CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-992

Approval Letter

ANDA 74-992 (0.6 mg/hr)

NOV 12 1999

Mylan Technologies, Inc.
Attention: Elizabeth Ash
110 Lake Street
St. Albans, VT 05478

Dear Madam:

This is in reference to your abbreviated new drug application dated October 25, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Nitroglycerin Transdermal System, 0.6 mg/hour.

Reference is also made to your amendments dated May 9, October 17, December 15, and December 22, 1997; February 12, April 16, August 28, 1998, and September 17, 1998; and September 16, 1999.

The listed drug product referenced in your application, Nitro-Dur Transdermal Infusion Systems of Key Pharmaceuticals, Inc., is subject to a period of patent protection which expires on February 16, 2010, (U.S. Patent No. 5,186,938, the '938 patent). Your application contains a Paragraph IV Certification to the '938 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, sale, offer for sale, or importation of this drug product will not infringe on this patent, or that the patent is invalid or unenforceable. Section 505(j)(5)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five dats from the date the notice provided under paragraph (2)(B)(i) is received. You have notified the agency that Mylan Technologies, Inc. (Mylan) has complied with the requirements of Section 505(j)(2)(B) of the Act and as a result Key Pharmaceuticals, Inc. initiated a patent infringement action against you in the United States District Court for the Western District of Pennsylvania (Key Pharmaceuticals, Inc. v. Mylan Laboratories, Inc., Mylan Pharmaceuticals, Inc., Bertek Inc., and Bertek Pharmaceuticals, Inc., Civil Action No. 97-1462). You have also notified us that on March 15, 1999, the court entered a Joint Stipulation And Order Of Dismissal, which terminated the patent litigation. The agency has also been notified by Key Pharmaceuticals, Inc. (Key)

that Key has waived any and all objections and consents to the approval of this application.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Nitroglycerin Transdermal System, 0.6 mg/hour, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug [Nitro-Dur® Transdermal Infusion System, 0.6 mg/hour, of Key Pharmaceuticals, Inc.]. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaign. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) that requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

[S] 11/12/99

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-992

FINAL PRINTED LABELING

How to use
Nitroglycerin Transdermal Patch
for the prevention of angina

℞ only

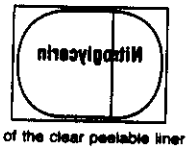
The Nitroglycerin Transdermal Patch is easy to use - it has a clear peelable liner, and a special adhesive that keeps the patch firmly in place.

Where to place the Nitroglycerin Transdermal Patch

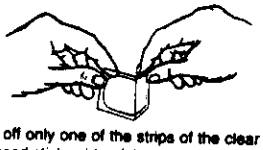
Select any area of skin on the body, EXCEPT the extremities below the knee or elbow. The chest is the preferred site. The area should be clean, dry, and hairless. If hair is likely to interfere with patch adhesion or removal, it can be clipped but *not* shaved. Take care to avoid areas with cuts or irritations. Do NOT apply the patch immediately after showering or bathing. It is best to wait until you are certain the skin is completely dry.

How to apply the Nitroglycerin Transdermal Patch

1. Each Nitroglycerin Transdermal Patch is individually sealed in a protective package. Open the pouch at the tear mark. Carefully remove the patch. The patch is printed with the wording 'Nitroglycerin' and the amount of nitroglycerin delivered each hour. The patch is attached to a clear peelable liner. The liner has a slit which divides it into two strips. Hold the patch with the wording facing *away* from you. The slit should now be facing *toward* you. Rotate the patch as necessary to place the slit in an up and down position.



2. Bend both sides of the clear peelable liner *away* from you at the slit.



3. Slowly peel off only one of the strips of the clear liner. Do not touch the exposed sticky side of the patch.

4. Using the remaining strip as a "handle", apply the exposed sticky side of the patch to the skin. Press the sticky side on the chosen skin site and smooth down.

5. Fold back the unattached side of the patch. Grasp the remaining strip and remove it while applying the remainder of the patch to the skin. Press the patch on the skin and smooth down with the palm of your hand. Once the patch is in place, do not test the adhesion by pulling on it.

When the Nitroglycerin Transdermal Patch is applied to your body, the nitroglycerin contained in the patch begins to flow from the adhesive surface through your skin at a uniform rate.

6. After applying the patch, wash hands to remove any drug.

7. At the time recommended by your doctor, remove and discard the patch.

8. Place a new patch on a different site (following steps 1 through 6) according to your doctor's instructions.

Please Note:

Contact with water, as in bathing, swimming, or showering will not affect the patch. In the unlikely event that a patch falls off, discard it and put a new one on a different skin site.

Precautions:

The most common side effect is headache, which often decreases as therapy is continued, but may require treatment with a mild analgesic. Although uncommon, faintness, flushing, and dizziness may occur, especially when suddenly rising from the recumbent (lying horizontal) position. If these symptoms occur, remove the patch and notify your physician.

Skin irritation may occur. If it persists, consult your physician.

Keep these patches and all drugs out of the reach of children.

Important:

Your doctor may decide to increase or decrease the size of the patch, or prescribe a combination of patches, to suit your particular needs. The dose may vary depending on your individual response to the patch.

This patch is to be used for preventing angina, not for treating an acute attack.

STORE AT ROOM TEMPERATURE 15° -30°C (59° -86°F).

DO NOT REFRIGERATE.

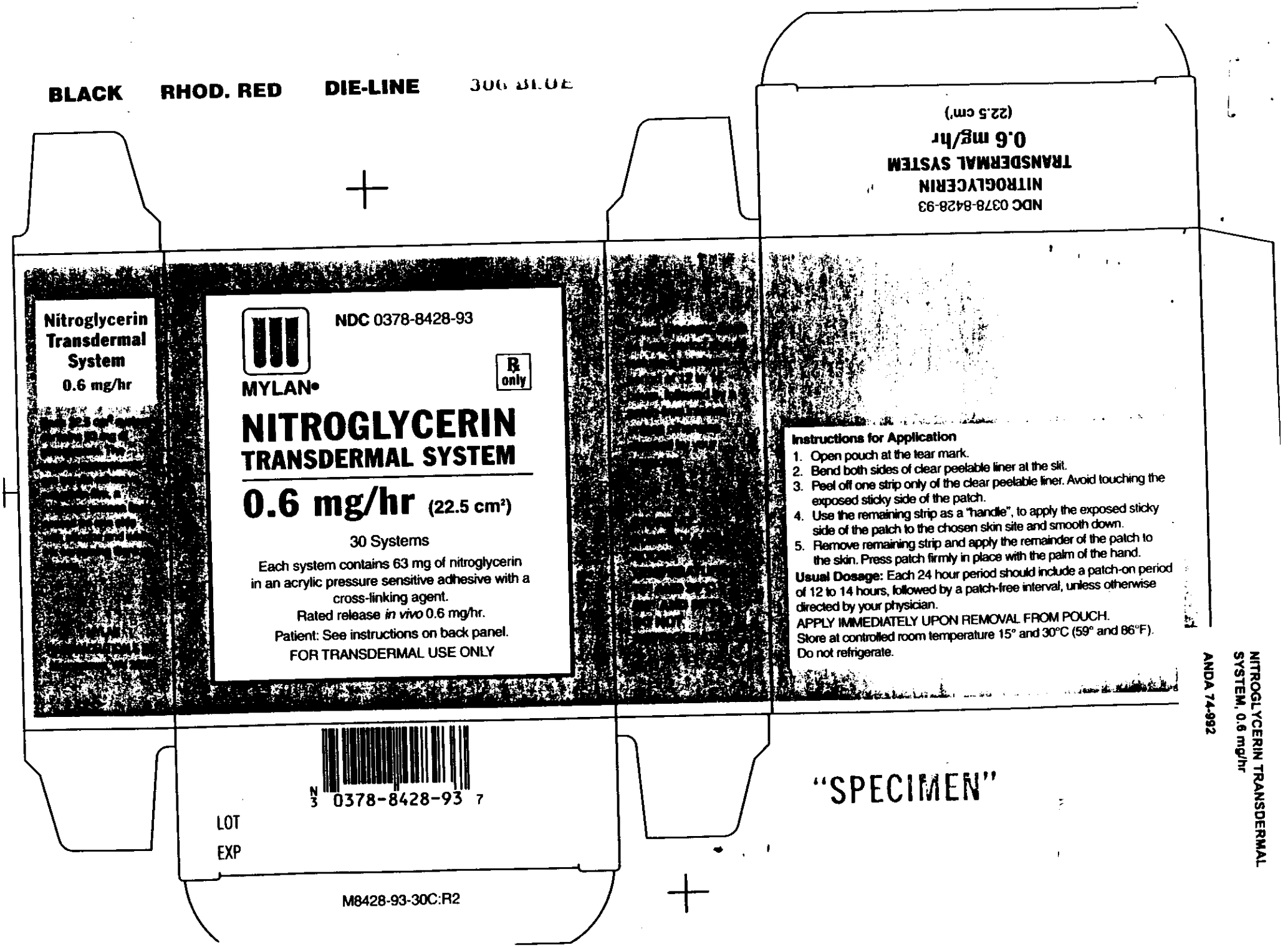
Do not store outside of the protective package. Apply immediately upon removal from the protective package.

MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505

REVISED JUNE 1999
PL NDS R2

"SPECIMEN"

BLACK RHOD. RED DIE-LINE 306 BLUE



NDC 0378-8428-16

8428:2

MYLAN•

NITROGLYCERIN
TRANSDERMAL SYSTEM

0.6 mg/hr (22.5 cm²)

Each 22.5 cm² system contains 63 mg of nitroglycerin.
Approximate rated release *in vivo* 0.6 mg/hr.

KEEP OUT OF REACH OF CHILDREN.
FOR TRANSDERMAL USE ONLY.

MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505

℞ only

Contents: 1 System

"SPECIMEN"

Instructions for Application

1. Open the pouch at the tear mark.
2. Bend both sides of clear peelable liner at the slit.
3. Peel off one strip only of the clear peelable liner. Avoid touching the exposed sticky side of the patch.
4. Use the remaining strip as a "handle", to apply the exposed sticky side of the patch to the chosen skin site and smooth down.
5. Remove remaining strip and apply the remainder of the patch to the skin. Press patch firmly in place with the palm of the hand.

8428:2

Usual Dosage: Each 24 hour period should include a patch-on period of 12 to 14 hours, followed by a patch-free interval, unless otherwise directed by your physician.
APPLY IMMEDIATELY UPON REMOVAL FROM POUCH.
Store at controlled room temperature
15° and 30°C (59° and 86°F). Do not refrigerate.

Face prints PMS 306 Blue, Rhodamine Red, and Black.

Back prints Black.

MYLAN TECHNOLOGIES INC.
NITROGLYCERIN TRANSDERMAL SYSTEM, 0.6 mg/hr
ANDA 74-992

CENTER FOR DRUG EVALUATION AND RESARCH

Application Number 74-992

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW
DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS REVIEW
December 4, 1998

ANDA 74-992
Drug Product: Nitroglycerin Transdermal System, 0.1 mg
Sponsor: Bertek, Inc.

The Dermatologic reviewer agreed that the study has shown that the Mylan Nitroglycerin TDS and Nitro-Dur TDS have comparable skin irritation.

Mary M. Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs

MEDICAL OFFICER REVIEW
OCTOBER 6, 1998

ANDA 74-992
Drug Product: Nitroglycerin Transdermal System, 0.1 mg/hr
Sponsor: Bertek, Inc.

Amendment: 21-Day Cumulative Skin Irritation Study

Protocol Title: Evaluation of Cumulative Irritation Potential in Humans 21-Day Test for Nitroglycerin Transdermal System Patch
Protocol Number: NITR 9831

CRO:
CRO Project Number: 100377

Regulatory History:

The sponsor had initially requested that they be allowed to reference the skin irritation study conducted for ANDA 74-559. This request was declined as that study, conducted a number of years ago, did not meet the standards of 1998 for this type of study. The sponsor replied to our letter of 2/27/98 by submitting a protocol for such a study April 16, 1998. The protocol was found to be acceptable and the sponsor has completed the study and submitted it as part of this amendment.

Study Objective:

To evaluate test articles of low irritation potential for human skin irritation elicited by repetitive topical application over a 21-day period.

Study Design:

The study was conducted between May 20, 1998 and June 18, 1998. Twenty-one consecutive applications of the test articles were applied under occlusion to the same site on the skin for approximately 24 hours on para spinal skin sites. The sites of application of each of the test articles described in the next section were randomized according to a schedule provided by

Scoring of each site was done after patch removal and prior to reapplication by a blinded trained observer. Scoring was done using the following number and letter scales:

0 = No evidence of erythema
1 = Minimal erythema
2 = Definite erythema
3 = Erythema and papules
4 = Definite edema
5 = Erythema, edema and papules
6 = Vesicular eruption
7 = Strong reaction spread beyond site
A(0) = Slight glazed appearance
B(1) = Marked glazing
C(2) = Glazed with peeling and cracking
F(3) = Glazing with fissures
G(3) = Film of dried serous exudate
H(3) = Small petechial erosions and/or scabs

Test articles applied to the skin of each subject were:

1. Mylan Nitroglycerin transdermal system 0.1 mg (A)
   Lot # 26E003D
2. Nitro-Dur (Nitroglycerin transdermal system) 0.1 mg/hr (B)
   Lot # D7518112
3. Mylan transdermal system, placebo ©
   Lot # 26E002D
4. Sodium Lauryl Sulfate Lot # 904608 (D)
5. Normal Saline Lot # G911289 (E)

Statistical Analysis:

The skin evaluation scores were converted to a single number by assigning each letter the number listed in the scoring schema above. An upper limit of 3 was defined since the study was intended to compare treatments that are relatively mild. Once an individual reached a score of 3 or greater the score at that site remained 3 throughout the rest of the study. The Friedman Rank Test was used to evaluate the five test articles. The test article scores for each day and overall were ranked with each subject and then analyzed using the Friedman rank sum test. The hypothesis tested was:

H_0: The rank sums of the five test articles are identical.
H_a: At least two of the rank sums differ.

If significant differences ($p>0.05$) were found, Fisher's LSD test was performed. In addition, the average number of days until a removal grade score was reached for each test article was calculated and analyzed using analysis of variance techniques.

Results:

Patient Enrollment:

Fifty individuals were screened for entry into the study. Of these, thirty-eight subjects were enrolled. Twenty-seven completed the study and all individual visits. Subjects ranged in age from 18 to 60, with the majority in the 20-49 group. Most (89.5%) were Caucasian. The sex of the subjects is not specified in the report although both men (6) and women (32) were enrolled.

Adverse Event Monitoring:

All but 2 subjects experienced an adverse event. The most frequent was headache. In addition, several subjects complained of burning itching and sensitization-like sensation at their patch sites. The events whose relationship to study drug was determined to be "Probable" and "Possible" are depicted in Table I and II.

Table I. Adverse Events - "Probable" relationship to study drug

Adverse Event	# of Subjects	Mild	Moderate	Severe	# of Occurrences
Headache	40	217	77	57	351
Faint Feeling	1	0	0	1	1
Heart Racing	1	1	0	0	1
Fatigue	1	0	0	1	1
Skin					36
Sensitization-like reactions A, B, C	1	0	0	1	1
Sensitization-like reactions A and B	1	0	0	1	1
Itching Site A	3	3	3	0	6
Itching Site B	2	1	2	0	3
Itching Site D	3	5	3	0	8
Itching Site E	1	1	1	0	2

Adverse Events	# of Subjects	Mild	Moderate	Severe	# of Occurrences
Itching Site A/B	1	1	0	1	2
Itching Site A, B, C	1	0	0	1	1
Burning Site A	4	2	1	4	7
Burning Site D	2	1	2	2	5

Table II. Adverse Events - "Possible" relationship to study drug

Adverse Event	# of Subjects	Mild	Moderate	Severe	# of Occurrences
Nausea	12	4	3	10	17
Lightheadedness	5	2	0	3	5
Dizziness	2	0	2	0	2
Upper Body Muscle Tightness	1	0	0	1	1
Body Aches	1	1	0	0	1
Neck Pain	1	1	1	0	2
Chest Tightness	1	0	1	0	1
Shortness of Breath	1	0	1	0	1
Vomiting	1	0	0	1	1
Stomach Ache	1	0	0	1	1
Sinus Congestion	1	2	0	0	2

Mean Irritation Scores:

The Friedman Rank Sum analysis showed significant differences among the test articles. The Mean Irritation Scores for the test and reference drug products only are shown in Table III. These data show that there are some differences in the scores with the

test product having a higher mean irritation score between Day 5 and Day 12. This is reflected in the difference noted between the two products in overall mean irritation score (Table IV).

Table III. Mean Irritation Scores, Daily and Overall

Evaluation Day	Test	Reference		Test	Reference
Day 1	0.1143	0.0000	Day 12	2.1667	1.7083
Day 2	0.1290	0.0000	Day 13	2.0870	1.7826
Day 3	0.3929	0.2143	Day 14	2.1818	1.8636
Day 4	0.4000	0.2667	Day 15	2.1818	1.9545
Day 5	0.6552	0.3103	Day 16	2.1905	2.0000
Day 6	0.7037	0.4074	Day 17	2.0952	2.0000
Day 7	1.0714	0.7143	Day 18	2.2857	1.9048
Day 8	1.4231	0.8846	Day 19	2.0000	1.8571
Day 9	1.6538	0.8846	Day 20	2.1905	1.8571
Day 10	1.9167	1.1250	Day 21	2.1429	2.0000
Day 11	1.9583	1.3750	Overall	28.6111	22.2778

The Friedman Rank Sum test was set to determine whether any two of the test articles differed at each time point. The Fisher's LSD test provided more discriminant analysis of which articles differed at which time point. Table IV shows this analysis and reports on comparisons of all the test articles.

Table IV. Fisher's LSD Test Significant Comparisons

B	Days 5-12 Overall			
C	Days 7-21 Overall	Days 2, 11-19		
D	Days 2-9 Overall	Days 2-14, 16-21 Overall	Days 3-21 Overall	
E	Days 3-16 Overall	Days 7-21 Overall	Days 2,5-21 Overall	Days 2-21 Overall
TEST ARTICLE	A	E	C	D

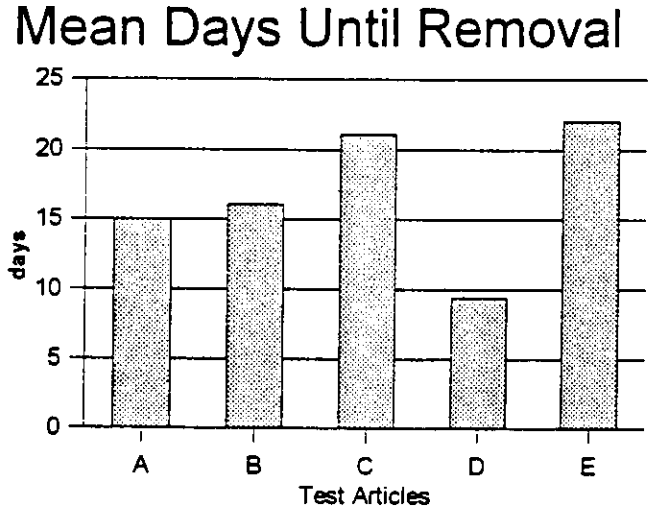
A = Mylan Nitroglycerin TDS
B = Nitro-Dur TDS
C = Mylan Placebo TDS
D = Sodium Lauryl Sulfate
E = Normal Saline

This analysis does not indicate which product has a significantly higher score at the time points at which they differ. This information is provided in the composite table of daily mean irritation scores. The table has been partially reproduced in this review to show the scores for the items of interest, the test and the reference products. The test patch had higher scores at the time points listed above in Table IV. The Mylan placebo patch had lower scores than the test or the reference patch. As expected, the high irritancy control, SLS, was more irritating than the other products and the low irritancy control, Normal Saline, was less irritating.

