=18).

Accuracy:

(Percent recovery of actual study quality controls)

98.7% at 50.0 ng/mL, 97.3% at 10.0 ng/mL and 98.4% at 2.00 ng/mL.

Stability:

See Assay Methodology/Stability under Fasting/Single-Dose Study above.

The maximum study sample storage duration was 38 days (between January 5 and February 12, 1997).

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : $AUC(0\text{-Infinity}) = AUC(0\text{-T}) + [\text{last measured concentration}/KEL]$. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments for the above pharmacokinetic parameters. The ANOVA model included terms for subject, period, treatment, residuals 1 and 2(primary and secondary residuals).

Results:

All 19 enrolled volunteers completed the clinical portion of the study. Nineteen data sets were statistically analyzed.

There were significant differences ($\alpha=0.05$) between treatments for CMAX ($p=0.0214$), TMAX ($p=0.0432$) and $\ln CMAX$ ($p=0.0068$). The results for the statistical analysis are summarized in the tables below:

Table V
Nifedipine Comparative Pharmacokinetic Parameters
Dose=2x30 mg; n=19
Non-Fasting Study

<u>Parameters</u>	<u>Mylan's</u> <u>Mean (CV%)</u> <u>(Fasting-C)</u>	<u>Mylan's</u> <u>Mean (CV%)</u> <u>(Non-Fasting-B)</u>	<u>Procardia XL®</u> <u>Mean (CV%)</u> <u>(Non-Fasting-A)</u>	<u>Ratio</u> <u>T/R</u> <u>(B/A)</u>
AUC (0-T) ng.hr/mL	546.8*	650.2*	686.1*	0.95
AUC (0-Inf) ng.hr/mL	698.4*	663.7*	560.6*	1.18
C _{MAX} (ng/mL)	39.82*	42.31*	31.18*	1.36
T _{MAX} (hrs)	14.0(42)	18.9(37)	10.4(72)	
K _{EL} (1/hrs)	0.150(43)	0.142(34)	0.148(43)	
T _{1/2} (hrs)	5.39(38)	5.56(41)	5.36(35)	

*Geometric LSMeans

Table VI
Comparative Mean Plasma Levels of Nifedipine
Dose=2x30 mg; n=19
ng/mL(CV%)
Non-Fasting Study

<u>Hour</u>	<u>Test(Fasting)</u>	<u>Test(Non-Fasting)</u>	<u>Reference(Non-Fasting)</u>
0	0	0	0
1	0.316(283)	0	0
2	3.16(125)	0	0.670(123)
3	5.59(79)	0.107(436)	8.54(88)
4	8.27(82)	1.42(315)	20.1(43)
5	10.6(65)	4.55(184)	28.3(46)
6	17.5(67)	16.3(105)	32.8(43)
7	15.4(53)	16.5(78)	26.6(50)
8	17.3(54)	14.5(74)	25.2(57)
10	23.1(68)	15.1(72)	24.1(69)
12	30.3(56)	22.5(75)	27.0(72)
14	30.8(49)	23.6(79)	23.7(53)
16	28.0(50)	23.7(74)	23.3(55)
20	22.1(56)	23.2(71)	20.8(72)
24	22.2(63)	31.4(103)	23.3(54)
28	16.7(77)	26.8(95)	16.3(68)
32	8.26(90)	21.7(126)	10.1(133)
36	4.48(92)	13.7(134)	6.00(126)
40	2.86(108)	8.06(129)	2.83(114)
44	1.51(127)	4.27(135)	2.26(136)
48	0.851(170)	3.06(145)	1.18(163)
54	0.251(263)	1.41(142)	0.582(169)
60	0.094(436)	0.613(201)	0.184(303)
AUC(0-T) _{ng.hr/mL}	655(51)	798(57)	711(48)
AUC(0-Inf) _{ng.hr/mL}	667(50)	813(57)	723(47)
C _{MAX}	35.5(44)	50.4(58)	40.8(43)

Adverse Effects:

There was no serious adverse effect. There were 7 probably drug related, mild adverse events - headache - reported by 5 subjects (4 by Test treatment (fasting), 1 by Test (non-fasting) and 2 by Reference (non-fasting)).

