CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-138

CORRESPONDENCE

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

DEC 14 1998

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

AC

BIOEQUIVALENCE AMENDMENT
(CMC DATA ENCLOSED)

RE: VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
120MG, 180MG and 240MG
ANDA #75-138
RESPONSE TO AGENCY CORRESPONDENCE DATED DECEMBER 7, 1998

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Application identified above, which is currently under review, and to the comments from the Agency pertaining to this application which were provided to Mylan in correspondence dated December 7, 1998 from the Office of Generic Drugs' Division of Bioequivalence. In response to the Agency's comments of December 7, Mylan wishes to amend the application as follows:

A. REGARDING BIOEQUIVALENCE ISSUES:

FDA COMMENT 1. 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 900 mL of 0.1N HCl at 37°C using USP 23 Apparatus II (paddle) at 100 rpm. Based on the submitted data the following tentative specifications are recommended:

2 hours :
4 hours :
8 hours :
24 hours :

RECEIVED

DEC 16 1998

G:\PROJECT\ANDA\VERAPAMIL-ER-240-CAPS\BIO-AGENCY-LETTER-DATED_120798.WPD

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

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.

MYLAN RESPONSE: The dissolution testing requested by the Division of Bioequivalence will be incorporated into Mylan's stability and quality control programs as of the date of this amendment. Mylan has revised the finished product specifications, dissolution procedure, and post-approval stability protocol for Verapamil Hydrochloride Extended-release Capsules, 120mg, 180mg and 240mg to incorporate the requested change in the specifications for dissolution. These revised documents are provided in Attachments A, B, and C, respectively.

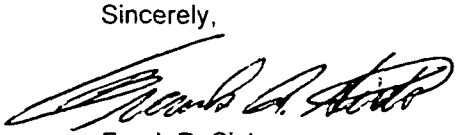
It is also acknowledged and understood that the bioequivalency comments expressed in the letter dated December 7, 1998 are preliminary and may be revised after review of the entire application.

For your reference, a copy of the December 7, 1998 Agency correspondence is provided in Attachment D. Responses to the labeling comments contained in the December 7th correspondence will be forwarded in a separate amendment to this application.

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

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

Sincerely,



Frank R. Sisto
Vice President
Regulatory Affairs

FRS/maa

enclosures

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

December 14, 1998

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

LABELING AMENDMENT

RE: VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 120MG, 180MG AND 240MG
ANDA 75-138
RESPONSE TO AGENCY CORRESPONDENCE DATED DECEMBER 7, 1998

Dear Mr. Sporn:

We wish to amend the above-referenced application with a revised final printed outsert. Enclosed in Attachment 3 are twelve (12) copies of the final printed outsert CODE CVERER:R2; revised December 1998. The labeling was revised in accordance with the Agency's correspondence of December 7, 1998. A copy of this correspondence is provided in Attachment 1. To facilitate the review, a side-by-side comparison of Mylan's revised outsert to the previously submitted outsert is provided in Attachment 2.

It is noted that prior to approval of this application the agency reserves the right to request further changes in the Mylan labeling based upon changes in the approved labeling of the listed drug or upon further review of the application.

The bioequivalence issues regarding dissolution testing raised in the Agency's December 7, 1998 correspondence were addressed in a separate amendment also submitted to the referenced application on December 14, 1998.

Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

ABM/cam

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DEC 16 1998

G:\PROJECT\ANDA\VERAPAMIL-ER-240-CAPS\AGENCY-LETTER-DATED-120798.wpd

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

4.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-138 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Verapamil HCl Extended-Release Capsules, 240 mg 180 mg and 120 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 900 mL of 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 100 rpm. Based on the submitted data the following tentative specifications are recommended:

2	hours NT
4	hours NT
8	hours NT
24	hours NT

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,

Dale P. Conner

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

VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 120MG, 180MG, AND 240MG
DISSOLUTION PROFILE SUMMARY