Mean Days Until Removal:

The mean number of days until a subject developed a skin reaction which was of such severity that the application of patches to that site had to be stopped was used as another measure of the irritation potential of the test articles. The comparative data is shown below in Figure 1.

Figure 1.



Both the test and reference product were similar in this measure of skin irritation. On average, subjects could wear the test patch for 15 days before they developed sufficient irritation to indicate that the patch had to be removed. Subjects wore the reference patch for 16.07 days. This difference was not found to be statistically significant.

Daily Irritation Score:

The proportion of subjects with each letter and number score daily is depicted for both the test and the reference products in the Figures below. Once a score of 3 or greater was achieved, this score was assigned for the duration of the study.

Figure 2.

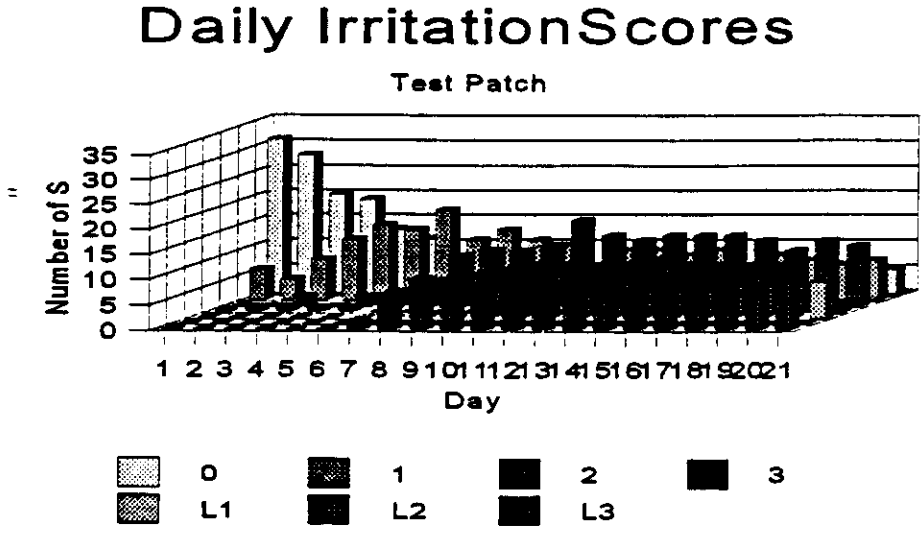
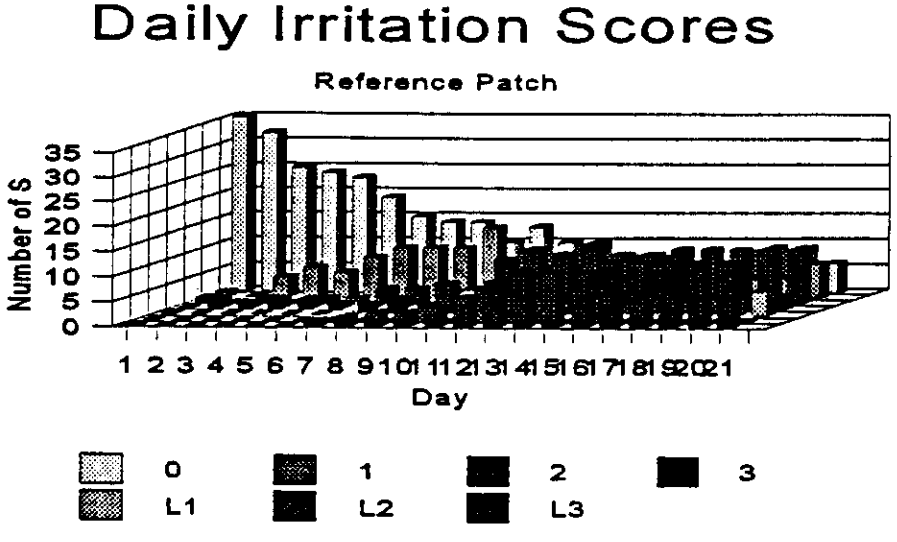


Figure 3.



These figures confirm that the test patch elicits earlier irritation, Grade 1, than does the reference patch as well as Grade 2 to some degree. However, the reference patch has slightly more Grade 3 irritation throughout the observation period. The test patch overall elicits more Grade 2 responses in the last two weeks of the study than the reference patch which has a higher rate of letter Grade 3 responses. These figures confirm the similarity overall of the irritation responses and therefore, the validity of using the Mean Days Until Removal Grade comparison to decide on comparability of the irritation potential of the two products.

DISCUSSION:

This study compared the Mylan Nitroglycerin Transdermal System with its reference listed drug, Nitro-Dur, for skin irritation in a 21-day cumulative skin irritation study. The results indicate that both patches are more irritating than the Mylan placebo patch and the low irritancy control, Normal Saline, and more irritating than the high irritancy control, SLS. The test patch was found to lead to higher mean daily irritancy scores between Days 5 and 12 compared to the reference patch. Subsequently, they had comparable mean daily scores. Both products have a similar average time until removal is indicated because of significant irritation. The profile of daily scores shows some initial disproportionate increase in irritation of the test patch to a Grade 1 primarily and subsequent equalization of the irritation of the two products.

RECOMMENDATION:

This study indicates that the test and reference Nitroglycerin patches have comparable cumulative skin irritation.

/S/

Mary M. Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs

MEDICAL OFFICER REVIEW

Date: February 25, 1998

ANDA #75-073, 75-075, 75-076 and 74-992

Product: Nitroglycerin Transdermal Systems, 0.2 mg/hr, 0.4 mg/hr, 0.1 mg/hr and 0.6 mg/hr

Firm: Bertek

The skin irritation study submitted for ANDA 74-559 has been referenced for these applications to fulfill the bioequivalence requirement for a skin irritation study. This study cannot be referenced to waive the skin irritation study requirement for the above stated applications. The skin irritation study submitted for ANDA 74-559 is not an adequate assessment of the relative cumulative skin irritation of the test product compared to the reference product by 1998 standards for the following reasons:

A. The study should have a randomized, double-blind controlled design.

B. The study should compare the cumulative skin irritation of the test product and the reference listed drug.

C. The study duration should be 21 days to evaluate cumulative irritation. Patches should remain in place for at least 23 hours each day.

D. The skin irritation scores should be determined daily throughout the study using a validated scoring system. This should include erythema and edema, at a minimum, and other signs of irritation which can include scaling, papules or vesicles, et al. at the site of application. The validation process for the current scoring system should be described if this is to be used.

/S/

Mary M. Fanning, MD, Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-992

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-992

3. NAME AND ADDRESS OF APPLICANT
Mylan Technologies, Inc
Attention: Elizabeth Ash
110 Lake Street
St. Albans, VT 05478

4. LEGAL BASIS for ANDA SUBMISSION
Reference Drug: Nitro-Dur/Key Pharmaceuticals, Inc.
Patent and Exclusivity - Paragraph IV Patent Challenge/Patent 5,186,938 Expires **2/16/2010**, Key Pharmaceuticals has brought an action against Bertek for patent infringement on **8/11/97** (as per Key letter dated **8/20/97**).
Patent Certification - page **8**.
Basis for Submission - page **6**.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Nitroglycerin Transdermal System 0.6 mg/hr.

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
10/25/96 - Original Submission
12/10/96 - Amendment
4/23/97 - New Correspondence.
Undated - New Correspondence (BIO, Received **5/9/97**).
6/11/97 - New Correspondence (Labels/labeling).
Undated - Amendment (Dated **7/2/97**, on the Form FDA 356h. Received **7/3/97**).
8/14/97 - Amendment.
8/20/97 - New Correspondence.
2/12/98 - Amendment (Labels/labeling).
4/16/98 - Amendment (BIO).

8/28/98 - Amendment (BIO).
9/17/98 - Amendment.
9/17/98 - Amendment (Labels/labeling).
2/19/99 - NC from Schering-Plough (Patent issue).
3/22/99 - NC from Schering-Plough (Patent issue).
9/16/99 - Amendment (**Subject of this review**).

FDA:

1/3/97 - Acceptable for filing.
5/29/97 - NA MINOR/FAX.
11/25/97 - BIO Deficiency FAX.
2/27/98 - BIO Deficiency FAX.
6/9/98 - BIO (Protocol acceptable).
6/22/98 - Chemistry FAX (Chemistry Sat., but, response is necessary for BIO MAJOR FAX of **2/27/98**.
6/3/99 - FAX.

10. PHARMACOLOGICAL CATEGORY
Antiangina and coronary artery disease

11. Rx or OTC
R_x

12. RELATED IND/NDA/DMF(s)
75-073 (0.2 mg/hr.), 75-075 (0.4 mg/hr.), 75-076 (0.1 mg/hr.), 74-559 (0.6 mg/hr.) - Mylan Nitroglycerin Transdermal System.
NDA 20-145 - Key Pharmaceuticals
See DMF list, review element 37.

13. DOSAGE FORM
Transdermal Patch

14. POTENCY
0.6 mg/hr.

15. CHEMICAL NAME AND STRUCTURE
1,2,3-propanetriol trinitrate (See USP for structure).
M.W. 227.09

16. RECORDS AND REPORTS:
N/A

17. COMMENTS:
The **3/22/99**, NC from submitted on behalf of their wholly owned subsidiary Key Pharmaceuticals includes a copy of the **3/15/99**, U.S. District Judge for the Western District of Pennsylvania Joint Stipulation and Order of Dismissal for infringement on the Key patent for Nitro-Dur patches. Key waives any/all objections and consents to approval by the FDA of this and companion ANDA's.

9/16/99, Amendment: This was sent to all 4 ANDA's, and addresses the outstanding issues for this ANDA in our NA FAX dated **6/3/99**. The cited #'s are from the NA FAX. Each is followed by the applicant's response in sections 28., 29., and 32. of this review.

This ANDA is a companion to ANDA's
submitted by Mylan née Bertek. Review of this ANDA was conducted with reference to ANDA's
to ensure consistency in the review process.

The firm had resolved all issues concerning the CMC sections of the ANDA's ANDA's the time of Review # 2.

1. CMC - Satisfactory .
2. Labels/Labeling - Satisfactory per A. Vezza review dated **9/24/99**.
3. BIO - Acceptable per D. Conner review dated **12/23/98**.
4. EER - Acceptable, through **12/9/97**, and update on **9/3/99**.
5. MV - will not be requested since the methods were validated for ANDA **74-559** which is incorporated by reference in this ANDA.

18. CONCLUSIONS AND RECOMMENDATIONS:
Recommend Approval.

19. REVIEWER:
Robert C. Pernisohn
/S/

DATE COMPLETED:
9/30/99
9/30/99
10/26/99

Page(s) 25

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

10/20/99.

Chemistry Review

#3

Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

6/3/99

Chemistry Community

#38

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

6/22/98.

Chemistry Comments

#3P

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

5/29/97

Chemistry Comments

#38

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-992

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-992 SPONSOR :Bertek Pharmaceuticcal
DRUG & DOSAGE FORM : Nitroglycerin Transdermal Patch
STRENGTH (s) : 0.6 mg/hr
TYPE OF STUDY:SD
STUDY SITE: CLINICAL :Drug Studies Unit Morgantown W.Va. ANALYTICAL :Drug Studies Unit, Morgantown W.Va

STUDY SUMMARY :Parameters for Parent-Metabolites Not Given but Acceptable

Parameter	test	ref	ratio	90% CI (log).
Cmax(ng/ml)	0.55	0.48	1.14	105-121
AUC(0-T) ngxhr/ml	3.74	3.31	1.13	102-119
AUC(0-Inf)ngxhr/ml	3.97	3.72	1.07	101-121
Tmax hr	6.85	8.1		
Half-life hr	0.35	0.36		

DISSOLUTION :
Conditions:Paddle over disk in 600ml water

Time(min)	Test Mean(range)	Ref. Mean(range)
30	64(62-66)	45(43-46)
60	78(76-80)	63(61-64)
120	91(89-92)	77(76-78)
240	95(94-97)	83(82-84)

Q = NLT 85% in 4 hr

PRIMARY REVIEWER :Andre Jackson BRANCH :I

INITIAL : /S/ DATE : 1/12/98

BRANCH CHIEF : Y.C. Huang BRANCH :I

INITIAL : /S/ DATE : 1/12/98

DIRECTOR Dale P. Conner
DIVISION OF BIOEQUIVALENCE
INITIAL : /S/ DATE : 1/12/98

OFFICE OF GENERIC DRUGS
INITIAL : /S/ DATE :

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-992
75-075
75-073
75-076

APPLICANT: Bertek, Inc.

DRUG PRODUCT: Nitroglycerin Transdermal Systems, 0.6mg/hr, 0.4mg/hr, 0.2mg/hr, 0.1mg/hr

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

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-992
75-075
75-073
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APPLICANT: Bertek, Inc.

DRUG PRODUCT: Nitroglycerin Transdermal Systems, 0.6mg/hr, 0.4mg/hr, 0.2mg/hr, 0.1mg/hr

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

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

FEB 27 1998

3.1

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-073, -075, 076 and 74-992 APPLICANT: Bertek

DRUG PRODUCT: Nitroglycerin Transdermal Systems, 0.2 mg/hr, 0.4 mg/hr, 0.1 mg/hr, and 0.6 mg/hr

The Division of Bioequivalence provides the following comments for your consideration:

The skin irritation study submitted for ANDA 74-559 can not be referenced to waive this study for the above stated applications. The skin irritation study submitted for ANDA 74-559 is not an adequate assessment of the relative cumulative skin irritation of the test product compared to the reference product by 1998 standards for the following reasons:

A. The study should have a randomized, double-blind controlled design.

B. The study should compare the cumulative skin irritation of the test product and the reference listed drug.

C. The study duration should be 21 days to evaluate cumulative irritation. Patches should remain in place for at least 23 hours each day.

D. The skin irritation scores should be determined daily throughout the study using a validated scoring system. This should include erythema and edema, at a minimum, and other signs of irritation which can include scaling, papules or vesicles, et al. at the site of application. The validation process for the current scoring system should be described if this is to be used.

Sincerely yours,

/S/

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

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-073, -075, 076 and 74-992 APPLICANT: Bertek

DRUG PRODUCT: Nitroglycerin Transdermal Systems, 0.2 mg/hr, 0.4 mg/hr, 0.1 mg/hr, and 0.6 mg/hr

The Division of Bioequivalence provides the following comments for your consideration:

The skin irritation study submitted for ANDA 74-559 can not be referenced to waive this study for the above stated applications. The skin irritation study submitted for ANDA 74-559 is not an adequate assessment of the relative cumulative skin irritation of the test product compared to the reference product by 1998 standards for the following reasons:

A. The study should have a randomized, double-blind controlled design.

B. The study should compare the cumulative skin irritation of the test product and the reference listed drug.

C. The study duration should be 21 days to evaluate cumulative irritation. Patches should remain in place for at least 23 hours each day.

D. The skin irritation scores should be determined daily throughout the study using a validated scoring system. This should include erythema and edema, at a minimum, and other signs of irritation which can include scaling, papules or vesicles, et al. at the site of application. The validation process for the current scoring system should be described if this is to be used.

Sincerely yours,

/S/

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74992
APPLICANT:Bertek Pharmaceuticals

DRUG PRODUCT: Nitroglycerin Transdermal Patch

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 600 mL of water , at 37 C using paddle over disk at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the drug in the dosage form is dissolved in 4 hours.

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

Nitroglycerin Transdermal Patch	Bertek Pharmaceutical
ANDA # 74-992-0.6 mg/hr	St. Albans, Vt.
Reviewer: Andre Jackson	Submission Dated:
WP# 74992A.D97	December ~~13~~ 12, 1997

Review of Amendment

The firm submitted an ANDA #74-992 on October 25, 1996 for their 0.6 mg/hr patch versus Key Nitro-Dur. The study was found to be incomplete and the firm has responded to the cited deficiencies in the current submission.

FDA COMMENT 1:

Please present a comparison of the performance of the four instruments GC01, GC02,, GC3A and GC3B used to analyze the plasma samples.

Bertek Response

Analyte	Standard Curve Range	Limit of Quantitation
Nitroglycerin (NITR)	0 - 2.5 ng/ml	0.025 ng/ml (25 pg/ml)
Glyceryl 1,2-dinitrate (1,2-GDN)	0 - 10 ng/ml	0.100 ng/ml (100 pg/ml)
Glyceryl 1,3-dinitrate (1,3-GDN)	0 - 10 ng/ml	0.100 ng/ml (100 pg/ml)

A comparison of instrument performance for extracted biological matrix samples can best be made by looking at the accuracy and precision of both quality control samples and back calculated concentrations of standard curve points generated during the course of the biostudy. This summary data can be found in Tables 4A, 4B and 4C of the analytical report. They are included here as Attachment 1. Additionally the data is also grouped by instrument. These data are presented in Tables 1 through 6 of this response (Appendix I). Attachment 2 contains the raw data found in the analytical report.

The data presented in summary tables 4A, 4B and 4C of Attachment 1 demonstrate a consistent level of performance for all instruments used during the course of the biostudy with a coefficient of variation (CV) of 11.2% or less. The data grouped by instrument, and presented in Tables 1 through 6, again demonstrates consistent performance between each of the instruments used during the course of the biostudy. The CV for this data set is 6.2% or less.

Table 7 presents a comparison of the mean slopes for each instrument. This is a direct function of the analyte/internal standard peak response ratio. These data show a consistent analyte/internal standard response ratio across the four instruments used during the three month period of analysis with a CV of 7.3% or less. Individual slope data can be found in Tables 1A, 1 B and 1 C of the analytical report. They are included here as Attachment 3.

In **summary, the data presented in** Tables 1 through 6 of this response and Tables 4A, 4B and 4C in Attachment 1 demonstrate a consistent level of performance within all instruments used during the course of the biostudy. The data also show a consistent level of performance between each instrument used during the course of the biostudy. This was accomplished by observing the back calculated concentrations of both standard curve and quality control samples. Additionally, a comparison was made of mean slope for each instrument which is a reflection of the analyte/internal standard peak response. Again, the data in Table 7 show a consistent response for each analyte and each instrument.

FDA Response

The firm's response to FDA Comment 1 is acceptable.

FDA COMMENT 2:

Please submit stability data to cover the 123 day period of storage for the repeat samples. The data submitted only covered 68 days.

Bertek Response

Long term frozen stability was initiated on June 27, 1996 at -70°C. At the time of submission for the referenced biostudy long-term frozen stability was an active ongoing project with 68 days of frozen stability accumulated and reported in the analytical report. The analysis of long-term frozen stability was complete November 11, 1996 when 137 days of frozen stability had been accumulated. Please reference Attachment 4 (Appendix II) to find the amended validation table demonstrating frozen stability of NITR, 1,2-GDN and 1,3-GDN for a period of 137 days.