III. Dissolution Testing: Presently there is no official USP or FDA dissolution methods and specification for the drug product; however, there have been two different methods with their own specifications proposed in the Pharmacopeial Forum. The firm has found both of the proposed UPS methods inappropriate for its formulation and is proposing its own method and specification, which are employed below.

Drug (Generic Name): Nifedipine ER Tablets
Dose Strength: 30 mg
Submission Date: April 7, 1997

Firm: Mylan
ANDA # 75-108

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXIII Apparatus 3 Basket__ Paddle __ Rate 20 dips/min Units Tested: 12

Medium: SGF with 0.25% TWEEN 80 for the first hour Volume: 250 ml

0.01 M Phosphate buffer pH 6.8 with 0.25% TWEEN 80 for the next 2, 8, 12 and 24 hours

Volume: 250 ml

Reference Drug: (Manuf.) Procardia XL Tablets, 30 mg (Pratt)

Assay Methodology:

Firm's Specification:

Time (hours)

Amount Dissolved (%)

II. Results of In-Vitro Dissolution Testing:

Sampling Times (hr.)	Test Product			Reference Product		
	Mean % Dissolved	Range	(CV)	Mean % Dissolved	Range	(CV)
1	0		(0 %)	0		(0%)
2	4		(25%)	1		(62%)
8	47		(3.7%)	39		(7.5%)
12	74		(3.2%)	64		(6.0%)
24	91		(4.4%)	103		(1.8%)

IV. Deficiencies:

1. The ratio of CMAX geometric means of the test to reference product in the non-fasting study (for non-fasting treatments B and A) exceeded 1.25. The ratio was 1.36. The non-fasting study is therefore considered unacceptable.

2. Long-term stability data are insufficient. Long-term stability of frozen samples was demonstrated using frozen control samples which were prepared and stored at unspecified temperature for only 21 days and compared with the control nominal values. The actual maximum sample freezer storage length was 49 days (between November 25, 1996 and January 13, 1997) for the single-dose, fasting study, 51 days (between January 21 and March 13, 1997) for the multiple-dose study, and 38 days (between January 5 and February 12, 1997) for the non-fasting study. The duration studied is therefore not sufficient. The firm should also specify the freezer temperature of these stability control samples.

3. The dissolution testing and data for the test and reference products are acceptable. However, the specifications are recommended by the agency to modify as follows:

1 hr	No release
2 hr	NMT 15%
8 hr	35-55%
12 hr	65-85%
24 hr	NLT 80%

The limits as recommended by the agency are considered more closely reflect the observed data.

V. Comments:

1. The study results demonstrate that, under fasting (single-dose) and steady-state conditions, the test and reference products are equivalent in the rate and extent of absorption as measured by log-transformed CMAX and AUCs. The 90% confidence interval for these parameters in the single-dose fasting study and the multiple-dose study meets the bioequivalence acceptance criteria of being within [0.80;1.25].

2. Since the release mechanisms of the test and reference products are distinctly different, a question has been raised as whether the individual plasma concentration profiles are also distinctly different between the two products, despite of equivalent results of CMAX and AUCs. Currently there is no available statistical criteria or method for qualifying "individual PK profile differences" between test and reference treatments, and therefore, the question can not be answered without bias.

TMAX was determined for all three studies. TMAX was consistently higher for the test product, and ANOVA for the multiple-dose and non-fasting studies (standard ANOVA model) showed statistical differences ($p=0.0011$ and $p=0.0021$, respectively) between treatments in TMAX. Mean ratio of test to reference product for TMAX in the single-dose, fasting study, multiple-dose study and non-fasting study (test(fed)/reference(fed)), respectively, are 1.11, 1.61 and 1.82. Intrasubject CV% for TMAX in the respective studies are 37 (as compared to 23 for CMAX, 15 for AUC(0-Inf) and 16 for AUC(0-T)), 53 (as compared to 27 for CMAX and 24 for AUC(0-24)), and 47 (as compared to 30 for CMAX, 28 for AUC(0-Inf) and 29 for AUC(0-T)). Intersubject CV% for TMAX are widely different between the test and reference product, with the reference product having higher variability in TMAX (See study result summaries above for comparison). Whether these differences in TMAX observed between the test and reference treatments correlate with the difference in the release mechanism of the two products, or whether they are clinically significant, remain to be determined.