	2 HOUR	4 HOURS	8 HOURS	24 HOURS
120mg				
Mylan Lot 2D001J				
Mean	15%	26%	48%	88%
Range				
RSD	13.0%	6.7%	3.3%	2.9%
120mg				
Verelan® Lot 442-444				
Mean	18%	29%	65%	96%
Range				
RSD	9.9%	8.4%	3.8%	2.3%
180mg				
Mylan Lot 2D002J				
Mean	15%	25%	48%	87%
Range				
RSD	8.8%	5.9%	3.1%	2.3%
180mg				
Verelan® Lot 432-896				
[illegible]	18%	30%	61%	95%
[illegible]	10.3%	6.7%	2.9%	3.8%
240mg				
Mylan Lot 2C004J				
Mean	17%	31%	54%	94%
Range				
RSD	7.3%	4.3%	3.6%	2.7%
240mg				
Verelan® Lot 428-233				
Mean	18%	32%	63%	95%
Range				
RSD	7.7%	4.1%	3.1%	2.2%

CONDITIONS: Dissolution Medium: 0.1N HCl, 900 mL, @ 37.0°C ± 0.5°C
Apparatus: 2 (Paddles)
Speed: 100 rpm
Sample Times @ 2, 4, 8 and 24 hours
Limits:
%
%
%

Detailed reports follow.

COMPARATIVE QUANTITATIVE COMPOSITIONS
VERAPAMIL HCl EXTENDED-RELEASE CAPSULES, 120 mg, 180 mg and 240 mg

	120MG		180MG		240MG	
COMPONENTS	**MG PER CAPSULE**	**%**	**MG PER CAPSULE**	**%**	**BIO MG PER CAPSULE**	**%**
Verapamil HCl Immediate Release Beads (635 mg/gram)	18.9	9.2%	28.3	9.2%	37.8	9.2%
Verapamil HCl Extended Release Beads, (534.8 mg/gram)	33.7	16.4%	50.5	16.4%	67.3	16.4%
Talc, Micronized, USP	0.15	0.1%	0.225	0.1%	0.30	0.1%
Verapamil HCl Extended Release Beads (587.4 mg/gram)	153.2	74.4%	229.8	74.4%	306.4	74.4%
TOTAL	**205.95**	**100%**	**308.8**	**100%**	**411.8**	**100%**

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

MAY 27 1998

BIOAVAILABILITY
N/AB

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

ELECTRONIC DATA ENCLOSED

BIOEQUIVALENCE AMENDMENT

RE: ANDA 75-138; VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 120MG, 180MG AND 240MG
RESPONSE TO AGENCY CORRESPONDENCES DATED NOVEMBER 30, 1997 AND MAY 1, 1998

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Application identified above, which is currently under review and to the comments from the Agency regarding this application which were provided to Mylan in two facsimiles dated November 30, 1997 and May 1, 1998. A copy of the referenced correspondences are included in Attachment A, for the convenience of the reviewer. In response to the Agency's comments Mylan wishes to amended this application as follows:

REGARDING BIOEQUIVALENCY DEFICIENCIES

NOVEMBER 30, 1997 FACSIMILE

FDA COMMENT 1. Please submit a sprinkling bioequivalence study. A study to demonstrate bioequivalence of the generic version *versus* the innovator product (Verelan®) when capsules contents are sprinkled on applesauce. The recommended design is, two-treatment, two-period, two sequence, crossover comparing the test product with the reference product sprinkled on a spoonful of applesauce under fasting conditions.

MYLAN RESPONSE: Mylan has completed a fasting *in vivo* bioequivalence study comparing Mylan's Verapamil Hydrochloride Extended-release Capsules, 240 mg to Verelan® Capsules, 240mg when the contents of the capsule were sprinkled on applesauce. The study was conducted pursuant to protocol VERA-9784: *Comparative Single-Dose Bioequivalence Study of Verapamil HCl ER Capsules in Normal Healthy Male Volunteers--Fasting Study, Dosed with Applesauce.* This protocol is provided in Attachment B.