FDA Response

The firm's response to FDA Comment 2 is acceptable.

FDA COMMENT 3:

The Division of Bioequivalence would like to propose the following interim dissolution specifications based upon the data submitted, since the dissolution specifications you have proposed underestimate the product's dissolution characteristics:

However, if you have additional data to support your proposed dissolution specifications, you should submit the data to the Division for review.

Bertek Response

As requested, Bertek has revised the Nitroglycerin Transdermal System specifications to those listed above. Attachment 5 contains copies of both the revised drug product specifications and the post-approval stability protocol which was also affected by the change in dissolution specifications. (Please note that the term, "Dissolution," has been revised to, "Drug Release," in order to reflect the current USP terminology.)

FDA Response

The firm's response to FDA Comment 3 is acceptable.

Recommendation

The bioequivalence study conducted by Bertek Pharmaceutical on its 0.6 mg/hr transdermal nitroglycerin patch, lot no. 26C010B, comparing it to Key Pharmaceuticals Nitro-Dur 0.6 mg/hr patch Lot No. D5005513 has been found to be acceptable by the Division of Bioequivalence. Therefore, the transdermal nitroglycerin patch 0.6 mg/hr manufactured by Bertek Pharmaceutical should be deemed bioequivalent to Nitro-Dur 0.6 mg/hr transdermal patch manufactured by Key Pharmaceuticals.

Andre Jackson, Ph.D. /S/
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/ : 1/9/98

Concur: /S/ Date: 1/9/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Appendix II

Table 1

Comparison of Mean Back Calculated Standard Curve Concentrations (by Instrument)
NITROGLYCERIN (NITR)

NITR (ng/ml)	GC01	GC02	GC3A	GC3B	Mean	Std. Dev.	% CV
0.025	0.024	0.023	0.023	0.024	0.024	0.0006	2.5
0.050	0.053	0.054	0.052	0.051	0.053	0.0013	2.5
0.100	0.109	0.117	0.115	0.109	0.113	0.0041	3.6
0.200	0.211	0.224	0.207	0.207	0.212	0.0081	3.8
0.250	0.263	0.265	0.252	0.253	0.258	0.0067	2.6
0.500	0.505	0.519	0.524	0.501	0.512	0.0110	2.1
1.000	0.973	0.946	0.976	1.018	0.978	0.0297	3.0
2.000	1.833	1.694	1.897	1.837	1.824	0.0908	5.0
2.500	2.277	2.100	2.124	2.352	2.213	0.1213	5.5

Table 2

Comparison of Mean Back Calculated Standard Curve Concentrations (by Instrument)
GLYCERYL 1,2-DINITRATE (1,2-GDN)

1,2-GDN (ng/ml)	GC01	GC02	GC3A	GC3B	Mean	Std. Dev.	% CV
0.100	0.096	0.093	0.096	0.095	0.095	0.0014	1.5
0.200	0.210	0.211	0.207	0.217	0.211	0.0042	2.0
0.400	0.420	0.451	0.441	0.415	0.432	0.0171	4.0
0.800	0.816	0.866	0.803	0.814	0.825	0.0281	3.4
1.000	1.026	1.016	0.979	0.963	0.996	0.0299	3.0
2.000	1.943	1.992	2.020	1.884	1.960	0.0597	3.0
4.000	3.853	3.681	3.821	3.915	3.818	0.0990	2.6
8.000	7.797	7.402	8.277	7.943	7.855	0.3626	4.6
10.000	9.819	9.510	9.200	10.282	9.703	0.4615	4.8

Table 3

Comparison of Mean Back Calculated Standard Curve Concentrations (by Instrument)
GLYCERYL 1,3-DINITRITE (1,3-GDN)

1,3-GDN (ng/ml)	GC01	GC02	GC3A	GC3B	Mean	Std. Dev.	% CV
0.100	0.096	0.094	0.098	0.099	0.097	0.0022	2.3
0.200	0.209	0.213	0.206	0.208	0.209	0.0029	1.4
0.400	0.424	0.443	0.427	0.392	0.422	0.0214	5.1
0.800	0.807	0.838	0.783	0.808	0.809	0.0225	2.8
1.000	1.007	0.983	0.946	0.936	0.968	0.0329	3.4
2.000	1.926	1.919	1.948	1.905	1.925	0.0179	0.9
4.000	3.841	3.730	3.863	3.992	3.857	0.1075	2.8
8.000	7.918	7.784	8.919	8.220	8.210	0.5065	6.2
10.000	9.977	9.926	9.388	10.654	9.986	0.5188	5.2

Table 4

Comparison of Mean Quality Control Concentrations (by Instrument)
NITROGLYCERIN (NITR)

NITR (ng/ml)	GC01	GC02	GC3A	GC3B	Mean	Std. Dev.	% CV
0.100	0.108	0.116	0.113	0.111	0.112	0.0034	3.0
2.500	0.259	0.274	0.269	0.261	0.266	0.0070	2.6
1.000	0.951	0.942	0.978	0.993	0.966	0.0236	2.4

Table 5

Comparison of Mean Quality Control Concentrations (by Instrument)
GLYCERYL 1,2-DINITRITE (1,2-GDN)

1,2-GDN (ng/ml)	GC01	GC02	GC3A	GC3B	Mean	Std. Dev.	% CV
0.400	0.433	0.455	0.438	0.427	0.438	0.0120	2.7
1.000	1.012	1.043	1.037	1.005	1.024	0.0186	1.8
4.000	3.757	3.671	3.876	3.922	3.807	0.1140	3.0

Table 6

Comparison of Mean Quality Control Concentrations (by Instrument).
GLYCERYL 1,3-DINITRITE (1,3-GDN

1,3-GDN (ng/ml)	GC01	GC02	GC3A	GC3B	Mean	Std. Dev.	% CV
0.400	0.422	0.441	0.426	0.418	0.427	0.0100	2.3
1.000	0.985	1.023	0.998	0.987	0.998	0.0175	1.8
4.000	3.741	3.717	3.934	4.001	3.848	0.1407	3.7

Table 7

Comparison of Mean Slope for Each Instrument

Instrument	NITR	1,2-GDN	1,3-GDN
GC01	0.36109	0.33884	0.39980
GC02	0.39942	0.33896	0.39743
GC3A	0.38001	0.35590	0.42080
GC3B	0.42787	0.34842	0.36960
Mean	0.39210	0.34553	0.39691
Std. Dev.	0.02852	0.00824	0.02102
% CV	7.3	2.4	5.3

Appendix II

STABILITY OF DRUG AND METABOLITES IN FROZEN PLASMA

The stability of nitroglycerin (NITR) and its two dinitrate metabolites (1,2-GDN and 1,3-GDN) was assessed by the quantitation of spiked plasma samples which were frozen during sample analysis. These frozen stability samples were assayed over the duration of the study; they contained approximate concentrations of 1.0 ng/ml (high) and 0.1 ng/ml (low) for NITR and 4.0 ng/ml (high) and 0.4 ng/ml (low) for 1,2-GDN and 1,3-GDN metabolites.

Assay results (Tables 1, 2 and 3) demonstrate the stability of NITR, 1,2-GDN and 1,3 GDN in frozen plasma for 137 days. Clinical samples for the NITR-9621 biostudy were first frozen 04/28/96 and last extracted 08/29/96. The encompassing time the samples were frozen was 123 days.

Table 1

NITROGLYCERIN (NITR-9621)
Frozen Nitroglycerin Plasma Stability

Days Stability	1.0 (ng/ml)	0.1 (ng/ml)
0		
.0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
68		
68		
68		
68		
68		
68		
137		
137		
137		
137		
137		
137		
N=	23	24
MEAN=	1.033	0.111
STD=	0.117	0.014
%CV=	11.361	12.451
%ERROR=	0.024	0.003

Day	Conc (ng) ml	$\bar{x}$ (ng) ml	% Diff
0	1.0	1.041	------
	0.1	0.111	------
68	1.0	1.101	(+) 5.76
	0.1	0.114	(+) 2.70
137	1.0	0.948	(-) 8.93
	0.1	0.109	(-) 1.80

Table 2

NITROGLYCERIN (NITR-9621)
Frozen 1,3 GDN Plasma Stability

Days Stability	4 (ng/ml)	0.4 (ng/ml)
0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
68		
68		
68		
68		
68		
68		
137		
137		
137		
137		
137		
137		
N=	23	24
MEAN=	4.139	0.425
STD=	0.506	0.042
%CV=	12.222	9.952
%ERROR=	0.105	0.009

Day	Conc (ng) ml	$\bar{x}$ (ng) ml	% Diff
0	4.0	4.303	------
	0.4	0.425	------
68	4.0	4.354	(+) 1.19
	0.4	0.456	(+) 7.29
137	4.0	3.622	(-) 15.83
	0.4	0.395	(-) 7.06

Table 3

NITROGLYCERIN (NITR-9621)
Frozen 1,2 GDN Plasma Stability

Days Stability	4 (ng/ml)	0.4 (ng/ml)
0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
68		
68		
68		
68		
68		
68		
137		
137		
137		
137		
137		
137		

N=	23	24
MEAN=	4.130	0. 31
STD=	0.472	0.)47
%CV=	11.423	10.)71
%ERROR=	0.098	0.)10

Day	Conc (ng) ml	$\bar{x}$ (ng) ml	% Diff
0	4.0	4.268	------
	0.4	0.423	------
68	4.0	4.300	(+) 0.75
	0.4	0.477	(+) 12.77
137	4.0	3.707	(-) 13.14
	0.4	0.401	(-) 5.20

BERTEK

DEC 15 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

BIOEQUIVALENCY AMENDMENT
(INCLUDES CMC INFORMATION)

Re: Nitroglycerin Transdermal System, 0.6 mg/hr ANDA #74-992
Response to Agency Correspondence Dated November 25, 1997

Dear Mr. Sporn,

Reference is made to the Abbreviated New Drug Application identified above and to the Agency correspondence submitted via facsimile on November 25, 1997 which contained deficiencies with regard to the bioequivalence information submitted in the application. In response to the November 25, 1997 letter, Bertek wishes to amend this application with the following:

FDA COMMENT 1:

Please present a comparison of the performance of the four instruments GC01, GC02,, GC3A and GC3B used to analyze the plasma samples.

BERTEK RESPONSE:

Analyte	Standard Curve Range	Limit of Quantitation
Nitroglycerin (NITR)	0 - 2.5 ng/ml	0.025 ng/ml (25 pg/ml)
Glyceryl 1,2-dinitrate (1,2-GDN)	0 - 10 ng/ml	0.100 ng/ml (100 pg/ml)
Glyceryl 1,3-dinitrate (1,3-GDN)	0 - 10 ng/ml	0.100 ng/ml (100 pg/ml)

A comparison of instrument performance for extracted biological matrix samples can best be made by looking at the accuracy and precision of both quality control samples and back calculated concentrations of standard curve points generated during the course of the biostudy. This summary data can be found in Tables 4A, 4B and 4C of the analytical report. They are included here as Attachment 1. Additionally the data is also grouped by instrument. These data are presented in Tables 1 through 6 of this response. Attachment 2 contains the raw data found in the analytical report.

The data presented in summary tables 4A, 4B and 4C of Attachment 1 demonstrate a consistent level of performance for all instruments used during the course of the biostudy with a coefficient of variation (CV) of 11.2% or less. The data grouped by instrument, and presented in Tables 1 through 6, again demonstrates consistent performance between each of the instruments used during the course of the biostudy. The CV for this data set is 6.2% or less.

Table 7 presents a comparison of the mean slopes for each instrument. This is a direct function of the analyte/internal standard peak response ratio. These data show a consistent analyte/internal standard response ratio across the four instruments used during the three month period of analysis with a CV of 7.3% or less. Individual slope data can be found in Tables 1A, 1B and 1C of the analytical report. They are included here as Attachment 3.

In summary, the data presented in Tables 1 through 6 of this response and Tables 4A, 4B and 4C in Attachment 1 demonstrate a consistent level of performance within all instruments used during the course of the biostudy. The data also show a consistent level of performance between each instrument used during the course of the biostudy. This was accomplished by observing the back calculated concentrations of both standard curve and quality control samples. Additionally, a comparison was made of mean slope for each instrument which is a reflection of the analyte/internal standard peak response. Again, the data in Table 7 show a consistent response for each analyte and each instrument.

FDA COMMENT 2:

Please submit stability data to cover the 123 day period of storage for the repeat samples. The data submitted only covered 68 days.

BERTEK RESPONSE:

Long term frozen stability was initiated on June 27, 1996 at -70°C. At the time of submission for the referenced biostudy long-term frozen stability was an active ongoing project with 68 days of frozen stability accumulated and reported in the analytical report. The analysis of long-term frozen stability was complete November 11, 1996 when 137 days of frozen stability had been accumulated. Please reference Attachment 4 to find the amended validation table demonstrating frozen stability of NITR, 1,2-GDN and 1,3-GDN for a period of 137 days.

FDA COMMENT 3:

The Division of Bioequivalence would like to propose the following interim dissolution specifications based upon the data submitted, since the dissolution specifications you have proposed underestimate the product's dissolution characteristics:

However, if you have additional data to support your proposed dissolution specifications, you should submit the data to the Division review.

BERTEK RESPONSE:

As requested, Bertek has revised the Nitroglycerin Transdermal System specifications to those listed above. Attachment 5 contains copies of both the revised drug product specifications and the post-approval stability protocol which was also affected by the change in dissolution specifications. (Please note that the term, "Dissolution," has been revised to, "Drug Release," in order to reflect the current USP terminology.)

Table 1

Comparison of Mean Back Calculated Standard Curve Concentrations (by Instrument)
NITROGLYCERIN (NITR)

NITR (ng/ml)	GC01	GC02	GC3A	GC3B	Mean	Std. Dev.	% CV
0.025	0.024	0.023	0.023	0.024	0.024	0.0006	2.5
0.050	0.053	0.054	0.052	0.051	0.053	0.0013	2.5
0.100	0.109	0.117	0.115	0.109	0.113	0.0041	3.6
0.200	0.211	0.224	0.207	0.207	0.212	0.0081	3.8
0.250	0.263	0.265	0.252	0.253	0.258	0.0067	2.6
0.500	0.505	0.519	0.524	0.501	0.512	0.0110	2.1
1.000	0.973	0.946	0.976	1.018	0.978	0.0297	3.0
2.000	1.833	1.694	1.897	1.837	1.824	0.0908	5.0
2.500	2.277	2.100	2.124	2.352	2.213	0.1213	5.5

Table 2

Comparison of Mean Back Calculated Standard Curve Concentrations (by Instrument)
GLYCERYL 1,2-DINITRITE (1,2-GDN)

1,2-GDN (ng/ml)	GC01	GC02	GC3A	GC3B	Mean	Std. Dev.	% CV
0.100	0.096	0.093	0.096	0.095	0.095	0.0014	1.5
0.200	0.210	0.211	0.207	0.217	0.211	0.0042	2.0
0.400	0.420	0.451	0.441	0.415	0.432	0.0171	4.0
0.800	0.816	0.866	0.803	0.814	0.825	0.0281	3.4
1.000	1.026	1.016	0.979	0.963	0.996	0.0299	3.0
2.000	1.943	1.992	2.020	1.884	1.960	0.0597	3.0
4.000	3.853	3.681	3.821	3.915	3.818	0.0990	2.6
8.000	7.797	7.402	8.277	7.943	7.855	0.3626	4.6
10.000	9.819	9.510	9.200	10.282	9.703	0.4615	4.8

Table 3

Comparison of Mean Back Calculated Standard Curve Concentrations (by Instrument)
GLYCERYL 1,3-DINITRITE (1,3-GDN)

1,3-GDN (ng/ml)	GC01	GC02	GC3A	GC3B	Mean	Std. Dev.	% CV
0.100	0.096	0.094	0.098	0.099	0.097	0.0022	2.3
0.200	0.209	0.213	0.206	0.208	0.209	0.0029	1.4
0.400	0.424	0.443	0.427	0.392	0.422	0.0214	5.1
0.800	0.807	0.838	0.783	0.808	0.809	0.0225	2.8
1.000	1.007	0.983	0.946	0.936	0.968	0.0329	3.4
2.000	1.926	1.919	1.948	1.905	1.925	0.0179	0.9
4.000	3.841	3.730	3.863	3.992	3.857	0.1075	2.8
8.000	7.918	7.784	8.919	8.220	8.210	0.5065	6.2
10.000	9.977	9.926	9.388	10.654	9.986	0.5188	5.2

Table 4

Comparison of Mean Quality Control Concentrations (by Instrument)
NITROGLYCERIN (NITR)

NITR (ng/ml)	GC01	GC02	GC3A	GC3B	Mean	Std. Dev.	% CV
0.100	0.108	0.116	0.113	0.111	0.112	0.0034	3.0
2.500	0.259	0.274	0.269	0.261	0.266	0.0070	2.6
1.000	0.951	0.942	0.978	0.993	0.966	0.0236	2.4

Table 5

Comparison of Mean Quality Control Concentrations (by Instrument)
GLYCERYL 1,2-DINITRITE (1,2-GDN)

1,2-GDN (ng/ml)	GC01	GC02	GC3A	GC3B	Mean	Std. Dev.	% CV
0.400	0.433	0.455	0.438	0.427	0.438	0.0120	2.7
1.000	1.012	1.043	1.037	1.005	1.024	0.0186	1.8
4.000	3.757	3.671	3.876	3.922	3.807	0.1140	3.0

Table 6

Comparison of Mean Quality Control Concentrations (by Instrument)
GLYCERYL 1,3-DINITRITE (1,3-GDN

1,3-GDN (ng/ml)	GC01	GC02	GC3A	GC3B	Mean	Std. Dev.	% CV
0.400	0.422	0.441	0.426	0.418	0.427	0.0100	2.3
1.000	0.985	1.023	0.993	0.987	0.998	0.0175	1.8
4.000	3.741	3.717	3.934	4.001	3.848	0.1407	3.7

Table 7

Comparison of Mean Slope for Each Instrument

Instrument	NITR	1,2-GDN	1,3-GDN
GC01	0.36109	0.33884	0.39980
GC02	0.39942	0.33896	0.39743
GC3A	0.38001	0.35590	0.42080
GC3B	0.42787	0.34842	0.36960
Mean	0.39210	0.34553	0.39691
Std. Dev.	0.02852	0.00824	0.02102
% CV	7.3	2.4	5.3

For ease of review, a copy of the Agency's correspondence, dated November 25, 1997, is provided in Attachment 6.

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

If you have questions regarding this amendment or require additional information, please contact the undersigned.

Sincerely,

Elizabeth Ash
for Lamont M. Fulton

Lamont M. Fulton
Manager of Regulatory Affairs

Bertek Inc.
110 Lake Street
St. Albans, VT 05478
phone: (802) 527-7792 ext. 341
fax: (802) 527-0486

NOV 25 1997

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 74-992 APPLICANT: ~~Mylan~~ Bertek Pharmaceuticals, Inc.

DRUG PRODUCT: Nitroglycerin Transdermal System, 0.6 mg/hr

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

1. Please present a comparison of the performance of the four instruments GC01, GC02 GC3A and GC3B used to analyze the plasma samples.