VI. Recommendations:

1. The **single-dose, fasting** bioequivalence study and the **multiple-dose** bioequivalence study conducted by Mylan Laboratories on the test product, Nifedipine ER Tablets, 30 mg, lot # 2C009G, comparing it with the reference product, Pratt 's Procardia XL® Tablets, 30 mg Tablets, lot # 57P016A, have been found **incomplete** by the Division of Bioequivalence due to the reasons cited in the Deficiency No. 2 above.

2. The **single-dose, non-fasting** bioequivalence study conducted by Mylan Laboratories on the test product, Nifedipine ER Tablets, 30 mg, lot # 2C009G, comparing it with the reference product, Pratt 's Procardia XL® Tablets, 30 mg Tablets, lot # 57P016A, has been found **unacceptable** by the Division of Bioequivalence due to the reasons cited in the Deficiency No. 1 above.

3. The **in-vitro** dissolution testing conducted by Mylan on its Nifedipine ER Tablets, 30 mg, and Pratt 's Procardia XL Tablets, has been found acceptable.

The dissolution testing should be conducted, in 250 ml of SGF with 0.25% TWEEN 80 for the first hour, and in 250 ml of 0.01 M phosphate buffer pH 6.8 between 2 and 24 hours, both at 37C using USP XXIII apparatus III at 20 dpm. The test product should meet the following tentative specifications, recommended by the agency and based on the data submitted:

1 hr	No release
2 hr	NMT 15%
8 hr	35-55%
12 hr	65-85%
24 hr	NLT 80%

Please note that the specifications are modified from those proposed by the firm.