RECEIVED
MAY 28 1998
GENERIC DRUGS

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

The study was conducted by Clinical and Pharmacologic Research, Inc. in Morgantown, WV. The samples from the study were analyzed at the analytical laboratories of Mylan Pharmaceuticals, Inc. in Morgantown, WV. The results of this study demonstrate that Mylan's Verapamil Hydrochloride Extended-release Capsules 240 mg are bioequivalent to Verelan® Capsules (Lederle) 240 mg following a single, oral 240 mg (1 x 240 mg) dose sprinkled over one tablespoon of applesauce. The report for the sprinkling bioequivalence study is provided in Attachment C.

The lot data for the products used in the sprinkling bioequivalence study is provided in Attachment D. This data includes Certificates of Analysis and Dissolution Profiles for the study medications. The Mylan test product is Verapamil Hydrochloride Extended-release Capsules, 240 mg, Lot #2C004J and the referenced product is Lederle's Verelan® Capsules, 240 mg, Lot #446-298. Mylan's Lot #2C004J is the same as that used to conduct the fasting (VERA-9669), post-prandial (VERA-9612) and steady-state (VERA-9674) bioequivalence studies submitted in the original application (ANDA 75-138) on May 28, 1997. However, the reference product, Lederle's lot #446-298, used in the sprinkling bioequivalence study is different from that used in the original food, post-prandial and steady-state bioequivalence studies due to the expiration of the original lot prior to the initiation of the sprinkling study.

MAY 1, 1998 FACSIMILE

FDA COMMENT 1. Waivers of *in vivo* bioequivalence study requirements for the test products Verapamil HCl ER Capsules, 120 mg and 180 mg can not be granted since the ANDA for Verapamil HCl ER Capsules, is incomplete. You are advised to resubmit the waiver request upon submitting a sprinkling bioequivalence study of Verapamil HCl ER Capsules, 240 mg.

MYLAN RESPONSE: The *in vivo* bioequivalence study requirements for Verapamil Hydrochloride Extended-release Capsules, 120mg and 180mg have been completed. Therefore, enclosed in Attachment E is Mylan's re-submission of the request for a waiver of the *in vivo* bioequivalence testing requirements for the two additional dosage strengths (120mg and 180mg) of Verapamil HCl Extended-release Capsules.

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

Sincerely,

Frank R. Sisto for
Vice President
Regulatory Affairs

FRS/tlr

enclosures

R:\ANDA\VERAPAMIL-ER-240-CAPS\AGENCY-LETTER-DATED_113097.WPD

MAR 6 1998

38. Chemistry comments to be Provided to the Applicant

ANDA: 75-138 APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Verapamil HCl Extended-release Capsules, 240 mg

The deficiencies presented below represent MAJOR DEFICIENCIES.

A. Deficiencies:

1. You stated that "A new solution was manufactured using reweighed PVP and fully release Purified Water USP. These actions are noted in the batch record on pages 1A and 3A" (p. 815). Actual Master Formula sheets superseding pages 793 and 794 (duplicate pages 7697 and 7698), should have been included. Apparently the manufacturing instructions do not correspond to the formulation. Please clarify and/or submit.

2. It is noted that the dates of encapsulation (9/03/96) and those of results and recontrol testing (9/23/96) of the beads, conflict with your statement to the effect that "Testing was conducted on the above mentioned beads for recontrol purposes prior to encapsulation". Please clarify and/or submit.

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

1. It is noted that approximately a 12 month time period elapsed between the manufacture of verapamil HCl immediate release beads 635 mg/gram, extended-release beads 587.4 mg/gram and 534.8 mg/gram, and the encapsulation of these beads for the in vivo bioequivalence. We are cognizant of your statement to the effect that for "commercial manufacturing purposes we do not intend to store bulk beads for longer than 3 months prior to encapsulation." Please confirm your understanding that the expiration dating period begins with the manufacture of the individual beads.