2. Please submit stability data to cover the 123 day period of storage for the repeat samples. The data submitted only covered 68 days.

3. The Division of Bioequivalence would like to propose the following interim dissolution specifications based upon the data submitted, since the dissolution specifications you have proposed underestimate the product's dissolution characteristics:

However, if you have additional data to support your proposed dissolution specifications, you should submit the data to the Division review.

Sincerely yours,

(S)

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

Nitroglycerin Transdermal Patch
ANDA # 74-992-0.6 mg/hr
Reviewer: Andre J. Jackson
WP# 74992SD.096

Bertek Inc
~~Mylan Pharmaceuticals~~
~~Morgantown, West Va.~~
Submission Dated:
October 25, 1996
April 23, 1997
May 9, 1997

REVIEW OF FASTING BIOEQUIVALENCE STUDY FOR 0.6 MG/HR PATCH AND DISSOLUTION DATA

Background

Nitroglycerin is 1,2,3-propanetriol trinitrate, an organic nitrate. The organic nitrates are vasodilators, active on both arteries and veins. Nitroglycerin Transdermal Infusion System is a flat unit designed to provide continuous controlled release of nitroglycerin through intact skin. The rate of release of nitroglycerin is linearly dependent upon the area of the applied system. Thus, a 30-cm(square) system for the reference product (Key Nitro-Dur) delivers approximately 0.6 mg of nitroglycerin per hour.

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle and consequent dilation of peripheral arteries and veins, especially the latter. Dilation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure.

The volume of distribution of nitroglycerin is about 3l/kg, and nitroglycerin is cleared very rapidly with a serum half-life of 3 minutes. There are believed to be extrahepatic sites of metabolism since the reported clearance rates exceed hepatic blood flow. Additional sites of metabolism include red cells and vascular walls. The first products in the metabolism of nitroglycerin are inorganic nitrate and the 1,2-and 1,3-dinitroglycerols. The dinitrates are less effective vasodilators than nitroglycerin but have longer half-lives. In healthy volunteers, steady-state plasma concentrations are reached by about 2 hours after application of a patch and are maintained for the duration of wearing the system. Upon removal of the patch, the plasma concentration declines with a half-life of about 1 hour.

The suggested starting dose is between 0.2 mg/hr and 0.4 mg/hr. Doses between 0.4 mg/hr and 0.8 mg/hr have shown continued effectiveness for 10-12 hours daily for at least one month.

Objective:

The aim of this study is to compare the transdermal absorption and elimination of a new formulation of transdermal nitroglycerin with NitroDur manufactured by Key Pharmaceuticals following transdermal application of a single 0.6 mg/hr dose to fasting volunteers.

Methods:

The study was conducted at the Clinical and Pharmacologic Research, Drug Study Unit, Morgantown, W.V. under the direction of Drs. Thomas S. Clark and Dorian Williams. Samples were analyzed by the Clinical and Pharmacologic Research, Drug Study Unit, Morgantown, W.V. under the direction of Patrick K. Noonan, Ph.D. The dosing dates were as follows:

	Treatment A	Treatment B
Period I	April 28, 1996	May 10, 1996
Period II	May 2, 1996	May 14, 1996
Period III	May 6, 1996	May 19, 1996
Period IV	May 10, 1996	May 23, 1996

Treatment A: Nitroglycerin patch (0.6 mg/hr) Mylan
Treatment B: NitroDur (0.6 mg/hr)- Key Pharmaceuticals

I. **Characterization of Study Group:**

A. **Inclusion criteria**

1. All volunteers selected for this study were male volunteers between the ages of 19 and 55 years. Weight range of the volunteers was within 10% of normal body weight relative to height and frame size.

2. Each volunteer was given a general physical examination within 2 weeks of initiation of the study. Each examination included blood pressure, general observations, history, complete hemogram (hemoglobin, hematocrit, WBC, differential), urinalysis (including microscopic), biochemistry (blood urea nitrogen, serum bilirubin [total]), HIV antibody screen. Volunteers selected for the study had no clinically significant abnormal findings.

3. Normal electrocardiogram

B. **Exclusion Criteria:**

1. Any subject who had donated blood within the past four weeks.

2. Volunteers with a history of serious systemic or organ disease, including, but not limited to, renal, gastrointestinal, hepatic or cardiovascular diseases, or mental illness.

3. History of alcohol or drug abuse.

4. Any noted EKG abnormality.

5. Hypersensitivity or idiosyncratic reaction to nitroglycerin, nitrates or topical adhesive tapes.

6. Participation in a previous clinical trial or the donation of one pint or more of blood within the past 28 days or who had received an investigational drug within that period.

7. Use of any OTC medication within 14 days.

8. Positive screen for drugs of abuse.

9. Positive HBsAg or HIV screen.

10. Subjects that smoke.

11. Exposure to known hepatic enzyme inducing or inhibiting agents within 30 days prior to the study.

12. History of headache.

13. Subjects who have ultra-violet light damage(i.e. burns, redness,peeling).

14. Subjects who have had ultra-violet light exposure without UVA/UVB block.

The consumption of alcohol- or xanthine-containing beverages and foods was prohibited for 48 hours before dosing and throughout the period of sample collection.

C. **Informed Consent:**
All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgment of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. **Study Conduct**

The study was begun in 48 healthy males with 45 subjects successfully completing the four phases of the clinical study. The clinical study was conducted as a randomized, replicate designed study(two treatment, four period single dose crossover).

A. Each treatment consisted of the application of a single transdermal nitroglycerin patch(1 x 0.6 mg/hr patch)to the subject's chest(hair was removed when required). After 12 hours the patches were removed and placed in empty foil pouches. Skin irritation was evaluated immediately following patch removal at 0.5 and 1 hour after removal. Whenever skin irritation persisted the subject was evaluated again at 3 hours after patch removal. Subjects fasted 10 hours before dosing and until four hours after their scheduled dosing times. Water was not allowed from two hours before until two hours after dosing but was allowed ad lib thereafter.

Standard meals were provided at four and approximately 10 hours after dosing.

B. The products employed in the study were:

1. Test: Mylan Pharmaceutical transdermal system
   1 patch x 0.6 mg/hr
   Lot # 26C010B
   Production lot size 310,800 patches

2. Reference product: NitroDur^{R}
   1 patch x 0.6 mg/hr
   Lot # D5005513
   Expiration Date:10/97

There was a four day washout between doses.

C. The randomization scheme is presented in Table 1.

Table 1. Random Assignment of 48 subjects

Sequence	SUBJECT
B,B,A,A	1, 8, 11, 16, 17, 21, 28, 30, 36, 39, 41, 46
B,A,A,B	2, 7, 12, 15, 19, 22, 27, 32, 34 40, 44, 47
A,B,B,A	3, 6, 9, 13, 18, 23, 26, 31, 33, 38, 42, 48

A,A,B,B	4, 5, 10, 14, 20, 24, 25, 29, 35, 37, 43, 45

Treatment A: Nitroglycerin patch (0.6 mg/hr) Mylan
Treatment B: NitroDur (0.6 mg/hr) Key Pharmaceuticals

The formulation for the 0.6 mg/hr formulation is presented in appended Table A1.

D. Following application of each product, serial plasma was collected pre-dose and at the following times post-dose: 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 12.5 and 13 hours. All samples were quick frozen and stored at -20°C.

E. During the study subjects were monitored for adverse reactions. Vital signs(including blood pressure, pulse and respiration rates were measured for safety during the study.

F. After 12 hours the patches were removed, placed in empty foil pouches and heat sealed. The alcohol wipes that were used were also heat sealed in separate pouches. The skin area was evaluated for irritation immediately following patch removal, 0.5 hours and 1 hour after removal. If irritation persisted the subject was evaluated at 3 hours after patch removal. Further evaluation was done at 12 hours and at 12 hour intervals thereafter.

III. **Analytical**

The GC/ECD assay procedure was specific for nitroglycerin and the dinitrate metabolites with no interfering chromatographic peaks. Sample and control concentrations were determined by interpolation of their peak height ratios from the standard curve obtained in the same run. The internal standard used in the assay was
The method used was
with The assay was run on four different phs. The first clinical samples were collected and frozen on 4/28/96; the last of the clinical samples were extracted 8/29/96. The time the samples were frozen was 123 days.

NITROGLYCERIN

Assay sensitivity:
The assay was linear over the range of 0.025 ng/ml to 2.5 ng/ml. The limit of sensitivity of the assay was defined as 0.025 ng/ml, with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of

standard samples assayed on different days. The coefficient of variation was 5.8% at a concentration of 0.025 ng/ml and 7.8% at 2.5 ng/ml.

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 111% at a concentration of 0.1 ng/ml and 96.3% at 1.0 ng/ml with coefficients of variation of 8.4% and 9.1% respectively.

1,2-DINITROGLYCERIN

Assay sensitivity:
The assay was linear over the range of 0.100 ng/ml to 10.0 ng/ml. The limit of sensitivity of the assay was defined as 0.100 ng/ml, with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 5.7% at a concentration of 0.10 ng/ml and 9.3% at 10.0 ng/ml.

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 109% at a concentration of 0.4 ng/ml and 94.9% at 4.0 ng/ml with coefficients of variation of 9.2 and 9.8% respectively.

1,3-DINITROGLYCERIN

Assay sensitivity:
The assay was linear over the range of 0.100 ng/ml to 10.0 ng/ml. The limit of sensitivity of the assay was defined as 0.100 ng/ml, with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 5.5% at a concentration of 0.10 ng/ml and 9.8% at 10.0 ng/ml.

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 106% at a concentration of 0.4 ng/ml and 95.7% at 4.0 ng/ml with coefficients of variation of 8.3 and 11.2% respectively.

Recovery and Stability

Recovery

Absolute recovery was assessed by comparing the peak heights of GTN, 1,2-GDN and 1,3-GDN in extracted plasma to the peak heights in standard solution. The results are presented in Table 2.

Long Term Stability -68 days

The long term stability study was done by comparing replicates of stored samples at the approximate concentrations of the low and high QC's for GTN, 1,2-GDN and 1,3-GDN over the study period. The values are presented in appended Tables 3,4 and 5 for GTN, 1,2-GDN and 1,3-GDN respectively. The actual number of days for sample storage are given in Table 6.

Freeze Thaw

The freeze thaw stability study was done by comparing replicates of stored samples of GTN, 1,2-GDN and 1,3-GDN which had been frozen and thawed 3 times at low and high concentrations. The data is presented in appended Tables 7, 8 and 9.

Processed Sample Stability

Stability of processed (extracted) and reconstituted samples was evaluated. Plasma samples were spiked with and 1,3- and extracted according to protocol. The processed samples were allowed to set at room temperature up to 72 hours before GC analysis. Samples were stable for up to 72 hours(Table 10).

Drug and Metabolite stability in Plasma at 0° C

Samples were thawed in an ice bath and analyzed and shown to be stable up to 3 hours at 0° C for up to 3 hrs. The data are presented in appended Table 11.

Reassays

77 out of 2295 samples were reanalyzed(3.2%) for analytical reasons and 50 out of 2295 (2.1%) because they were outside pharmacokinetic expectations. The data is presented in appended Table 12.

IV. **Pharmacokinetic Methodology**

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

V. **Statistical Evaluation**

The parameters were analyzed to detect for statistically significant differences in the pharmacokinetic parameters and to determine the Least Squares Means for the test to reference ratios of the pharmacokinetic parameters. An ANOVA was performed to assess the group effect. A model with terms for groups, sequences, group by sequence interaction, subjects within group by sequence interaction, carryover, treatments and periods were performed. Also, an ANOVA was performed to test for subject by treatment within sequence interaction.

Analysis is being conducted by Dr. Alfred Balch HFD-705, Quantitative Research Methods Branch, since the study was done with treatment replication.

Log-transformed data was submitted for analysis.

VI. **Results**

Table 13

Mean Nitroglycerin Plasma Concentrations (ng/mL)

	TREATMENT -Test		TREATMENT -Reference	
	MEAN	%CV	MEAN	%CV
TIME (hrs)				
0	0.002	469	0	0
0.5	0.063	165	0.081	102
1	0.210	86.5	0.164	68.4
1.5	0.264	74.5	0.196	61.5
2	0.306	76.8	0.211	60.7
2.5	0.304	72.4	0.230	59.8
3	0.344	71.7	0.247	63.8
4	0.314	70.2	0.251	70.8
5	0.295	65.1	0.245	60.8
6	0.341	61.0	0.311	60.5
8	0.357	56.0	0.324	60.2
10	0.322	69.6	0.316	67.7
12	0.333	69.1	0.334	56.7
12.5	0.062	133	0.071	102
13	0.018	148	0.023	102

Table 15

MEAN 1,2-DINITROGLYCERIN PLASMA CONCENTRATIONS (ng/ml):

	TREATMENT -Test		TREATMENT -Reference	
	MEAN	%CV	MEAN	%CV
TIME (hrs)				
0	0.00	0.00	0.00	0.00
0.5	0.258	153	0.39	109
1	1.05	67	1.03	49.3
1.5	1.73	55.8	1.43	45.6
2	2.16	52.0	1.68	43.9
2.5	2.52	52.2	1.93	39.9
3	2.74	54.3	2.16	41.6
4	2.97	45.8	2.41	38.6
5	2.91	44.9	2.38	41.0
6	2.87	43.8	2.48	40.1
8	2.96	39.8	2.75	38.2
10	2.88	42.0	2.77	41.0
12	2.51	45.1	2.46	39.7
12.5	1.76	35.2	1.79	44.2
13	1.05	40.7	1.22	69.0

TABLE 17

MEAN 1,3-DINITROGLYCERIN PLASMA CONCENTRATIONS (ng/ml):

	TREATMENT -Test		TREATMENT B-Reference	
	MEAN	%CV	MEAN	%CV
TIME (hrs)				
0	0.00	0.00	0.00	0.00
0.5	0.033	296	0.048	210
1	0.218	80.2	0.225	64.2
1.5	0.393	49.5	0.348	50.5
2	0.496	45.4	0.417	44.5
2.5	0.572	46.9	0.491	43.4
3	0.610	44.2	0.552	43.0
4	0.643	37.1	0.600	40.0
5	0.665	38.3	0.614	42.1
6	0.661	37.9	0.624	40.4
8	0.658	35.2	0.655	39.3
10	0.623	40.7	0.641	42.2
12	0.584	41.3	0.613	43.6
12.5	0.434	37.9	0.467	48.5
13	0.296	40.6	0.357	99.6

Table 14
SUMMARY STATISTICS: NITROGLYCERIN-Estimated By Firm

VARIABLE	TREATMENT		RATIO (T/R)	90% CONFIDENCE[5] INTERVAL
	Mylan	Reference		
AUCL[2] (ng/ml x hr)	3.74 ± 51.7[1]	3.31 ± 47.3	1.13	
LNAUCL[4]	1.17 ± 50.28 (3.26)[6]	1.08 ± 47.45 (2.95)	1.10	102-119%
AUCI[3] (ng/ml x hr)	3.97 ± 46.0	3.72 ± 43.7	1.07	
LNAUCI[4]	1.26 ± 39.50 (3.45)	1.21 ± 38.4 (3.12)	1.11	101-121%
CPEAK (ng/ml)	0.55 ± 47.4	0.48 ± 43.3	1.14	
LNCPEAK[4]	-0.72 ± -73.29	-0.83 ± -56.7		105-121%
KEL (hr^{-1})	2.59 ± 44.0	2.47 ± 45.4	1.05	-----
HALF (hr)	0.35 ± 64.7	0.36 ± 68.8	0.97	-----
TPEAK (hr)	6.85 ± 52.8	8.1 ± 38.4	0.84	-----

[1]Observed Mean ± %CV
[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 - infinity)
[4]Log Transformed
[5]Calculated by Firm
[6]Geometric mean

TABLE 16

SUMMARY STATISTICS: 1,2-DINITROGLYCERIN-Estimated by Firm

VARIABLE	TREATMENT		RATIO (T/R)	90% CONFIDENCE[5] INTERVAL
	Test	Reference		
AUCL[2] (ng/ml x hr)	32.1 ± 41.0[1]	28.7 ± 36.6	1.18	
LNAUCL[4]	3.37 ± 13.23 (29.60)[6]	3.28 ± 11.89 (26.83)	1.10	105-116%
AUCI[3] (ng/ml x hr)	33.0 ± 40.6	30.2 ± 36.9	1.09	
LNAUCI[4]	3.41 ± 13.02 (30.47)	3.33 ± 11.78 (28.16)	1.08	103-114%
CPEAK (ng/ml)	3.57 ± 40.6	3.13 ± 38.8	1.14	
LNCPEAK[4]	1.18 ± 37.12 (3.30)	1.06 ± 38.01 (2.91)	1.13	107-119%
KEL (hr^{-1})	1.05 ± 37.8	0.97 ± 40.5	1.08	-----
HALF (hr)	0.73 ± 32.9	0.81 ± 39.2	0.90	-----
TPEAK (hr)	6.82 ± 44.3	8.31 ± 31.8	0.82	-----

[1]Observed Mean ± %CV
[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 - infinity)
[4]Log Transformed
[5]Calculated by Firm
[6]Geometric mean

TABLE 18

SUMMARY STATISTICS: 1,3-DINITROGLYCERIN-Estimated by Firm

VARIABLE	TREATMENT		RATIO (T/R)	90% CONFIDENCE[5] INTERVAL
	Mylan	Reference		
AUCL[2] (ng/ml x hr)	7.19 ± 35.4[1]	7.01 ± 38.9	1.02	
LNAUCL[4]	1.90± 20.80 (6.73)[6]	1.86 ± 21.55 (6.49)	1.04	99% to 109%
AUCI[3] (ng/ml x hr)	7.73 ± 35.1	7.51 ± 36.3	1.03	
LNAUCI[4]	1.97 ± 19.94 (7.06)	1.94 ± 19.09 (6.97)	1.01	97%-106%
CPEAK (ng/ml)	0.79 ± 36.3	0.78 ± 49.7	1.01	
LNCPEAK[4]	-0.29 ± -129.41 (0.74)	-0.33 ± -121.46 (0.71)	1.04	99% to 110%
KEL (hr^{-1})	0.84 ± 47.4	0.78 ± 43.2	1.08	-----
HALF (hr)	1.01 ± 52.9	1.12± 60.0	0.90	-----
TPEAK (hr)	6.07 ± 45.6	7.93 ± 36.1	0.76	-----

[1]Observed Mean ± %CV
[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 - infinity)
[4]Log Transformed
[5]Calculated by Firm
[6]Geometric mean

Table 19. 90% confidence intervals for LNCmax, LNAUCL and LNAUCI calculated by QMRS.

	Compound			
	NTG	NTG[1]	1,3 DNTG	1,2 DNTG
Parameter				
LNCMAX	104.9-120.3	104-118	98.7-109.8	106.8-119.9
LNAUCL	101.5-120.0	100-118	98.6-108.9	104.4-116.5
LNAUCI	98.8-119.9	---	97.2-106.0	102.8-113.7

The complete results from the statistical consult completed by QMRS is appended to this report.

VII. **In Vivo Release**

The apparent dose for a subject was computed from:
Apparent Dose=Initial Patch Potency-Residual Amount
Residual Amount=Residual Patch Potency+ Skin Wipe

The control patch potency is the average of six patches corresponding to the group, phase and treatment in which the subject was participating. The residual patch value is the amount of drug remaining on the subjects patch. The wipe value is the amount of drug recovered from the subjects skin after removal of the patch.