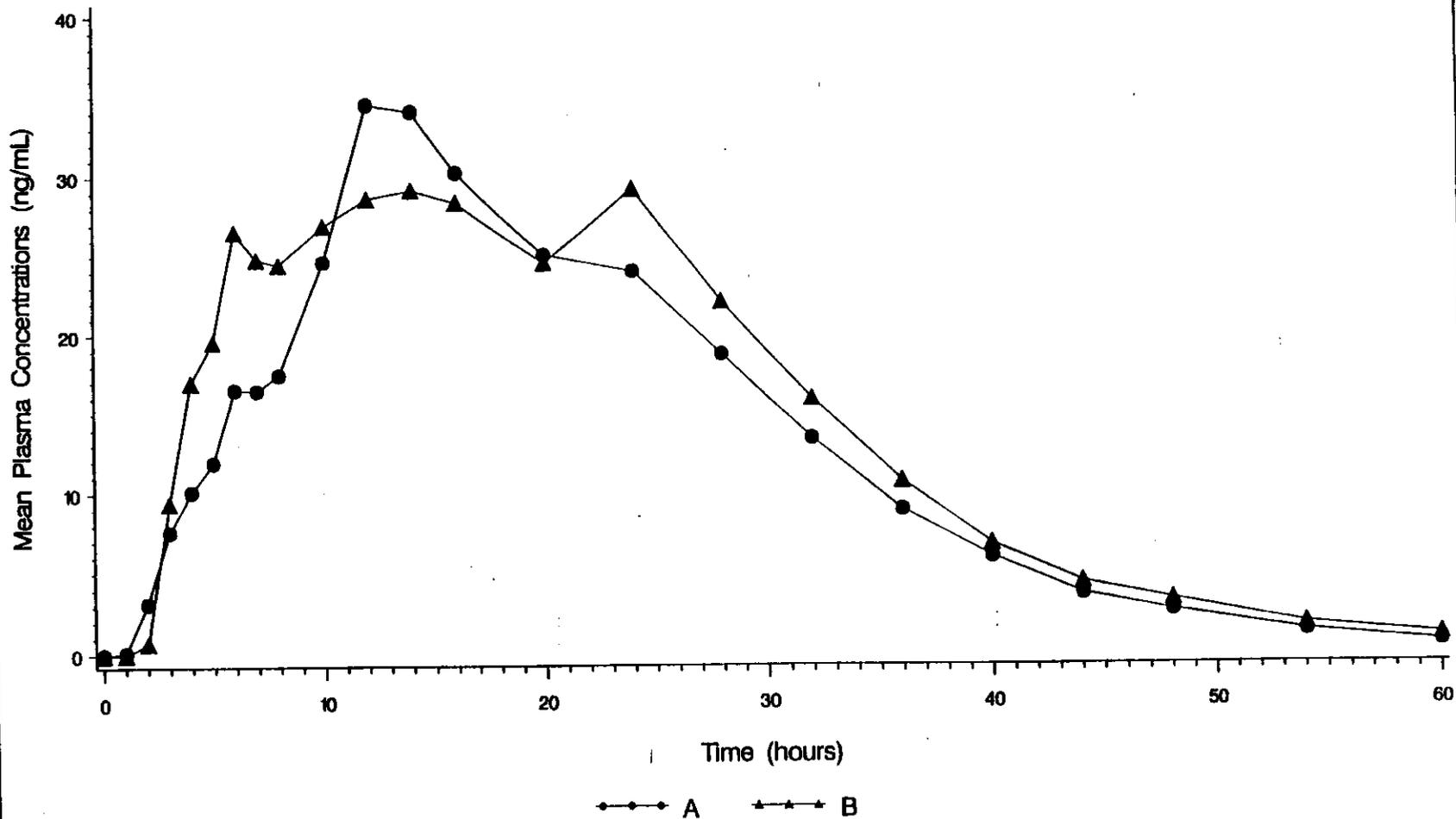
The firm should be informed of the Recommendations and Deficiencies.

NIFEDIPINE E. . (NIFE-9666a)

Total Dose: 60 mg (2x30mg Tablets), Study Type: Fasting

Mean Nifedipine Plasma Concentrations

N= 38



Treatment A is A (Nifedipine ER)
Treatment B is B (Procardia XL)