The testing dates should agree (within a reasonable range) with the stability testing stations as scheduled. Additionally, all testing procedures and specifications should be developed and approved before the release of the executed batch.

2. Bioequivalence of the drug product has not been established. Please refer to the deficiency comment dated November 30, 1997 provided via facsimile from the Division of Bioequivalence.

3. The amendment dated January 4, 1998 which provides for 120 mg and 180 mg strengths of the product will be reviewed in conjunction with your response to the above deficiencies.

Sincerely yours,

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

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

MAY 22 1998

Labeling received 7/10/98 Douglas Abes

ORIG AMENDMENT

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

MAJOR AMENDMENT

RE: VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 240MG
ANDA #75-138
RESPONSE TO AGENCY CORRESPONDENCE DATED MARCH 6, 1998

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to the comments from the Agency regarding this application which were forwarded to Mylan via facsimile on March 6, 1998. With regard to the March 6 comments, Mylan wishes to amend this application with the following information:

A. REGARDING CHEMISTRY ISSUES:

FDA COMMENT 1.

MYLAN RESPONSE:

FDA COMMENT 2.

RECEIVED
MAY 20 1998
GENERIC DRUGS

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

MYLAN RESPONSE:

B: REGARDING MISCELLANEOUS ISSUES:

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

FDA COMMENT 1. It is noted that approximately a 12 month time period elapsed between the manufacture of verapamil HCl

encapsulation of these beads for the in vivo bioequivalence. We are cognizant of your statement to the effect that for "commercial manufacturing purposes we do not intend to store for longer prior to encapsulation." Please confirm your understanding that the expiration dating period begins with the manufacture of the individual beads.

The testing dates should agree (within a reasonable range) with the stability testing stations as scheduled. Additionally, all testing procedures and specifications should be developed and approved before the release of the executed batch.

MYLAN RESPONSE: As requested by the Agency and as previously stated on page #7689 of this application, Mylan confirms that the expiration dating period begins with the manufacture of the individual beads.

Mylan agrees that the testing dates should agree (within a reasonable range) with the stability testing stations as scheduled. It is important to note that the time intervals presented in the Stability Protocol indicate the length of time the samples remain in the stability chambers, the samples are stored under ambient conditions until testing is initiated.

The storage of Mylan's Verapamil Hydrochloride Extended-release Capsules, 240mg stability samples under ambient conditions following their withdrawal from the stability chambers for periods past the scheduled testing intervals represents "worst case" storage conditions. Upon review of the updated stability data, under these "worst case" conditions no apparent detrimental stability trends for potency, related compounds, or dissolution are noted in relation to the dates of assay.

Mylan acknowledges the Agency's comment that stability testing dates should coincide with the test station program. For future stability testing of products being evaluated for ANDA approval, Mylan will make every effort to perform stability testing at each designated interval within a prudent period of time.

In addition, Mylan acknowledges the reviewer's comments regarding development and approval of testing procedures and specifications prior to the release of the executed batch. For compendial products, Mylan will evaluate the compendial methodology and have approved procedures and specifications for all compendial tests prior to release of the executed batch. For non-compendial products, Mylan will have developed and approved procedures for critical test methods, such as Dissolution/Drug release, Assay, Content Uniformity, and Identification prior to release of the executed batch. The specifications for Assay and Content Uniformity and tentative specifications for Dissolution/Drug release will be approved prior to release of the executed batch. Other test procedures and specifications may be deemed necessary by Mylan subsequent to release of the executed batch. In these cases, the specifications and test methods will be developed and approved in an appropriate timely fashion.

FDA COMMENT 2. Bioequivalence of the drug product has not been established. Please refer to the deficiency comment letter dated November 30, 1997 provided via facsimile from the Division of Bioequivalence.