Table 20. Apparent Dose, values are mean ± sd.

	Test	Reference
Control Patch,(mg)	63.65 ± 0.9	120 ± 1.64
Residual,(mg)	56.6 ± 2.80	112 ± 4.04
Apparent Dose,(mg,hr)	7.06 ± 2.63	8.10 ± 3.75

Adverse Effects

Observed adverse effects were mainly headaches and appeared to be equally distributed for both products. The results are listed in Attachment 4 Vol 1.2, pages 578-655.

Skin Irritation Studies

The skin irritation study data was only submitted as summary data and therefore could not be evaluated. A request for the raw data was made to the firm.

Subject Drop-outs

The study began with 48 volunteers and there were 3 drop outs. The Subjects # 6 and 21 withdrew for personal reasons that were not study related. Subject 10 withdrew due to adverse events in period 1. Statistics are presented for 44 subjects since the data for # 13 was not analyzed.

Dissolution

The dissolution study for nitroglycerin transdermal system was done as follows:

Apparatus:	(5)-Paddle over disk, 50 RPM
Medium:	600 ml Water
No. of Units Analyzed:	12
Specifications:	
(Firm's proposed)	
Pg 264,vol1.1	

Assay:

The results are presented in Table 21.

Comments:

1. The dissolution data for the test product are acceptable.

2. The 90% confidence intervals for LNCMAX, LNAUCL, and LNAUCI were within the acceptable limits of 80-125% for nitroglycerin, 1,2 dinitroglycerin, and 1,3 dinitroglycerin.

3. The plasma data for the following subjects (31 and 32) receiving the test formulation had 0 time plasma levels that were 1.5 to 2x LOQ. Levels for subject 31 were for period 1 while those for subject 32 were seer ir periods 2 and 3(See appended table 12). The data from these subjects were deleted and the data reanalyzed. Upon reanalysis the study was still acceptable.

   LCmax[104-118.8]
   Laucl[100-118.2]
   Lauci[98.3-117.6]

4. The Division of Bioequivalence would like to propose the following interim dissolution specifications based upon the

data in the submission since the dissolution specifications proposed by the firm underestimate the products dissolution characteristics.

Specifications:

However, if the firm has additional data to support their proposed dissolution specifications that data should be submitted to the Division of Bioequivalence for review.

Deficiencies:

1. The firm should present a comparison of the performance of the four instruments GC01, GC02 GC3A and GC3B used to analyze the plasma samples.

2. The firm should supply stability data to cover the 123 day period of storage for the repeat samples. The firm's data only covered 68 days.

Recommendation:

1. The bioequivalence study conducted by Mylan Pharmaceutical on its 0.6 mg/hr transdermal nitroglycerin patch, Lot No. 26C010B, comparing it to Key Pharmaceuticals Nitro-Dur^{R} 0.6 mg/hr patch Lot No. D5005513 has been found to be incomplete by the Division of Bioequivalence.

2. The dissolution testing data conducted by Mylan Pharmaceuticals on its Nitroglycerin transdermal patch 0.6 mg/hr, lot # 26C010B is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 600 ml of water at 37° C using paddle over disk at 50 rpm. The test product should meet the following specifications:

Not less than 85% of the labeled amount of the drug in the dosage form is dissolved in 4 hours.

Recommendation - deficiencies and comment #4 should be forwarded to the firm ASAP

Andre Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG

Date: 10/28/97

Concur: _____

Date: 11/18/97

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Table 21 . In Vitro Dissolution Testing

Drug (Generic Name):Nitroglycerin Transdermal System
Dose Strength:0.6 mg/hr
ANDA No.:74-992
Firm:Mylan Pharmaceutical
Submission Date:October 25, 1996
File Name:74992SD.096

Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: USP modified paddle over disk(5)
RPM: 50
No. Units Tested: 12
Medium: Water
Volume:600 ml
Specifications:
(Firm's proposed)

Reference Drug:Key Nitro-Dur
Assay Methodology:

Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 26C010B Strength(mg) 0.6 mg/hr			Reference Product Lot # D5005513 Strength(mg) 0.6 mg/hr		
	Mean %	Range	%CV	Mean %	Range	%CV
30	64.0		2.3	45		2.4
60	78.0		1.5	63		1.8
120	91		1.1	77		2.4
240	95		1.1	83		3.0

Page redacted due to confidential information.

Page 2: Table-2:

ABSOLUTE RECOVERY

NITROGLYCERIN (NITR-9621) NITR

NOMINAL SPIKED CONCENTRATION (ng/ml)	RECOVERY FROM PLASMA (PERCENT ± STD. DEV.)	COEFFICIENT OF VARIATION (PERCENT)
0.100 (n=6)	77.3 (± 6.2)	8.0%
0.250 (n=6)	80.3 (± 10.9)	13.6%
1.00 (n=6)	82.8 (± 12.8)	15.4%

ABSOLUTE RECOVERY

NITROGLYCERIN (NITR-9621) 1.2 GDN

NOMINAL SPIKED CONCENTRATION (ng/ml)	RECOVERY FROM PLASMA (PERCENT ± STD. DEV.)	COEFFICIENT OF VARIATION (PERCENT)
0.400 (n=6)	68.3 (± 5.8)	8.5%
1.00 (n=6)	73.4 (± 11.6)	15.8%
4.00 (n=6)	72.7 (± 11.7)	16.1%

ABSOLUTE RECOVERY

NITROGLYCERIN (NITR-9621) 1.3 GDN

NOMINAL SPIKED CONCENTRATION (ng/ml)	RECOVERY FROM PLASMA (PERCENT ± STD. DEV.)	COEFFICIENT OF VARIATION (PERCENT)
0.400 (n=6)	80.3 (± 5.9)	7.4%
1.00 (n=6)	80.4 (± 14.1)	17.6%
4.00 (n=6)	80.6 (± 15.2)	18.9%

3: Table-3:

frozen control samples spiked at high and low concentrations of drin (NITR-9621) NITR

Days Stability	1.00 Control (ng/mL)	0.100 Control (ng/mL)
0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
68		
68		
68		
68		
68		
68		
N =	17	18
MEAN =	1.06	0.112
STD =	0.12	0.016
% CV =	11.6	14.0
% ERROR =	6.2	12.0

ATTACHMENT 2B

STUDY.NITROGLYCERINNITR9621-ANAMETH

4 Table-4:

frozen control samples spiked at high and low concentrations of
in (NITR-9621) 1,2 GDN

Days Stability	4.00 Control (ng/mL)	0.400 Control (ng/mL)
0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
68		
68		
68		
68		
68		
68		
N =	17	18
MEAN =	4.28	0.441
STD =	0.46	0.047
% CV =	10.7	10.6
% ERROR =	7 0	10.3

ATTACHMENT 2B

STUDY.NITROGLYCERINNITR9621-ANAMETH

Table 6:

mary of frozen control samples spiked at high and low concentrations of oglycerin (NITR-9621) 1,3 GDN

Days Stability	4.00 Control (ng/mL)	0.400 Control (ng/mL)
0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
0		
68		
68		
68		
68		
68		
68		
N =	17	18
MEAN =	4.32	0.435
STD =	0.47	0.041
% CV =	10.6	9.3
% ERROR =	8.0	8.8

6 : Table-6

: Days Nitroglycerin (NITR-9621) Subject Samples Were Frozen From Date
a Draw to Date of Analysis

Subject	First Sample Collection	Date of Analysis	Maximum Number of Days Frozen
01			
02			
03			
04			
05			
07			
08			
09			
11			
12			
14			
15			
16			
17			
18			
19			
20			
22			
23			
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44			
45			
46			
47			
48			
*101			
*102			
*104			
*105			
*106			

* 101, 102, 104, 105 and 106 represent repeat analysis samples.

3IOSTUDY.NITROGLYCERINNITR9621-ANAMETH

ATTACHMENT 2B

Table-:7

7 : NITROGLYCERIN (NITR-9621) NITR: FREEZE-THAW STABILITY

	low concentration 0.100 ng/mL	high concentration 1.00 ng/mL
1ST F/THAW	N = 6 *MEAN = 0.025 CV % = 5.1	N = 6 *MEAN = 0.235 CV % = 1.9
2ND F/THAW	N = 6 *MEAN = 0.024 CV % = 7.6 CHANGE =-2.3%	N = 6 *MEAN = 0.243 CV % = 6.6 CHANGE = 3.5%
3RD F/THAW	N = 6 *MEAN = 0.024 CV % = 4.8 CHANGE =-1.6%	N = 6 *MEAN = 0.234 CV % = 3.5 CHANGE =-0.4%

glycerin frozen control samples were found to be stable through three e/thaw cycles.

ES ARE EXPRESSED AS DRUG/INTERNAL STANDARD PEAK HEIGHT RATIOS.

ATTACHMENT 2B

Table-8:

e 8 . NITROGLYCERIN (NITR-9621) 1,2 GDN: FREEZE-THAW STABILITY

	low concentration 0.400 ng/mL	high concentration 4.00 ng/mL
R 1ST ZE/THAW E	N = 6 *MEAN = 0.045 CV % = 5.0	N = 6 *MEAN = 0.436 CV % = 3.9
R 2ND ZE/THAW E	N = 6 *MEAN = 0.045 CV % = 4.6 CHANGE = 1.6%	N = 6 *MEAN = 0.447 CV % = 4.6 CHANGE = 2.6%
R 3RD ZE/THAW E	N = 6 *MEAN = 0.044 CV % = 5.4 CHANGE = -1.2%	N = 6 *MEAN = 0.436 CV % = 2.7 CHANGE = 0.1%

glyceryldinitrate frozen control samples were found to be stable through
e freeze/thaw cycles.

UES ARE EXPRESSED AS DRUG/INTERNAL STANDARD PEAK HEIGHT RATIOS.

ATTACHMENT 2B

TABLE 9 : NITROGLYCERIN (NITR-9621) 1,3 GDN: FREEZE-THAW STABILITY

	low concentration 0.400 ng/mL	high concentration 4.00 ng/mL
AFTER 1ST FREEZE/THAW CYCLE	N = 6 *MEAN = 0.106 CV % = 4.8	N = 6 *MEAN = 1.045 CV % = 4.1
AFTER 2ND FREEZE/THAW CYCLE	N = 6 *MEAN = 0.103 CV % = 4.5 CHANGE = -2.4%	N = 6 *MEAN = 1.059 CV % = 5.8 CHANGE = 1.3%
AFTER 3RD FREEZE/THAW CYCLE	N = 6 *MEAN = 0.108 CV % = 4.0 CHANGE = 2.0%	N = 6 *MEAN = 1.101 CV % = 5.7 CHANGE = 5.3%

,3 glyceryldinitrate frozen control samples were found to be stable through hree freeze/thaw cycles.

VALUES ARE EXPRESSED AS DRUG/INTERNAL STANDARD PEAK HEIGHT RATIOS.

TABLE 10: PROCESSED SAMPLE STABILITY

HOURS (POST EXTRACTION):	0	24	48	72
NITROGLYCERIN				
(0.25 ng/ml)				
	0.065	0.077	0.094	0.059
MEAN:	0.072	0.080	0.085	0.070
% CHANGE:		10.8%	18.9%	-2.9%
1,2 GLYCERYLDINITRATE				
(1.0 ng/ml)				
	0.109	0.130	0.127	0.098
MEAN:	0.118	0.129	0.123	0.111
% CHANGE:		9.3%	4.2%	-5.8%
1,3 GLYCERYLDINITRATE				
(1.0 ng.ml)				
	0.230	0.276	0.251	0.193
MEAN:	0.242	0.274	0.240	0.216
% CHANGE:		13.1%	-0.9%	-10.8%

Plasma samples were spiked at each of the following concentrations:

Low Concentration:	NITR/1,2 & 1,3 GDN	0.1/0.4 ng/mL
High Concentration:	NITR/1,2 & 1,3 GDN	1.0/4.0 ng/mL

samples from each control group were prepared and extracted at the wing time intervals: 0 hour (immediately after spiking), 1.0 hour, 2.0 , and 3.0 hours. The 1.0, 2.0, and 3.0 hour samples sat in ice until ssing. The processed samples were then injected onto the chromatographic m.

TS: The data are expressed as the peak height ratio of the drug to internal standard.

(ng/mL)	PEAK HEIGHT RATIO (% Difference from 0 Hr)			
	0 Hr	1 Hr	2 Hr	3 Hr
	NITR			
	0.033	0.035 (6.0)	0.033 (-2.1)	0.031 (-6.5)
	0.346	0.354 (2.3)	0.344 (0.6)	0.343 (-1.0)
	1,2 GDN			
	0.156			
	1.20			
	1,3 GDN			
	0.179	0.190 (6.1)	0.172 (-4.0)	0.170 (-5.2)
	1.47	1.50 (2.3)	1.50 (1.8)	1.51 (2.8)

JSIONS: No significant decrease of NITR, 1,2 GDN or 1,3 GDN was observed when spiked plasma samples were allowed to sit, on ice, up to 3.0 hours before processing.

TUDY_NITROGLYCERINNITR9621-ANAMETH

Page(s) 9

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Data

Statistical Report: Transdermal Nitroglycerin Delivery System;
Office of Generic Drugs ANDA 74-992, Mylan Pharmaceuticals Inc.

OGD reviewer: Andre Jackson

In this trial, 48 healthy male volunteers were dosed in two groups of equal number of subjects, the groups corresponding to slightly different starting dates for the study. Forty-five subjects successfully completed both phases of the clinical portion of the study. The data from one subject were excluded due to analytical reasons of the assay. Forty-four subjects' data are available.

Study Design and Model:

Open-label, randomized, single-dose, crossover bioequivalence study.

Experimental Treatment:

A = Mylan Transdermal Nitroglycerin (1 patch × 0.6mg/HR)
B = Key Transdermal Nitroglycerin (1 patch × 0.6mg/HR) (Reference)

Experimental Design: Four Periods, Four Sequences

BBAA	**(11 subjects)**
BAAB	**(12 subjects)**
ABBA	**(10 subjects)**
AABB	**(11 subjects)**

Plasma concentrations of the following compounds were evaluated:

Parent Drug
Metabolite1 -nt1_2gdn
Metabolite2 -nt1_3gdn

The following primary endpoints derived from these concentrations were analyzed:

lcmax = log(cmax);
lauct = log(auct);
laucinf = log(aucinf);

Secondary endpoints analyzed:

ltmax = log(tmax);
lthalf = log(thalf);
lkel = log(kel);

.r a given endpoint, (e.g. log(AUCT)), we used the following statistical model: let Y_{ijkl} be a measurement of this endpoint for subject j in sequence i, at period k, at which time this subject received treatment l, then

$$Y_{ijkl} = \mu + \alpha_i + s_{(i)j} + \gamma_k + T_l + \tau_{s(i)jl} + \varepsilon_{ijkl} \quad (1)$$

$$s_{(ij)} \sim N(0, \sigma_S^2)$$

$$\tau_{s(i)jl} \sim N(0, \sigma_{S\tau}^2)$$

$$\varepsilon_{ijkl} \sim N(0, \sigma^2)$$

μ = mean response
α_i = sequence effect
$s_{(ij)}$ = subject effect (nested within sequence)
γ_k = period effect
T_l = Treatment Effect
$\tau_{s(i)jl}$ = subject * treatment interaction

SAS code

We used the following SAS code to generate a mixed model analysis (random subject effect, ndom subject by treatment interaction, all other effects in the model assumed fixed)

```
proc mixed;
classes seq subj per trt;
model y = seq per trt;
random trt/type =un subject=subj;
lsmeans trt /cl pdiff alpha=0.1;
run;
```

The assumed covariance structure is block-diagonal, with a random treatment effect for each subject, i.e., subject-by-formulation interaction is modeled. This corresponds to the assumption that the random effects covariance matrix G is block diagonal, and the random error covariance matrix R is simple diagonal.

Definition of Bioequivalence

Bioequivalence of the compounds is concluded if each of the confidence intervals for the ratios (T/R) of each of the parameters for the parent compound and each of the metabolites lies entirely in the interval (0.8, 1.25).

sults of Analysis

For the primary endpoints, the 80-125% standard of bioequivalence was met in all cases. The parameters and 90% confidence intervals for the endpoints, backtransformed, are tabulated below. A summary of the listing is as follows: *DIFF* is the estimated difference between test and reference in log scale. This was calculated as *A-B*, where *A* corresponds to test and *B* corresponds to reference. *SE* is the standard error of the estimated difference *DIFF*. *DDF* are the degrees of freedom used to construct the confidence interval. Alpha, set at 0.10, corresponds to the fact that this is a two-one-sided procedure at a 0.05 level of significance. EL is the lower bound of the ratio of the estimated ratio of effects, EU is the upper bound. The metabolite and endpoint are indicated in the two final columns.

Table 1: Bioequivalence Ratios for Parent Compound and Two Metabolites for CMAX, AUCT and AUCINF parameters

LEVEL1	LEVEL2	DIFF (IN LOG)	SE	DDF	ALPHA	EL(A/B)	EDIFF(A/B)	EU (A/B)	METAB.	ENDPT
A = TEST	B = REF	.123	.035	83	0.1	1.068	1.131	1.199	NT12	CMAX
A = TEST	B = REF	.098	.032	83	0.1	1.044	1.103	1.165	NT12	AUCT
A = TEST	B = REF	.078	.03	83	0.1	1.028	1.081	1.137	NT12	AUCINF
A = TEST	B = REF	.04	.032	83	0.1	.987	1.041	1.098	NT13	CMAX
A = TEST	B = REF	.036	.03	83	0.1	.986	1.037	1.089	NT13	AUCT
A = TEST	B = REF	.015	.026	81	0.1	.972	1.015	1.06	NT13	AUCINF
A = TEST	B = REF	.117	.04	83	0.1	.049	1.124	1.203	PARENT	CMAX
A = TEST	B = REF	.099	.05	83	0.1	.015	1.104	1.2	PARENT	AUCT
A = TEST	B = REF	.084	.058	71	0.1	.988	1.088	1.199	PARENT	AUCINF

Analyses of secondary endpoints have been summarized at the end of this document in Table 2. The confidence intervals range from (0.69, 0.892) or the low end to (1.01, 1.192) on the high end.

mments on Sponsor's Analysis

The sponsor used the following model to test for group (cohort) effect:

```
roc glm;
lasses cohort seq trt per subj;
odel y = cohort seq cohort*seq subj(cohort*seq)
        trt per resid1/ss1 ss3;
est h=cohort e=subj(cohort*seq) / htype=3 etype=3;
un;
```

However, this code is incorrect for two reasons: (1) the numerator and denominator terms in the esulting F-test are biased, i.e., they contain the term cohort*seq and subj(cohort*seq); and (2) he term to be tested should be cohort*trt, instead of cohort. We used the following model to xamine the group effect:

```
roc mixed;
lasses cohort seq subj per trt;
odel y = cohort cohort*trt seq per trt;
ndom trt/type =un subject=subj;
n;
```

or none of the endpoints was the group effect present at a meaningful level. The group effect as not included in our final analysis.

he sponsor tested for subject by treatment interaction, and then dropped the term from the odel due to its lack of significance. Our policy has always been to include subject-by-eatment interaction due to the fact that we do not have enough power to conclude the term's gnificance.