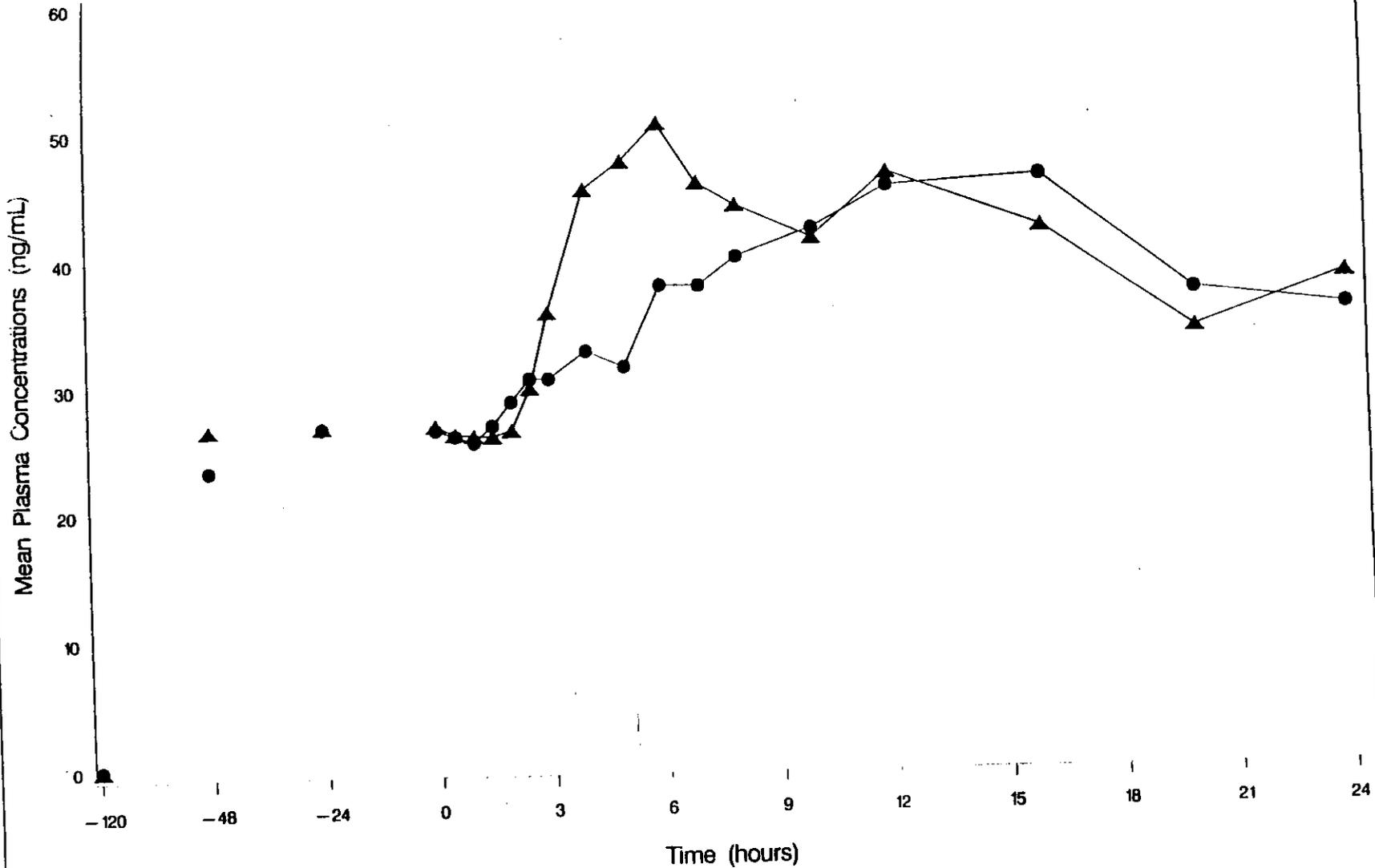
290

WP # 75108 sd. 497 Attachment
Page 1 of 10

5596

NIFEDIPINE ER (NIFE-9668)

Mean Nifedipine Plasma Concentrations



●—● A Mylan's ●●● A @ -120 hours ●●● A @ -24 hours ●●● A @ -48 hours
 ▲—▲ B Procordia XL ▲▲▲ B @ -120 hours ▲▲▲ B @ -24 hours ▲▲▲ B @ -48 hours