MYLAN RESPONSE: Mylan acknowledges the Agency's comment regarding the bioequivalence of the drug product. As recommended by the Division of Bioequivalence in their correspondence dated November 30, 1997, Mylan has conducted a study which demonstrates the bioequivalence of Mylan's Verapamil HCl Extended-release Capsules, 240mg to the innovator product, Verelan® Capsules, 240mg, when capsule contents are sprinkled on applesauce. The report of this bioequivalence study will be submitted in a separate amendment to this ANDA in response to the November 30, 1997 letter from the Division of Bioequivalence.

FDA COMMENT 3. The amendment dated January 4, 1998 which provides for 120 mg and 180 mg strengths of the product will be reviewed in conjunction with your response to the above deficiencies.

MYLAN RESPONSE: Mylan acknowledges that the amendment dated January 4, 1998 providing for the 120mg and 180mg strengths of the product will be reviewed in conjunction with our response to the above deficiencies.

C: REGARDING LABELING ISSUES:

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

BOTTLE LABELS

120 mg	100 capsules	Code RM6320A
	500 capsules	Code RM6320B
180 mg	100 capsules	Code RM6380A
	500 capsules	Code RM6380B
240 mg	100 capsules	Code RM6440A
	500 capsules	Code RM6440B

PACKAGE OUTSERT

Code - **CVERER:R1**; REVISED MAY 1998

The enclosed labeling incorporates the revisions requested in the Agency's letter dated March 6, 1998. A copy of this letter is provided in Attachment C for the convenience of the reviewer. In addition, this labeling was revised to provide for the 120 mg and 180 mg strengths. The enclosed labeling completely supercedes the labeling provided in the January 4, 1998 amendment.

In order to facilitate the review of this labeling, and in accordance with 21 CFR 314.94(a)(8)(iv), Attachment D contains a side-by-side comparison of the final printed labeling for the 120 mg, 180 mg and 240 mg strengths to the labeling for the 240 mg strength that was submitted in the original application on May 28, 1997. It is noted that prior to approval of this application, the agency reserves the right to request further changes in the Mylan labeling based upon the changes in the approved labeling of the listed drug or upon further review of the application.

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

For your reference, a copy of the Agency correspondence dated March 6, 1998, is enclosed in Attachment C.

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

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

enclosures

2.1

MAY 1 1998

BIOEQUIVALENCY COMMENTS

ANDA: 75-138 APPLICANT: Mylan Pharmaceuticals Inc

DRUG PRODUCT: Verapamil HCl ER Capsules, 120 mg, 180 mg and 240 mg

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

Waivers of *in vivo* bioequivalece study requirements for the test products Verapamil HCl ER Capsules, 120 mg and 180 mg can not be granted since the ANDA for Verapamil HCl ER Capsules, is incomplete. You are advised to resubmit the waiver request upon submitting a sprinkling bioequivalence study on Verapamil HCl ER Capsules, 240 mg.

Sincerely yours,

Dale P. Conner

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

BIOEQUIVALENCY COMMENTS

ANDA: 75-138 APPLICANT: Mylan Pharmaceuticals Inc

DRUG PRODUCT: Verapamil HCl ER Capsules, 120 mg, 180 mg and 240 mg

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

Waivers of *in vivo* bioequivalece study requirements for the test products Verapamil HCl ER Capsules, 120 mg and 180 mg can not be granted since the ANDA for Verapamil HCl ER Capsules, is incomplete. You are advised to resubmit the waiver request upon submitting a sprinkling bioequivalence study on Verapamil HCl ER Capsules, 240 mg.

Sincerely yours,

Dale P. Conner

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

Table II

PHARMACEUTICALS

VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 120MG, 180MG, AND 240MG
DISSOLUTION PROFILE SUMMARY