Conclusions

The outcome of our analysis differed somewhat from the analysis of the sponsor (ANDA Tables 8, 9 and 10). For example, for the parent compound, our confidence interval (CI) for the ratios of AUCI is (1.088,1.199), while the sponsor's quoted confidence interval is (1.01, 1.21). The difference is due to the fact that the sponsor adjusted for carry-over and we adjust for subject by treatment interaction.

Because all of the parameters of interest satisfy the 80-125% standard, we support approval of this ANDA.

/S/

Zhuanpu Hu, Ph.D.
Mathematical Statistician
June 26, 1997

/S/

Alfred H. Balch, Ph.D.
Mathematical Statistician
June 26, 1997

Concur: /S/

Stella G. Machado, Ph.D.
Director, QMR
June 26, 1997

Table 2: Bioequivalence Ratios for Parent Compound and Two Metabolites for TMAX, THALF, and KEL parameters

LEVEL1	LEVEL2	DIFF	SE	DDF	ALPHA	EL(A/B)	EDIFF(A/B)	EU(A/B)	METAB.	ENDPT
A = TEST	B = REF	-.238	.069	83	0.1	.703	.788	.884	NT12	TMAX
A = TEST	B = REF	-.093	.497	83	0.1	.839	.911	.99	NT12	THALF
A = TEST	B = REF	.093	.05	83	0.1	1.01	1.097	1.192	NT12	KEL
A = TEST	B = REF	-.305	.062	83	0.1	.665	.737	.817	NT13	TMAX
A = TEST	B = REF	-.073	.06	81	0.1	.841	.93	1.027	NT13	THALF
A = TEST	B = REF	.074	.06	81	0.1	.975	1.077	1.19	NT13	KEL
A = TEST	B = REF	-.243	.077	83	0.1	.69	.784	.892	PARENT	TMAX
A = TEST	B = REF	-.044	.079	71	0.1	.838	.957	1.092	PARENT	THALF
A = TEST	B = REF	.043	.079	71	0.1	.915	1.044	1.191	PARENT	KEL

CC: ANDA 74-992
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

Endorsements: (Draft and Final with Dates)
HFD-650/A. Jackson
HFD-650/Y. Huang
HFD-617/L. Sanchez 11/21/97

(x:new\firmsam\mylan\ltrs&rev\74992bio.fs1)

BIOEQUIVALENCY - DEFICIENCIES

1. **FASTING STUDY** (STF) Strengths: 0.6 mg/hr
Clinical: Drug Study Unit, Morgantown W.Va
Analytical: Drug Study Unit, Morgantown W.Va
Outcome: AC (IC) UN NC

2. **FOOD STUDY** (STP) Strengths: _____
Clinical: _____
Analytical: _____
Outcome: AC IC UN NC

3. **MULTIPLE DOSE STUDY** (STM) Strengths: _____
Clinical: _____
Analytical: _____
Outcome: AC IC UN NC

4. **DISSOLUTION DATA** (DIS) All Strengths
Outcome: AC IC UN NC

5. **STUDY AMENDMENT** (STA) Strengths: _____
Outcome: AC IC UN NC

6. **WAIVER** (WAI) Strengths: _____
Outcome: AC IC UN NC

7. **DISSOLUTION WAIVER** (DIW) Strengths: _____
Outcome: AC IC UN NC

8. **OTHER** (OTH) 9 May 97 Submission Exp. date Strengths: _____
Outcome: AC IC UN (NC)

9. **OTHER OPTIONS** (less common): Strengths: _____

a. Protocol (PRO)
b. Protocol Amendment (PRA)
c. Protocol/Dissolution (PRD)
d Special Dosage (STS)
e. Study/Dissolution (STD)
f. Bio study (STU)
Outcome: AC IC UN NC

OUTCOME DECISIONS:

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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-992

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

AADA or ANDA NUMBER: 74-992

DRUG PRODUCT: Nitroglycerin Transdermal System

FIRM: Mylan Technologies, Inc. (formerly Bertek)/Mylan Pharmaceuticals, Inc.

DOSAGE FORM: Transdermal System **STRENGTH:** 0.6 mg/hr

CGMP STATEMENT/EER UPDATE STATUS: Acceptable on **3/4/97**; an update is acceptable on **9/3/99**, per EES.

BIO STUDY: Satisfactory per the M. Fanning, M.D., A. Jackson, D. Conner review dated **12/23/98** of the skin irritation study which concludes that "The Division of Bioequivalence has completed its review and has no further questions at this time". This is reiterated in a **6/3/99**, FAX to the applicant.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Samples of the ds and this drug product were not tested at an FDA laboratory since validation of a companion product under ANDA **74-559** (incorporated in this application by reference) was conducted at WEAC. The procedures are acceptable for regulatory purposes in U.V. Venkataram Chemist's Review No. 4 for ANDA **74-559** dated **8/27/96**. The methodology is the same as that validated under ANDA **74-559** in U.V. Venkataram Chemistry Review No. 1 for this ANDA dated **4/31/97**. The firm has confirmed that all test methods for the ds, intermediate adhesive, intermediate laminate, and drug product are identical to those used in support of ANDA **74-559**, with minor exceptions, in their **undated amendment** (dated **7/2/97**, on the Form FDA 356h, received **7/3/97**), for this ANDA. Also, validation data for the testing procedures can be found in the ANDA.

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

Container/closure: Yes; described below.

Description: A pouch formed by heat sealing two layers of pouching material with the patch between the layers. The pouching material consists of 26#C1SPaper/7.2#LDPE/0.00035"F/14.4#LDPE. The pouches (in 30's and 100's) are boxed in cartons.

Supplier: will supply preprinted packaging material with the product name, potency, and name and address of the patch manufacturer.

Stability Protocol: Satisfactory.

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

Lot#	Batch Size	Stability Conditions
26C010B		40°C/75% RH/3 months,

30°C/60% RH/12 months,
25°C/60% RH/12 months.

1 Batch size of f "Intermediate Nitroglycerin Laminate" (lot # **R&D-I255**).
2 Theoretical yield of "Nitroglycerin Transdermal System" doses.
3 Actual yield of "Nitroglycerin Transdermal System" doses after the die cutting step.
4 Actual yield of "Nitroglycerin Transdermal System" doses after the packaging step.

LABELING:
Labeling is shared/common for companion ANDA's **74-992, 75-073, 75-075,** and **75-076** and all ANDA's should be approved at the same time as per "FOR THE RECORD" comment no. 4 in the A. Vezza review dated **9/24/99,** of an amendment dated **9/16/99.** Final print patch and immediate container labels (pouch), and carton and insert labeling in the same amendment are satisfactory per the same A. Vezza review.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS O.K.?):
BIO batch is the same as the stability batch. See **"STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?"** tion above. DMF for the manufacture of the ds is ADEQUATE per s reviewer.

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

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:
The manufacturing process for the executed batch is the same as the proposed batch size. Comparison of the proposed production batch with the test batch is as follows:

Parameter	*Executed Batch*	*Production Batches*
Size	oses.	

/S/

Chemist: Robert C. Permisohn **DATE:** September 30, 1999. 9/30/99

am Leader: Ubrani V. Venkataram, Ph.D. **DATE:** 10/8/99

UV

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

ANDA Numbers: **74-992, 75-073, 75-075, 75-076**

Date of Submissions: **September 17, 1998**

Applicant's Name: **Bertek, Inc.**

Established Name: **Nitroglycerin Transdermal System 0.6 mg/hr (74-992), 0.2 mg/hr (75-073), 0.4 mg/hr (75-075), 0.1 mg/hr (75-076)**

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Please note that because these four ANDAs share a common insert that they must be approved together or you will be asked to further revise the insert labeling.

   b. Revise your storage temperature recommendation to read "Store at controlled room temperature 15° and 30°C (59° and 86°F). Do not refrigerate." throughout your labels and labeling except for the patient package insert.

2. IMMEDIATE PATCH

   Satisfactory, in draft.

3. CONTAINER (Pouch)

   See GENERAL COMMENT (b).

4. CARTON 30s and 100s

   a. See GENERAL COMMENT (b).

   b. 30s - Back Panel - We note your comment that 1.25 inches of space will be left for the outsert to be attached to the box. Please ensure that no text appearing on the carton will be obscured.

c. 30s - Left Panel - ANDA 74-992 - "containing" (delete the hyphen)

5. PATIENT PACKAGE INSERT LABELING

a. See GENERAL COMMENT (b).

b. How to apply the Nitroglycerin Transdermal Patch - Number 1, fourth sentence - ... amount of nitroglycerin ... (rather than "if").

6 PROFESSIONAL PACKAGE INSERT

a. See GENERAL COMMENT (b).

b. PATIENT PACKAGE INSERT LABELING

How to apply the Nitroglycerin Transdermal Patch - Number 1, fourth sentence - ... amount of nitroglycerin ... (rather than "if").

Please revise your labels and labeling, as instructed above, and submit final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

ANDA Numbers: ~~74-992,~~ 75-073, 75-075, 75-076

Date of Submissions: **September 17, 1998**

Applicant's Name: **Bertek, Inc.**

Established Name: **Nitroglycerin Transdermal System 0.6 mg/hr (74-992), 0.2 mg/hr (75-073), 0.4 mg/hr (75-075), 0.1 mg/hr (75-076)**

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Please note that because these four ANDAs share a common insert that they must be approved together or you will be asked to further revise the insert labeling.

   b. Revise your storage temperature recommendation to read "Store at controlled room temperature 15° and 30°C (59° and 86°F). Do not refrigerate." throughout your labels and labeling except for the patient package insert.

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3. CONTAINER (Pouch)

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4. CARTON 30s and 100s

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   b. 30s - Back Panel - We note your comment that 1.25 inches of space will be left for the outsert to be attached to the box. Please ensure that no text appearing on the carton will be obscured.

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a. See GENERAL COMMENT (b).

b. How to apply the Nitroglycerin Transdermal Patch - Number 1, fourth sentence - ... amount of nitroglycerin ... (rather than "if").

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a. See GENERAL COMMENT (b).

b. PATIENT PACKAGE INSERT LABELING

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Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

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

Container (Pouch) Labels:

Carton Labeling: 30s and 100s

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Nitro-Dur®

NDA Number: 20-145

NDA Drug Name: Nitro-Dur® (Nitroglycerin Transdermal System)

NDA Firm: Key Pharmaceuticals, Inc.

Date of Approval of NDA Insert and supplement #: 2/7/96 (S-009)

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container (Pouch) Labels: labels on file

Basis of Approval for the Carton Labeling: labeling on file

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?	X		

	Yes	No	N.A.
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? NONE		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Does USP have labeling recommendations? If any, does ANDA meet them?			X

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

FOR THE RECORD: (some comments taken from previous review)

1. Label and labeling models

   Insert labeling - Nitro-Dur® manufactured by Schering-Plough (Key Pharmaceuticals, Inc.), revised 7/95 and approved 2/7/96

   Container label and carton - Primarily Nitro-Dur labels and labeling. Nitro-Dur labels are more current and have updated text. There are minor modifications, which were primarily based on other approved nitroglycerin patches.

   Patient information insert labeling - Transderm-Nitro

2. Generic firms may use terms "patch, unit or system" in their PPI [except in established name in the title] as long as they are consistent throughout the labeling. This is consistent with other approved applications. Bertek has used "system" throughout their labels and labeling except they have used "patch" in the PPI.

3. Packaging

   Transderm-Nitro 30s and 100s
   Nitro-Dur 30s
   ANDA 30s and 100s

4. ANDAs 75-073 (0.2 mg/hr), 75-075 (0.4 mg/hr) and 75-076 (0.1 mg/hr) all share a common insert with ANDA 74-992 (0.6 mg/hr)and thereby must be approved together.

5. This drug product is manufactured by Bertek Inc. for Mylan Laboratories Inc. Bertek, Inc. is a wholly owned subsidiary of Mylan so the firm may print either Bertek, Inc. or Mylan Pharmaceuticals Inc. on their labels/labeling.

6. Nitro-Dur's patent is scheduled to expire on 2/16/10. Mylan has indicated in their correspondence date 10/25/96 [Vol 1.1, section III] that in their opinion this patent is invalid.

7. The reference drug product is listed under "Nitroglycerin Transdermal Extended-Release Film" in the Orange Book 18th edition.

8. The firm was not requested to add the word "Approximate" to the statement "Rated release..." on the carton labeling, since it is not printed on Nitro-Dur's most current approved carton labeling [approved 4/12/95]. Please note that Nitro-Dur's insert labeling [approved 2/7/96] reads "deliver approximately..." in the DESCRIPTION section and "Approximate" is printed on Nitro-Dur's container pouch label [permitted 12/30/93]. This is not consistent. It appears that we have requested generic firms to use "approximate" on their container labels and "deliver approximately..." in the DESCRIPTION section of their insert labeling. However, since Nitro-Dur's new carton labeling omits "approximately..." we will not ask generic firms to add "approximately..." to their carton labeling if they omitted it. In addition, if the generic firm has included "approximately..." on their carton labeling we will not ask them to delete it. However, we will request generic firms to add "approximately..." to both their container labels as well as the DESCRIPTION section of their insert labeling.

9. There are two innovators for this drug product Nitro-Dur and Transderm-Nitro. Nitro-Dur's patches contain nitroglycerin in an acrylic-based polymer adhesive and Transderm-Nitro's patches contain nitroglycerin in a drug reservoir, followed by a semipermeable membrane and then adhesive. This firm has two sets of ANDA's for nitroglycerin transdermal system, one based on Nitro-Dur and the other based on Transderm-Nitro. However, both sets of ANDA's actually have the same delivery system as Nitro-Dur. The two sets of ANDAs also have the same release rate but differ in size [cm^2].

Note the following:

a. "... FDA has reached the conclusion that the drug release mechanism, patch drug content and either

Buck

M E M O R A N D U M

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

DATE: November 10, 1998

FROM: Phyllis A. Huene, M.D.
Medical Officer
Division of Dermatologic and Dental Drug Products
(HFD-540)

THROUGH: Susan Walker, M.D. /S/ - 11/16/98
Team leader, Dermatology
Division of Dermatologic and Dental Drug Products
(HFD-540)

THROUGH: Jonathan Wilkin, M.D. /S/ 11/22/98
Director
Division of Dermatologic and Dental Drug Products
(HFD-540)

THROUGH: Robert DeLap, M.D. /S/ 11/24/1998
Director
Office of Drug Evaluation II (HFD-105)

TO: Director
Office of Generic Drugs (HFD-600)

SUBJECT: ANDA 74-992
Nitroglycerin Transdermal System, 0.1 mg/hr (Bertek)

Date of request: October 7, 1998

HFD-540 Trac No: 981829
Document ID #: 2343

The Office of Generic Drugs has requested our review of an MOR by Dr. Mary Fanning on a cumulative irritation study performed on Nitroglycerin Transdermal System, 0.1 mg/hr (Bertek, Inc.). The study was done by for Mylan Pharmaceuticals.

The protocol for this 21 day study was approved by the Agency prior to initiation of the study. As described by Dr. Fanning, the results showed a higher mean irritation score between days 5 and 12

for the Mylan product as compared with the test reference product, Nitro-Dur Transdermal System, but subsequent scores were comparable for the two products. A second measurement of irritation potential was the mean number of days to reach an irritation score of 3 (erythema and papules), at which time in accordance with the protocol the applications were terminated and a score of 3 was carried forward daily to the end of the study. Results for this measurement were a mean score of 15 days for the Mylan product and 16 days for the reference product; the difference was not statistically significant.

Conclusions: This reviewer is in agreement with Dr. Fanning that this study has shown that the Mylan Nitroglycerin TDS and Nitro-Dur TDS have comparable cumulative skin irritation.

Phyllis A. Huene, M.D.

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

TO (Division/Office)	FROM:
HFD Lacw - Dr Mary Fenning	HFD 615 · Regulatory Support Branch -

DATE:	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/30, 1998	—	74-992	21-day cumulative Skin Study	August 28, 1998

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nitroglycerin Transdermal System, 0.1mg	high		

NAME OF FIRM: Bertek, Inc

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (*Attach additional sheets if necessary*) HFD-540 has completed their concurrent review of your pending review of the 21-day cumulative irritation study. Please provide a summary of recommendations for the firm.

Thanks,
Harry

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY (*Check one*)
827-5713	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

REQUEST FOR CONSULTATION

TO (Division/Office)	FROM:
Forward ODE-II M.J. Welling - HFD-510	Office of Generic Drugs / HFD-600

IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
7149	9	ANDA 74-552	21-day Cumulative Skin Study	August 28, 1998

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nitroglycerin Transdermal Systems 0.1 mg	Routine		12/7/98

NAME OF FIRM: Barr Labs, Inc

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary) Dr Nancy Fleming has completed review of a 21-day cumulative irritation potential Skin Study. Please review & comment. When completed please provide an electronic transfer, disk or e-mail and return.

HARVEY A. GREENBERG, R.Ph.
Office of Generic Drugs
Ctr. for Drug Evaluation & Research
Metro Park North II, HFD-615
7500 Standish Place
Rockville, MD 20855-2773
(301) 827-5862
FAX (301) 594-1174
Email: Greenberg@CDER.FDA.GOV

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
H Greenberg	
SIGNATURE OF RECEIVER 827-5713	SIGNATURE OF DELIVERER

ANDA

6/13/97 (jp)

I initiated a coversation with Mike Fulton, concerning correspondence dated 6/11/97 . The concern of the firm is having two NTG Transdermal ANDA's with different RLD's but will have the same established name. I concurred with the firm that this was a problem that the Agency was currently trying to address with General Counsel, etc. (Listing the TE rating on the container label and linking the RLD to the label). I informed the firm that the Center was actively pursuing a solution to this problem and that we hope to have a decision soon. In the interim, I encouraged the firm NOT to make a lot of FPL for the product, since there is a possiblity that the Agency may suggest a plan which would require the firm to revise their container/carton labeling.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-992

CORRESPONDENCE

Labeling review drafted 9/24/99 a Vezza

MYLAN TECHNOLOGIES INC.

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

SEP 16 1999

MINOR AMENDMENT
(CHEMISTRY, LABELING, BIOEQUIVALENCE)

Re: NITROGLYCERIN TRANSDERMAL SYSTEM, 0.6 mg/hr ANDA 74-992 ✓
NITROGLYCERIN TRANSDERMAL SYSTEM, 0.4 mg/hr ANDA 75-075
NITROGLYCERIN TRANSDERMAL SYSTEM, 0.2 mg/hr ANDA 75-073
NITROGLYCERIN TRANSDERMAL SYSTEM, 0.1 mg/hr ANDA 75-076
Response to Agency Correspondence Dated June 3, 1999, June 11, 1999 and July 26, 1999

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Applications identified above and to the Agency's comments submitted via facsimile on the referenced dates. Copies of the Agency correspondence are provided in Attachment A for the reviewer's convenience.

Effective April 5, 1999, Bertek Inc. changed its name to MYLAN TECHNOLOGIES, INC. The change is in name only and a copy of MYLAN TECHNOLOGIES, INC.'s name change notification is provided in Attachment B for the reviewer's convenience.