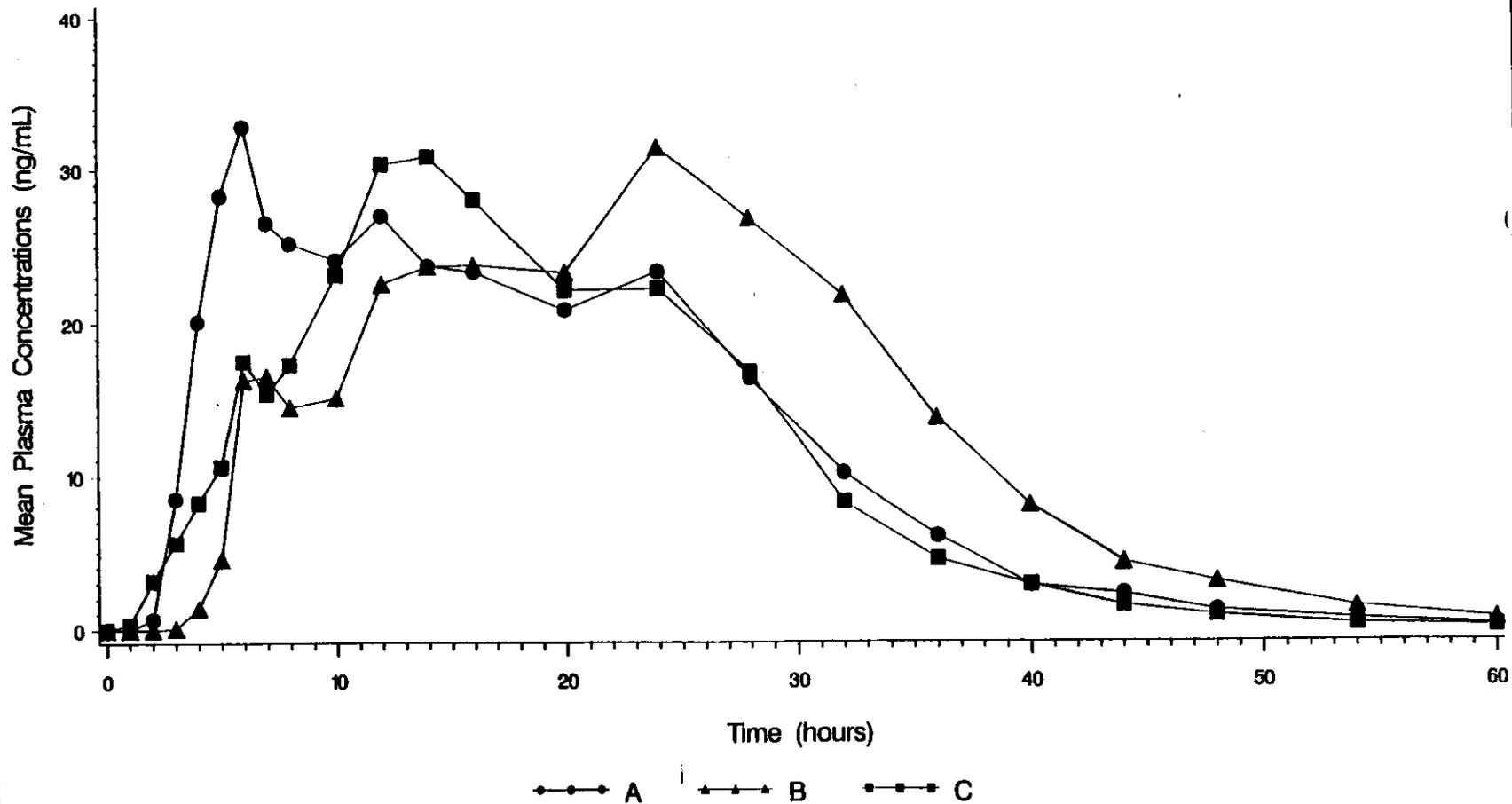
WP # 75108 sd. 497 Attachment
Page 2 of 10

NIFEDIPINE L . (NIFE-9661a)

Total Dose: 60 mg (2x30mg Tablets), Study Type: Fed

Mean Nifedipine Plasma Concentrations

N= 19



Treatment A is A (Procordia XL-Fed)
Treatment B is B (Nifedipine ER-Fed)
Treatment C is C (Nifedipine ER-Fast)

4164

Page 3 of 10

WP # 75108 sd. 497 Attachment

MYLAN PHARMACEUTICALS INC.

QUALITATIVE COMPOSITION
NIFEDIPINE EXTENDED-RELEASE TABLETS
30 MG

ACTIVE COMPONENT

PHARMACEUTICAL FUNCTION

Nifedipine,

Active Ingredient

INACTIVE COMPONENTS

Polyethylene Glycol,

Purified Water, ¹

Clear Opadry II⁽¹⁾

Sodium Stearyl Fumarate,

NF

ethyl Citrate, NF

Polysorbate

Silicon Dioxide,

Sodium Hydroxide,

(Y-22-16577)

Fine Black Pharmaceutical Ink⁽⁵⁾

Ink Thinner

3
3
3

note

net wt.