	2 HOUR	4 HOURS	8 HOURS	24 HOURS
120mg				
Mylan Lot 2D001J				
Mean	15%	26%	48%	88%
Range				
RSD	13.0%	6.7%	3.3%	2.9%
120mg				
Verelan® Lot 442-444				
Mean	18%	29%	65%	96%
Range				
RSD	9.9%	8.4%	3.8%	2.3%
180mg				
Mylan Lot 2D002J				
Mean	15%	25%	48%	87%
Range				
RSD	8.8%	5.9%	3.1%	2.3%
180mg				
Verelan® Lot 432-896				
Mean	18%	30%	61%	95%
Range				
RSD	10.3%	6.7%	2.9%	3.8%
240mg				
Mylan Lot 2C004J				
Mean	17%	31%	54%	94%
Range				
RSD	7.3%	4.3%	3.6%	2.7%
240mg				
Verelan® Lot 428-233				
Mean	18%	32%	63%	95%
Range				
RSD	7.7%	4.1%	3.1%	2.2%

CONDITIONS: Dissolution Medium: 0.1N HCl, 900 mL, @ 37.0°C ± 0.5°C
Apparatus: 2 (Paddles)
Speed: 100 rpm
Sample Times @ 2, 4, 8 and 24 hours
Limits:

Detailed reports follow.

BIOAVAILABILITY

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

DEC 31 1997

NDA ORIG AMENDMENT
AA

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

RE: VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 240 MG
ANDA #75-138
AMENDMENT TO PROVIDE FOR THE ADDITION
OF 120 MG AND 180 MG CAPSULES

Dear Mr. Sporn:

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

Verapamil HCl Extended-release Capsules, 120 mg and 180 mg will be manufactured, tested, packaged and labeled by Mylan Pharmaceuticals Inc. in Morgantown, WV following the procedures for the 240 mg capsules, as currently provided in the ANDA. All three dosage strengths of Verapamil HCl Extended-release Capsules are compositionally proportional as they consist of a combination of three beads:

A specific amount of the aforementioned beads is weighed for use in encapsulation based on the potency of the extended release beads and strength of the capsule. Based on the compositional proportionality of these products and the bioequivalence of the 240 mg capsule versus the reference listed drug (Verelan® Capsules, 240 mg), as demonstrated in the data provided in the original application, this amendment contains an *in vivo* biowaiver request for the 120 mg and 180 mg dosage strengths.

RECEIVED
JAN 0 2 1998
GENERIC DRUGS

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

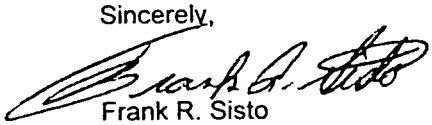
Archival Copy - 3 volumes.
Review Copy - 4 volumes.
Technical Section For Chemistry - 3 volumes.
Technical Section For Pharmacokinetics - 1 volume.
Analytical Methods - 2 extra copies; 1 volume each.

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

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

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

Sincerely,



Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

enclosures

NOV 30 1997

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-138 APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Verapamil Hydrochloride, Extended-release Capsules, 240 mg

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

Please submit a sprinkling bioequivalence study. A study to demonstrate bioequivalence of the generic version *versus* the innovator product (Verelan^{R}) when capsules contents are sprinkled on applesauce. The recommended design is, two-treatment, two-period, two sequence, crossover comparing the test product with the reference product sprinkled on a spoonful of applesauce under fasting condition.

Sincerely yours,

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

ANDA 75-138

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

Dear Sir:

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

NAME OF DRUG: Verapamil Hydrochloride Extended-release Capsules 240 mg

DATE OF APPLICATION: May 28, 1997

DATE OF RECEIPT: May 29, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

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

7/28/97

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

Amanda Miller 6/19/97

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

MAY 28 1997

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

RE: VERAPAMIL HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 240 MG

Dear Mr. Sporn:

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

Proprietary Name: None
Established Name: Verapamil Hydrochloride Extended-release Capsules
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 data diskette for the bioequivalence studies conducted in support of this application. An electronic data set, using the Office of Generic Drugs new EVA software program, is currently being prepared and will be submitted as an amendment to this application as soon as it becomes available.

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

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

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310, or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto

MAY 29 1997

Frank R. Sisto
Executive Director
Regulatory Affairs

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

[RDLIB.ANDA.VERAPAMIL-ER-240-CAPS]SECTIONS-01THRU07