MYLAN TECHNOLOGIES, INC. wishes to amend this application with the following:

JUNE 3, 1999 FDA CORRESPONDENCE

REGARDING CHEMISTRY DEFICIENCIES:

Page(s) 3

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

9/16/99

REGARDING BIOEQUIVALENCY ISSUES:

MYLAN TECHNOLOGIES, INC. understands that the Division of Bioequivalence has completed its review and has no further questions at this time.

We 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. MYLAN TECHNOLOGIES, INC. takes under advisement 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.

JUNE 11, 1999 FDA CORRESPONDENCE

Per the FDA correspondence dated June 11, 1999, MYLAN TECHNOLOGIES, INC. has added the following labeling text to the physician insert in bold print as the first warning under WARNINGS:

> **Amplification of the vasodilatory effects of nitroglycerin by sildenafil can result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.**

The physician insert labeling contains the referenced warning. See Attachment F for representative final printed labeling.

JULY 26, 1999 FDA CORRESPONDENCE

Per the FDA correspondence dated July 26, 1999, MYLAN TECHNOLOGIES, INC. understands that the original Facsimile Amendment was reclassified to a Minor Amendment due to a failure to respond to the original facsimile within the specified 30 day time frame.

As required by 2 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 Boston 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 (802) 527-7792 or via facsimile at (802) 527-0486.

Sincerely,

Elizabeth Ash

Elizabeth Ash, M.S., RAC
Regulatory Manager, CMC
MYLAN TECHNOLOGIES, INC.
110 Lake Street
St. Albans, VT 05478

Schering-Plough

Schering-Plough Corporation
Patent Department K-6-1 1990
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Telephone (908) 298-4000
Telefax (908) 298-5388

March 22, 1999

CERTIFIED MAIL - RETURN RECEIPT REQUESTED

Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
United States Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

NEW CORRESP

RE: ANDA 74-992-Bertek, Inc.
ANDA 75-073-Bertek, Inc.
ANDA 75-075-Bertek, Inc.
ANDA 75-076-Bertek, Inc.

Dear Sir:

This is written on behalf of our wholly-owned subsidiary Key Pharmaceuticals, Inc. ("Key"), the owner of United States Patent No. 5,186,938 ("the '938 patent").

As I advised you in my letters of August 10, 1997 and April 3, 1998, Key brought an action against Bertek, Inc. ("Bertek") in the United States District Court for the Western District of Pennsylvania (Civil Action No. 97-1462) for infringement of the '938 patent as a consequence of receiving notice of Bertek's Paragraph IV Certification with respect to the '938 patent for ANDA 74-992, and subsequently amended that civil action for infringement of the '938 patent to add Bertek's ANDAs 75-073, 75-075 and 75-076.

On March 15, 1999, the Honorable Robert J. Cindrich, U.S. District Judge for the Western District of Pennsylvania, entered a Joint Stipulation And Order Of Dismissal which terminated that civil action (copy enclosed). Accordingly, Key hereby waives any and all objections and consents to the approval by the FDA of the above identified ANDAs.

Please put a copy of this letter in the FDA's files for each of the above-identified ANDAs. Three additional copies of this letter are enclosed for your convenience.

RECEIVED

GENERIC DRUGS

If you are in need of further information, please contact me by telephone at (908) 298-4249.

Very truly yours,

Richard J. Grochala

Richard J. Grochala
Senior Director, Patents

RJG/lm

cc: Roger L. Foster, Esq.
Vice-President and General Counsel
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
Morgantown, West Virginia 26505

NAI Notice of court judgement Hercon case to give exclusivity to not applicable. H. Greely 3/15/99

Schering-Plough

Schering-Plough Corporation
Patent Department K-6-1 1990
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Telephone (908) 298-4000
Telefax (908) 298-5388

February 19, 1999

CERTIFIED MAIL - RETURN RECEIPT REQUESTED

NEW CORR
NC

Director
Office of Generic Drugs (HFD-600)
Center of Drug Evaluation and Research
United States Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

Re: ANDA 74-992 - Bertek, Inc.
ANDA 75-073 - Bertek, Inc
ANDA 75-075 - Bertek, Inc
ANDA 75-076 - Bertek, Inc

Dear Sir:

This is written on behalf of our wholly-owned subsidiary Key Pharmaceuticals, Inc. ("Key"), the owner of United States Patent No. 5,186, 938 ("the '938 patent").

Further to my letter of April 3, 1998 to you, I am enclosing a copy of the November 25, 1998, Judgement of the Court of Appeals for the Federal Circuit, affirming the U.S. District Court for the District of Delaware which had held in favor of Key and against Hercon Laboratories Corporation on all issues of infringement, validity and enforceability of the '938 patent.

Please put a copy of this letter and its attachment in the FDA's files for each of the above identified ANDAs. Three additional copies of this letter and its attachment are enclosed for your convenience.

RECEIVED
FEB 22 1999
GENERIC DRUGS

Andrew 2-24-99

If you are in need of further information, please contact me by telephone at (908) 298-4249.

Very truly yours,

Richard J. Grochala

Richard J. Grochala
Senior Director, Patents

Enclosure
RJG:nr

United States Court of Appeals for the Federal Circuit

98-1067, -1180

KEY PHARMACEUTICALS,

Plaintiff-Appellee,

v.

HERCON LABORATORIES CORPORATION,

Defendant-Appellant.

JUDGMENT

ON APPEAL from the U. S. DISTRICT COURT DISTRICT OF DELAWARE

in CASE NO(S). 95-CV-479

This CAUSE having been heard and considered, it is

ORDERED and ADJUDGED: AFFIRMED.

ENTERED BY ORDER OF THE COURT

DATED NOV 25 1998.

Jan Horbaly, Clerk

ISSUED AS A MANDATE: JANUARY 15, 1999

BERTEK

AMENDMENT
N/AF

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

SEP 17 1998

Labeling review drafted 11/30/98

LABELING AMENDMENT

Re: NITROGLYCERIN TRANSDERMAL SYSTEM, 0.6 mg/hr ANDA #74-992

Dear Mr. Sporn:

Reference is made to the Agency's comments submitted via facsimile on March 27, 1998 regarding labeling revisions of Nitroglycerin Transdermal Systems 0.4 mg/hr, 0.2 mg/hr and 0.1 mg/hr (ANDAs 75-075, 75-073 and 75-076, respectively.) For consistency, the revisions requested for the indicated applications were applied to the above referenced application for the Nitroglycerin Transdermal System, 0.6 mg/hr product. A copy of the Agency correspondence is provided in Attachment A for the reviewer's convenience Bertek wishes to amend this application with the following:

Labeling Deficiencies:

BERTEK RESPONSE: Attachment C contains four copies of the draft labeling for patch, pouch, carton, package insert and patient package insert for Nitroglycerin Transdermal System. The enclosed labeling incorporates the revisions requested in the Agency's letter dated March 27, 1998. A copy of the letter is provided in Attachment A for the convenience of the reviewer.

In order to facilitate the review of this labeling and in accordance with 21 CFR 314.94(a)(8)(iv), Attachment B contains a side-by-side comparison of the proposed draft labeling to the previously submitted labeling.

Bertek notes that the Agency reserves the right to request further changes in our labels and / or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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SEP 18 1998
GENERIC DRUGS

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 Boston 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 (802) 527-7792 or via facsimile at (802) 527-0486.

Sincerely,

Lamont Fulton
Manager of Regulatory Affairs

Bertek Inc.
110 Lake Street
St. Albans, VT 05478

AUG 28 1998

BERTEK

NDA ORIG AMENDMENT

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

BIOEQUIVALENCY AMENDMENT

Re: NITROGLYCERIN TRANSDERMAL SYSTEM, 0.6 mg/hr ANDA #74-992
Response to Agency Correspondence Dated February 27, 1998

Dear Mr. Sporn:

Reference is made to the ANDA identified above, which is currently under review, and to the February 27, 1998 correspondence pertaining to this application which was forwarded to Bertek from the office of Generic Drugs' Division of Bioequivalence. In the Agency's February 27, 1998 correspondence, the Division notified Bertek that a relative cumulative skin irritation study of the test product compared to the reference product would need to be conducted pursuant to 1998 standards. For the convenience of the reviewer, a copy of the February 27, 1998 correspondence is provided in Attachment 1.

In response to the Agency's correspondence of February 27, 1998, Bertek has conducted the required skin irritation study. Enclosed in Attachment 2 of this amendment is the final report of this study, entitled "Evaluation of Cumulative Irritation Potential in Humans 21-Day Test for Nitroglycerin Transdermal Patch". This study was conducted pursuant to Protocol NITR9831 which was submitted to the Agency on April 16, 1998. The Agency found this protocol to be acceptable as documented in a letter to Bertek dated June 15, 1998. Lot data including an executed batch record, certificate of analysis, and release profiles for the clinical supplies used in the conduct of study NITR9831 is provided in Attachment 3.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (802) 527-7792 or via facsimile at (802) 527-0436.

Sincerely,

Lamont Fulton
Manager of Regulatory Affairs
Bertek Inc.
110 Lake Street
St. Albans, VT 05478

RECEIVED
AUG 31 1998
GENERIC DRUGS

3.1
Pennigah

ANDA 75-076, 75-073, 75-075, 74-992

JUN - 9 1998

Bertek, Inc.
Attention: Lamont M. Fulton
110 Lake Street
St. Albans, VT 05478

Dear Sir:

Reference is made to the proposed skin irritation study protocol, submitted to the Office of Generic Drugs (OGD) for review, dated April 16, 1998, for Nitroglycerin Transdermal Systems, 0.1 mg/hr, 0.2, 0.4, and 0.6 mg/hr.

The protocol has been reviewed by the Medical Officer in the Office of Generic Drugs, and we have no further questions at this time. The protocol has been found acceptable.

The guidance offered in this correspondence represents the best judgement the Office can offer based on the submitted information, current scientific knowledge, and the proposed issue(s) at hand. Revisions of our statements may be necessary as needed. Should you have any questions, please call Lizzie Sanchez, Pharm.D., at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

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

BERTEK

ORIGINAL

APR 16 1998

N/A6

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

BIOEQUIVALENCY AMENDMENT

RE: Nitroglycerin Transdermal System, 0.6 mg/hr ANDA #74-992
Nitroglycerin Transdermal System, 0.4 mg/hr ANDA #75-075
Nitroglycerin Transdermal System, 0.2 mg/hr ANDA #75-073
Nitroglycerin Transdermal System, 0.1 mg/hr ANDA #75-076

Dear Mr. Sporn:

This letter is in reference to our Abbreviated New Drug Applications, 74-992, 75-075, 75-073 and 75-076 dated October 28, 1196 and February 7, 1997, submitted pursuant to Section 505(j) of the Federal FD&C Act for Nitroglycerin Transdermal Systems, 0.6 mg/hr, 0.4 mg/hr, 0.2 mg/hr, 0.1 mg/hr.

Reference is also made to your telephone notification dated February 18, 1998, and your Bioequivelance Deficiency Letter dated February 27, 1998.

Reference is also made to your Major Deficiency Notice dated March 27, 1998.

In response, Bertek, Inc. would like to submit for you review our protocol, "Evaluation of Simulated Irritation Potential in Human 21 Day Test for NTS Patch."

This protocol follows the recommendations stated in your February 27, 1998 correspondence. This study was also designed to be performed on the lowest strength patch, since the same amount of drug is delivered per area of application.

Please see attached.

Sincerely,

Lamont M. Fulton
Manager, Regulatory Affairs

cjc/LMF
Enclosures

RECEIVED
APR 17 1998
GENERIC DRUGS

BERTEK

labeling received
drafted 4/14/98
G Vazquez
labels + labeling are OK

FEB 12 1998

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

MINOR AMENDMENT

re: NITROGLYCERIN TRANSDERMAL SYSTEM, 0.6 mg/hr
ANDA # 74-992
Response to Agency Correspondence Dated 1/9/98

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above and to the Agency's comments submitted via facsimile on January 9, 1998. Bertek wishes to amend this application with the following:

REGARDING LABELING ISSUES:

1. GENERAL COMMENTS

FDA COMMENT 1a: Please use "63 mg" rather than "63.0 mg" when expressing the total nitroglycerin content of the system.

BERTEK RESPONSE: The labeling has been revised to read "63 mg" rather than "63.0 mg" when expressing total nitroglycerin content of the system.

FDA COMMENT 1b: We acknowledge your comment that this application has been transferred to Bertek Inc. but that you are still producing the product for Mylan Pharmaceuticals Inc.

BERTEK RESPONSE: We are producing the product for Mylan Pharmaceuticals Inc. but we have transferred the application to Bertek Inc.

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FEB 13 1998

GENERIC DRUGS

2. INTERMEDIATE PATCH

FDA COMMENT: Satisfactory in draft

BERTEK RESPONSE: Bertek acknowledges that the labeling for the Immediate Patch is satisfactory in draft.

3. CONTAINER (Pouch)

FDA COMMENT 3a: See GENERAL COMMENT. ("Please use "63 mg" rather than "63.0 mg" when expressing the total nitroglycerin content of the system.")

BERTEK RESPONSE: The pouch labeling has been revised to read "63 mg" instead of "63.0 mg" when expressing total nitroglycerin content of the system.

FDA COMMENT 3b: We acknowledge your comment that you will differentiate your labels from your other approved Nitroglycerin Transdermal Systems by color.

BERTEK RESPONSE: The labeling for each dosage of the Nitroglycerin Transdermal System will be differentiated by color.

4. CARTON 30s and 100s

FDA COMMENT: See GENERAL COMMENT. ("Please use "63 mg" rather than "63.0 mg" when expressing the total nitroglycerin content of the system.")

BERTEK RESPONSE: The labeling for the cartons of 30 systems and 100 systems has been revised to read "63 mg" instead of "63.0 mg" when expressing total nitroglycerin content of the system.

5. PATIENT PACKAGE INSERT LABELING

FDA COMMENT: We note that the statement "NITROGLYCERIN 0.4 mg/hr" as seen on the submitted draft labeling for this piece may confuse the patient if the system is actually 0.6 mg/hr. Please delete "0.4 mg/hr" or revise so that each strength system has its own strength on this labeling piece.

BERTEK RESPONSE: We have removed the "0.4 mg/hr" from the drawing on the patient package insert so as not to confuse the patient.

6. PROFESSIONAL PACKAGE INSERT

FDA COMMENT 6a: We acknowledge your comment that you will be printing the patient leaflet at the end of the insert labeling. Please ensure that this text is present when you submit final printed insert labeling.

BERTEK RESPONSE: The patient leaflet text is printed at the end of the insert labeling. This text is provided in the final printed labeling enclosed in this amendment.

FDA COMMENT 6bi: DESCRIPTION - Delete the trailing zeros in the last sentence of the second paragraph (e.g. "21 mg" rather than "21.0 mg").

BERTEK RESPONSE: The description has been revised to read "21, 42 and 63 mg" instead of "21.0, 42.0 and 63.0 mg" in the last sentence of the second paragraph.

FDA COMMENT 6bii: Fourth paragraph, penultimate sentence - "Each system...." rather than "Each unit....".

BERTEK RESPONSE: The fourth paragraph has been revised to read "Each system..." instead of "Each unit...".

FDA COMMENT 6biii: Please include a picture of your system in this section as seen in your previous submission.

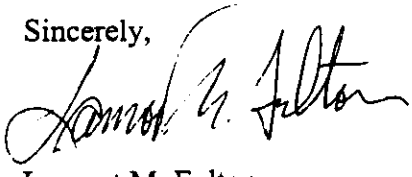
BERTEK RESPONSE: The picture of the system was omitted in error and has been added back to this section.

Enclosed, please find a copy of the original correspondence dated January 9, 1998, and the labeling listed below, which has been revised to incorporate the changes addressed in this amendment.

1. 1 copy annotated labeling text describing changes made
2. 12 copies representative labeling - patch
3. 12 copies final printed labeling - pouch
4. 12 copies final printed labeling - cartons of 30 systems
5. 12 copies final printed labeling - cartons of 100 systems
6. 12 copies final printed labeling - patient package insert
7. 12 copies final printed labeling - package insert

Should you require additional information or have any questions regarding this amendment, please contact the undersigned by telephone at (802) 527-7792, or via facsimile at (802) 527-0486.

Sincerely,



Lamont M. Fulton
Manager of Regulatory Affairs

enclosures

Schering-Plough

Schering-Plough Corporation
Law Department
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Telephone (908) 298-4000

NEW CORRES.

VIA FACSIMILE (301) 594-0183
CONFIRMATION BY CERTIFIED MAIL - RETURN RECEIPT

August 20, 1997

Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
United States Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

Re: ANDA 74-992

Dear Sir:

This is written on behalf of Key Pharmaceuticals, Inc. ("Key"), the owner of United States Patent No. 5,186,938 (the "938 patent").

Bertek, Inc. ("Bertek"), applicant for the above-identified ANDA, has notified Key of its certification to FDA under 21 U.S.C. Section 355 (j)(2)(A), that it believes the claims of the '938 patent are not infringed by the manufacture, use or sale of the drug products for which the application was submitted.

In response to Bertek's notice, and pursuant to 35 U.S.C. Section 271(e)(2)(A) and 21 U.S.C. Section 355 (j)(4)(B)(iii), on August 11, 1997 Key brought an action against Bertek for infringement of the '938 patent, in the United States District Court for the Western District of Pennsylvania. That action has been assigned Civil Action No. 97-1462 by the Court.

It is our understanding that you will now apply the provisions of 21 U.S.C. Section 355(j)(4)(B)(iii) to your review of Bertek's ANDA.

If you are in need of further information, please contact me by telephone at (908) 298-4249.

Very truly yours,

Richard J. Grochala

Richard J. Grochala
Senior Director, Patents

copy of facsimile (certified mail confirmation) to:

cc: Bart G. Newland
Rothwell, Figg, Ernst & Kurz
Columbia Square, Suite 701 East Tower
555 Thirteenth Street, N.W.
Washington, D.C. 20004

BERTEK

ORIG AMENDMENT

N/A N/A

August 14, 1997

Timothy W. Ames
Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
MPN II, HFD-617
Rockville, MD 20855

TELEPHONE AMENDMENT
re: Nitroglycerin Transdermal System, 0.6 mg/hr
ANDA # 74-992

Dear Mr. Ames,

As per our telephone conversation on Thursday, July 17, 1997, I am forwarding stability data for the above abbreviated application. On July 17, during a conversation with you and the Review Chemist, Ubrani Venkataram, Ph.D., a question was raised as to the high values noted for the Total Related Compounds at the 12 month interval. Bertek is providing data here which continues to support a 24 month expiration date for the product. At 15 months, the Nitroglycerin Transdermal System, 0.6 mg/hr shows no significant change in related compounds values.

Bertek strongly believes that stability studies will continue to support our proposed expiration date. Please contact me with any further questions or comments.

Sincerely,

Lamont M. Fulton
Manager of Regulatory Affairs

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AUG 15 1997
GENERIC DRUGS

BERTEK, INC., 110 LAKE STREET, ST. ALBANS, VT 05478. 802-527-7792. FAX 802-527-0486. TELEX 11 710-991-8483

BERTEK

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

MINOR AMENDMENT

re: NITROGLYCERIN DELIVERY SYSTEM, 0.6 mg/hr
ANDA #74-992
Response to Agency Correspondence Dated May 29, 1997

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above and to the Agency's comments submitted via facsimile on May 29, 1997. Bertek wishes to amend this application with the following:

REGARDING CHEMISTRY ISSUES:

A. Deficiencies

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

REGARDING LABELING ISSUES: (Four copies of draft revised labeling are included - see Attachment 6)

A. Deficiencies

FDA COMMENT 1a: Revise "Nitroglycerin Delivery System" to read "Nitroglycerin Transdermal System" on all labels and labeling.