Drug: Nifedipine ER Tablets 30 mg

Company: Mylan

ANDA# 75-108

Reviewer: Hoainhon Nguyen

Date: August 13, 1997

Statistical Consultation Request

Don,

I have the two following questions:

(1) The subjects of the single-dose, fasting study for the test product were divided into 2 groups: Group A (with subjects numbered 1 through 29, Period 1: November 25, 1996 and Period 2: December 2, 1996), and Group B (with subjects numbered 30 through 38, Period 1: December 3, 1996 and Period 2: December 10, 1996).

The group effects were assessed. Representative print-outs of the ANOVA results are attached. Please comment on the model used, and indicate which terms of the model are important for consideration of the group effects. According to the results shown, it was concluded that there was no significant group effects, and the standard model of ANOVA was used for the final statistical analysis.

(2) Vital signs such as blood pressure and heart rate were also measured in this study hourly for the first 8 hours and at 12, 24, 48 and 60 hours post-dose.

The vital signs were statistically analyzed for treatment differences. Representative print-outs of the ANOVA results are attached. Please comment on the model used, and indicate if the statistical analysis has any relevance to the bioequivalence determination (That is, is it valid based on the model used to conclude that there was no difference between treatment for the vital signs measured).

Thank you in advance. Hnguyen

WP#a:\75-108con.897

Hoi Nguyen
8/13/97

WT # 151085d.497 Attachment
Page 6 of 10

75-108
Nifedipine ER
Mylan

Two Groups

11/25	12/2	12/3	12/10
T	R		
R	T		
		T	R
		R	T

The first issue is whether or not we (CDER) are worried about the possibility of GROUP*TRT interaction. That is, are we worried about the possibility that the difference between T and R is not the same in Group B as it was in Group A?

In attempting to answer this question, we should ask: Why did the firm do the study in two groups? Was it for purely Logistical reasons (e.g. their clinical facility could not handle as many subjects as they wanted to study)? Was it done to replace dropouts?

Things that I (Dan) feel might make us worry about the possibility of GROUP*TRT interaction are:

(2)

1. Were the Groups studied at different sites?

2. Were the groups widely separated in time?

3. Were the subjects in the two groups recruited from different subject populations?

In the case of the Mylan study, ~~neither~~ I assume that neither 1. nor 2. is the case (that is, both groups were studied at the same clinical site, and Group B began only a day after Group A finished). I have no way of knowing if the groups came from different subject populations.

Anyway, it appears that we may not even have to worry about GROUP * TRT in this case. But, certainly, Mylan did not ~~investigate~~ include this factor in their model.

The second issue is ~~not~~ how to characterize the period effect (PER). In terms of the calendar days of the periods, periods 1 and 2 for Group A (11/25 and 12/2) differed from periods 1 and 2 for Group B (12/3 and 12/10). I therefore feel that the statistical model should include PER(GROUP) [in the terminology of Mylan, this would be PER(COHORT)] instead of PER.

If we really wanted to investigate statistically whether or not the effect of periods 1 and 2 was the same in Group A as in Group B, we could do it

3

by including PER and GROUP*PER in the model (instead of PER(GROUP)). The test of GROUP*PER would be the test of whether the period effect was the same in the two groups. Mylan did not do this.

However, I (Don) believe that we should not do this GROUP*PER test, but should instead always put PER(GROUP) in the model.

My recommendation: If you are satisfied that the subjects in the two groups did not come from different subject populations (and if you don't have other concerns that I have not thought of), then I would forget about GROUP*TRT, and would use the following model (or ask Mylan to do it):

```
CLASS SEQ SUBJ PER TRT GROUP;  
MODEL Y = SEQ SUBJ(SEQ) PER(GROUP) TRT;
```

second issue: vital signs

1. Model used

since the vital sign data came from the same experimental design as the PK parameters, I think the same statistical model should be used.

(4)

I do not know if there is precedent for deleting Period Effects from the model when analyzing vital signs. You might ask Rabi.

~~2. Conclusions~~

~~Let us assume for the moment~~

Another issue is whether or not vital sign endpoints should or should not be log transformed. I have no idea. Once again, there may be precedent in OGD.

2. Conclusions

Let us assume for the moment that the sponsor's model is valid. Based on the non significant p-values (SYS1 $p = .9573$, SYS2 $p = .4984$) for TREAT, what can Mylan conclude?

1. They may make the statement "There is no evidence in the study that the two treatments differ with respect to vital signs"

2. They absolutely may not make the statement "The study establishes that the two treatments do not differ with respect to vital signs"

If Mylan wants to make a positive statement (as opposed to a negative statement such as "There is no evidence in the study..."), equivalence

⑤

limits must be established for vital sign endpoints. Then we can see if the confidence interval falls within these equivalence limits.

First Generic

B-97-080

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : April 10, 1997

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch *Wm. L. ... 4/10/97*
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Nifedipine Extended-release Tablets, 30 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355(4)(B)(iv).

Mylan Pharmaceuticals Inc. has submitted ANDA 75-108 for Nifedipine Extended-release Tablets, 30 mg. The ANDA contains a certification pursuant to 21 USC 355(j)(2)(A)(vii)(iv) stating that a patent expiring November 23, 2010 will not be infringed by the manufacture or sale of the proposed product. In order to accept an ANDA for filing that contains such a patent certification, the Agency must formally make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by Mylan on April 7, 1997 for its Nifedipine product satisfies the statutory requirements of "completeness" so that the ANDA may be filed and that a period of six months of market exclusivity can be granted to the applicant who submitted the first substantially complete ANDA under 21 USC 355(j)(4)(B)(iv).

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 75-108 DRUG NAME Nifedipine ER FIRM Mylan

DOSAGE FORM(S) 30mg TABLETS

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol	✓				
Assay Methodology	✓				
Procedure SOP	✓				
Validation	✓				
Study Results Log/Lin	✓				
Adverse Events	✓				
IRB Approve	✓				
Dissolution	✓				
Pre-screening of patients	✓				
Chromatograms	✓				
Consent form	✓				
Composition					
Summary of study	✓				
Individual Data & Graphs , Linear & Semi-linear	✓				
PKPD data disk	N/A				
Randomization Schedule	✓				
Protocol Deviations	✓				

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site	✓				
Analytical site	✓				
Study investigators	✓				
Study dates	✓				
Analysis dates	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory	✓				
BIO Batch Size	✓				
Assay of active content drug	✓				
Content uniformity	✓				
Date of manufacture	✓				
Exp. Date RLD	✓				
Biostudy lot numbers	✓				
Other Composition	✓				

Recommendation: COMPLETE / INCOMPLETE

Reviewed by

Date 4/15/97

ANDA/AADA PROCESSING RECORD

ANDA/AADA NO. 75-108

DATE		INITIALS
<u>4/8/97</u>	Date received by Document Room	<u>meB</u>
<u>4/9/97</u>	Date received by Program Support Staff	<u>meB</u>
<u>4/10/97</u>	Date forwarded to CSO/CSO Tech. for review	<u>meB</u>
<u>4/21/97</u>	Date filling review completed/forwarded for supervisory review	<u>lf</u>
<u>5/4/97</u>	Date sent to typing	<u>lf</u>
_____	Date typing completed	_____
_____	Date sent for Director's signature	_____
_____	Date of OGD signature	_____



MYLAN PHARMACEUTICALS INC

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

APR 7 1997

**ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED**

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

RE: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None

Established Name: Nifedipine Extended-release Tablets

This application consists of a total of 37 volumes.

Archival Copy - 17 volumes.

Review Copy - 18 volumes.

Technical Section For Chemistry - 3 volumes.

Technical Section For Pharmacokinetics - 15 volumes.

Analytical Methods - 2 extra copies; 1 volume each.

NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a set of data diskettes for the bioequivalence studies.

This application provides for the manufacture of Nifedipine Extended-release Tablets, 30 mg. All operations in the manufacture, packaging, and labeling of the drug product are performed by Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730.

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

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

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

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