BERTEK RESPONSE: All the labeling has been revised to read "Nitroglycerin Transdermal System"

FDA COMMENT 1b: We note your application has been transferred to Bertek, Inc. If necessary, please revise your labels accordingly or comment.

BERTEK RESPONSE: The application has been transferred to Bertek, Inc. but we are still producing the product for Mylan Pharmaceuticals Inc.

FDA COMMENT 2: Immediate Patch - Satisfactory in draft

BERTEK RESPONSE: Printing on the patch has changed from random print to registered print of the drug and strength.

FDA COMMENT 3a: We encourage you to differentiate your labels from your other approved Nitroglycerin Transdermal Systems labels by using contrasting colors and/or boxing.

BERTEK RESPONSE: Product name has been changed to read "Nitroglycerin Transdermal System" and each dosage will be differentiated by color.

FDA COMMENT 3bi: To be consistent with your carton and insert labeling, we encourage you to revise "unit" to read "systems" on your container labels.

BERTEK RESPONSE: The carton and insert labeling has been revised to read "system" instead of "unit".

FDA COMMENT 3bii: Add the following statements: A) Contents: 1 System B) FOR TRANSDERMAL USE ONLY

BERTEK RESPONSE: The pouch has been revised to include "Contents: 1 System" and "FOR TRANSDERMAL USE ONLY".

FDA COMMENT 3ci: Instruction for Application. Revise as follows:
#2: ...clear liner. Avoid touching the exposed sticky side of the patch.

BERTEK RESPONSE: Revised step number 2 to include "Avoid touching the exposed sticky side of the patch".

FDA COMMENT 3cii: Add the statement "APPLY IMMEDIATELY UPON REMOVAL FROM POUCH".

BERTEK RESPONSE: The following statement has been added to the pouch back "APPLY IMMEDIATELY UPON REMOVAL FROM POUCH".

FDA COMMENT 3ciii: We encourage you to add the "Usual Dosage: Each 24 hour..." statement, following Instruction for Application #4.

BERTEK RESPONSE: The "Usual Dosage" statement has been added to the Instructions for Application section.

FDA COMMENT 3civ: If space permits, add the storage recommendation statement.

BERTEK RESPONSE: The storage recommendations have been added to the Instructions for Application section.

FDA COMMENT 4a: See comment 3(a) under CONTAINER.

BERTEK RESPONSE: Product name has been changed to read "Nitroglycerin Transdermal System" and each dosage will be differentiated by color on the carton.

FDA COMMENT 4bi: Center Panel: Add the statement, "FOR TRANSDERMAL USE ONLY".

BERTEK RESPONSE: Added the statement "FOR TRANSDERMAL USE ONLY" to the center panel of the carton.

FDA COMMENT 4bii: Revise the first sentence to read, "Each system contains 63 mg of nitroglycerin in an acrylic pressure sensitive adhesive with a cross-linking agent'.

BERTEK RESPONSE: Revised the first sentence to read, "Each system contains 63 mg of nitroglycerin in an acrylic pressure sensitive adhesive with a cross-linking agent".

FDA COMMENT 4c: Back Panel - See comment 3 (b) (I) and 3 (b) (ii) (B) under CONTAINER.

BERTEK RESPONSE: Replaced the word "unit" with "system" and added the statement "FOR TRANSDERMAL USE ONLY".

FDA COMMENT 5: Revise your patient package insert labeling to be in accord with the enclosed mock-ed up copy your approved patient package insert labeling for ANDA 74-559 [Nitroglycerin Transdermal System, approved 8/30/96 and revised 5/95].

BERTEK RESPONSE: The patient package insert labeling has been revised to match the mock-ed up copy.

* Changed the word "patch" to "system" as indicated.
* Added an underline to the word "not" in the application section.
* Added "exposed sticky side" as indicated.
* Added the "palm of the hand" to step 5 as indicated.
* Revised storage statement to remove the word "controlled" as indicated.

FDA COMMENT 6ai: Description: In the last sentence of the third paragraph delete the text, "in an acrylic pressure sensitive adhesive".

BERTEK RESPONSE: The last sentence of the third paragraph that had the following text, "in an acrylic pressure sensitive adhesive" has been removed.

FDA COMMENT 6aii: Add the following as the first sentence of the last paragraph, "Each system contains nitroglycerin in an acrylic pressure sensitive adhesive with a cross-linking agent to provide a continuous source of active ingredient".

BERTEK RESPONSE: The following sentence has been added to last paragraph as the first sentence, "Each system contains nitroglycerin in an acrylic pressure sensitive adhesive with a cross-linking agent to provide a continuous source of active ingredient".

FDA COMMENT 6aiii: We note some of the inactive ingredients listed on your carton labeling are not listed in the DESCRIPTION section. Please comment and/or include the sentence, "The inactive components are.... with silicone" in this section.

BERTEK RESPONSE: The carton and professional package insert have been revised to include a complete list of inactive ingredients.

FDA COMMENT 6aiv: Include the dyes in the imprinting ink in your list of inactive ingredients.

BERTEK RESPONSE: The inactive ingredient list has been updated to include the white ink "containing titanium dioxide" for all the labeling.

FDA COMMENT 6av: Revise the last paragraph to read as follows: ...to the skin, these layers are: 1) ....to nitroglycerin and is printed with the name of the drug and strength; 2)...

BERTEK RESPONSE: The last paragraph has been revised to read as follows: ...to the skin these layers are: 1) ....to nitroglycerin and is printed with the name of the drug and strength; 2)...

FDA COMMENT 6b: Add the following as the last paragraph of this subsection: The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

BERTEK RESPONSE: The last paragraph of this subsection has been revised to include the following sentence: "The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute anginal episode".

FDA COMMENT 6ciA: Drug Interactions A.) In the first and last sentence revise "addictive" to read "additive".

BERTEK RESPONSE: The word "addictive" has been changed to "additive" in the first and last sentence of Drug Interactions.

FDA COMMENT 6ciB: Add the following as the last sentence of the subsection: Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

BERTEK RESPONSE: The last sentence of this subsection has been revised to include the following sentence: Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

FDA COMMENT 6cii A: Revise the second paragraph to read as follows: ...of dietary nitroglycerin for 2 years developed dose-related fibrotic and neoplastic changes in liver, including carcinomas, and interstitial cell tumors in testes. At high dose, the incidences of hepatocellular carcinomas in both sexes were 52% vs. 0% in controls, and incidences of testicular tumors were 52% vs. 8% in controls. Lifetime dietary administration of up to 1058 mg/kg/day of nitroglycerin was not tumorigenic in mice.

BERTEK RESPONSE: The second paragraph has been revised to read as follows: ...of dietary nitroglycerin for 2 years developed dose-related fibrotic and neoplastic changes in liver, including carcinomas, and interstitial cell tumors in testes. At high dose, the incidences of hepatocellular carcinomas in both sexes were 52% vs. 0% in controls, and incidences of testicular tumors were 52% vs. 8% in controls. Lifetime dietary administration of up to 1058 mg/kg/day of nitroglycerin was not tumorigenic in mice.

FDA COMMENT 6ciiB: In the last paragraph delete the hyphen from the word "generation".

BERTEK RESPONSE: The hyphen has been deleted from the word "generation" in the last paragraph.

FDA COMMENT 6di: Add the following as the second paragraph: Allergic reactions to nitroglycerin are also uncommon, and the great majority of those reported have been cases of contact dermatitis or fixed drug eruptions in patients receiving nitroglycerin in ointments or patches. There have been a few reports of genuine anaphylactoid reactions, and these reactions can probably occur in patients receiving nitroglycerin by any route.

BERTEK RESPONSE: The second paragraph has been added as follows: Allergic reactions to nitroglycerin are also uncommon, and the great majority of those reported have been cases of contact dermatitis or fixed drug eruptions in patients receiving nitroglycerin in ointments or patches. There have been a few reports of genuine anaphylactoid reactions, and these reactions can probably occur in patients receiving nitroglycerin by any route.

FDA COMMENT 6dii: In the third paragraph, revise "....this diagnosis" to read ".... its diagnosis".

BERTEK RESPONSE: Replaced "....this diagnosis" with "....its diagnosis" in the third paragraph.

FDA COMMENT 6e: Please assure that the entire text of your patient package insert labeling (patient leaflet) is also reprinted at the end of your insert labeling. We refer you to CFR 201.57(f) (2) for further guidance.

BERTEK RESPONSE: The patient leaflet is being printed at the end of the insert labeling.

FDA COMMENT: Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

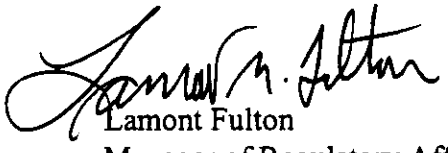
BERTEK RESPONSE: Bertek understands that revisions may be made to the labels and/or labeling based upon the request of the FDA.

FDA COMMENT: To facilitate review of your next submission, and in accordance with 21 CFR 314.94 (a) (8) (iv). Please provide a side-by-side comparison of your proposed labeling with your last submission and the enclosed patient package insert with all differences annotated and explained.

BERTEK RESPONSE: Bertek has provided a side-by-side comparison of the proposed labeling with the last submission. All differences have been annotated and explained.

Please contact me at the address below with any further questions.

Sincerely,



Lamont Fulton
Manager of Regulatory Affairs

Bertek Inc.
110 Lake Street
St. Albans, VT 05478

Wait a response on G-drive / Fax from Fulton / Phillips on 6/13/97 Jerry

BERTEK

June 11, 1997

1.1

Correspondence

(Sent Via Facsimile 6/11/97)

Mr. Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

Dear Jerry:

This correspondence is being submitted in response to comments received from the Office of Generic Drug's Labeling Review Branch via facsimile on May 29, 1997. The facsimile of May 29 provided comments resulting from the Agency's review of the proposed draft labeling submitted in ANDA 74-992 for Nitroglycerin Delivery System, 0.6 mg/hr. Of particular concern is the following comment:

> ***General comment 1.a: Revise "Nitroglycerin Delivery System" to read "Nitroglycerin Transdermal System" on all labels and labeling.***

Prior to making the requested change, Bertek wishes to discuss with the Labeling Review Branch the potential confusion that a revision of this type would create in the market place. Bertek currently has an approved product, Nitroglycerin Transdermal System, 0.6 mg/hr (ANDA 74-559), which is bioequivalent and generically substitutable for Ciba-Geigy's product, "Transderm-Nitro®. Our current application (ANDA 74-992) is for Nitroglycerin Delivery System, a product which we have demonstrated as being bioequivalent to Key Pharmaceuticals' product, "Nitro-Dur®". The approved Bertek product (vs. Transderm-Nitro®) has a surface area of 24 cm^2 while the submitted product (vs. Nitro-Dur®) has a surface area of 22.5 cm^2 and, therefore, cannot be used interchangeably.

The primary concern we have is for the safety of the patient. To name both products "Nitroglycerin Transdermal System", with no other differentiation, would be extremely confusing with regard to prescribing and dispensing the appropriate product. This, in turn, could put the patient at risk should the wrong product be dispensed. If use of the name "Nitroglycerin Delivery System" is not acceptable for product differentiation, we would like to submit an alternate name for your consideration and subsequent discussion. Bertek's proposal is to allow use of the generic portion of the product name of the reference listed drug:

> ***Reference Listed Drug Label: Nitro-Dur® Nitroglycerin Transdermal Infusion System, 0.6 mg/hr.***

- ***Proposed Bertek Label: Nitroglycerin Transdermal Infusion System, 0.6 mg/hr.***

BERTEK, INC., 110 LAKE STREET, ST. ALBANS, VT 05478, 802-527-7792, FAX 802-527-0486, TELEX 11-710-991-8493

We would appreciate the opportunity to discuss this issue at your earliest convenience. If you should have any additional questions or concerns, please do not hesitate to contact me directly by phone (802) 527-7792 or via facsimile at (802) 527-0486.

Sincerely,

Lamont Mike Fulton
Manager, Regulatory Affairs

LMF/slc

cc: B. Ash
S. Govil
F. Sisto

BERTEK

June 11, 1997

Mr. Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

Correspondence
(Sent Via Facsimile 6/11/97)

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- ***Reference Listed Drug Label: Nitro-Dur® Nitroglycerin Transdermal Infusion System, 0.6 mg/hr.***

  Proposed Bertek Label: Nitroglycerin Transdermal Infusion System, 0.6 mg/hr.

BERTEK, INC., 110 LAKE STREET, ST. ALBANS, VT 05478, 802-527-7792, FAX 802 527-0486, TELEX [illegible]

REF: K:\REGULATO\FDA\PHILLPLT.611

Copy

We would appreciate the opportunity to discuss this issue at your earliest convenience. If you should have any additional questions or concerns, please do not hesitate to contact me directly by phone (802) 527-7792 or via facsimile at (802) 527-0486.

Sincerely,

Lamont Mike Fulton
Manager, Regulatory Affairs

LMF/slc

cc: B. Ash
S. Govil
F. Sisto

REF: K:\REGULATO\FDA PHILLPL .611

BERTEK

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

NEW CORRESP
BIOAVAILABILITY
NC / [illegible]

TELEPHONE AMENDMENT

RE: NITROGLYCERIN TRANSDERMAL SYSTEM, 0.6mg/hr
ANDA #74-992
RESPONSE TO AGENCY TELEPHONE REQUESTS OF MARCH 24, AND APRIL 23, 1997

Dear Mr. Sporn:

Reference is made to the pending ANDA identified above and to the March 24, and April 23, 1997 telephone calls from the Division of Bioequivalence requesting additional biostudy information. The purpose of this amendment is to provide responses to the March 24, and April 23, 1997 telephone requests. For ease of review the Agency's requests are noted below, followed by our response.

AGENCY REQUEST: In the March 24, 1997 telephone discussion the Agency requested the following information pertaining to study NITR-9621:

- blood level data for Subject #10 for period 1 and any other period where blood was taken, and
- more specific information as to why Subject #13 was not analyzed.

BERTEK RESPONSE: In response to the Agency's inquiry, Subject #10 was withdrawn from Study NITR-9621 during period 1 after 9 blood samples were taken (pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 hours). As per the study protocol (page 261 of the original ANDA submission), "only data pertaining to subjects who complete the study will be analyzed in the final report," therefore, samples for subject #10 were not analyzed analytically or pharmacokinetically.

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GENERIC DRUGS

With regard to Subject #13, the plasma volume for this subject was exhausted due to multiple sample extractions. The initial analytical data was not acceptable due to greater than 20% of the subject's samples calculating over the highest standard of the curve. The

second and third analyses were unacceptable due to chromatographic interferences. Further analytical attempts could not be supported due to lack of four freeze-thaw cycles stability and insufficient sample volume.

Clinical data for Subjects #10 and #13 can be found in Attachments 3 and 4 of the study report for NITR-9621, which is located in Volume 2 of the original ANDA submission. The case report forms for these two subjects are located in Volume 7 of the original ANDA submission, on pages 3409 and 3455, respectively.

AGENCY REQUEST: In the April 23, 1997 telephone discussion the Agency requested "whatever data we have" on Subjects #6 and #21, who withdrew from study NITR-9621.

BERTEK RESPONSE: Subjects #6 and #21 withdrew from Study NITR-9621 prior to period 2 dosing for reasons that were not study related. As noted in the previous response only data pertaining to subjects who complete the study will be analyzed in the final report. Samples for Subjects #6 and #21 were, therefore, not analyzed analytically or pharmacokinetically.

Clinical data for Subjects #6 and #21 can be found in Attachments 3 and 4 of the study report for NITR-9621, which is located in volume 2 of the original ANDA submission. The case report forms for these two subjects are located in Volume 7 of the original ANDA submission, on pages 3350 and 3582, respectively.

Should you require additional information or have any questions regarding this amendment, please contact the undersigned by telephone at (802) 527-7792, or via facsimile at (802) 527-0486.

Sincerely,

Lamont M. Fulton
Manager,
Regulatory Affairs

enclosures

BERTEK

April 23, 1997

NEW CORRESP

NC

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

CORRESPONDENCE

Re: Nitroglycerin Delivery System, 0.6 mg/hr
ANDA 74-992
Transfer of Ownership

Dear Mr. Sporn,

On April 22, 1997, Mylan Pharmaceuticals Inc. transferred ownership of the Abbreviated New Drug Application for Nitroglycerin Delivery System, 0.6 mg/hr (ANDA 74-992) to Bertek, Inc., located at 110 Lake Street, St. Albans, VT 05478. Bertek, Inc. is a wholly owned subsidiary of Mylan Laboratories Inc. and is the manufacturer of the Nitroglycerin Delivery System, 0.6 mg/hr.

As per 21 CFR 314.72 (a)(2)(i), Bertek commits to agreements, promises and conditions made by the former owner, Mylan Pharmaceuticals Inc., and commits to all other conditions described in the referenced application. Bertek shall advise the FDA about any changes in the conditions in the submitted application.

Please contact me if you have any questions regarding the change in ownership for application 74-992.

This correspondence is submitted in duplicate.

Sincerely,

Lamont M. Fulton
Manager of Regulatory Affairs

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APR 2 . 1997
GENERIC DRUGS

BERTEK, INC., 110 LAKE STREET, ST. ALBANS, VT 05478. 802-527-7792. FAX 802-527-0486. TELEX 11 710-991-8483

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

NEW LETTER

December 10, 1996

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

TELEPHONE CORRESPONDENCE

RE: Nitroglycerin Delivery System, 0.6 mg/hr
ANDA 74-992
Response to December 6, 1996 Telephone Request

Dear Mr. Sporn:

Reference is made to the ANDA identified above and to a December 6, 1996 telephone call from the Agency requesting that certain documentation be revised or provided prior to the application being accepted for filing. In response to the Agency's request, please find enclosed the following documents for inclusion in the application:

1) A replacement Generic Drug Enforcement Act Certification letter on Mylan letterhead and signed by the applicant (replacement page 4-R).

2) A replacement cGMP Certification letter on Mylan letterhead and signed by the applicant (replacement page 4168-R).

3)

4) A certification of compliance that the methods used in the manufacture of the drug product comply with applicable local, state, and federal environmental regulations (page 5007-A).

RECEIVED
DEC 11 1996
GENERIC DRUGS

(RDUP ANDA NITROGLYCERIN.6-BER)AGENCY-CALL-DATED-12-06-96

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		

This correspondence is submitted in duplicate to the above referenced application. A copy has also been forwarded by facsimile to the attention of Mr. Harvey Greenberg.

In compliance with the requirements set forth in 21 CFR 314.96(b) a true copy of this submission, as submitted to the Office of Generic Drugs, has been provided to FDA's Boston District Office.

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

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

enclosures

ANDA 74-992

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

JAN 3 1997

Dear Sir:

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

Reference is also made to your correspondence dated December 10, 1996.

NAME OF DRUG: Nitroglycerin Transdermal System, 0.6 mg/hr

DATE OF APPLICATION: October 25, 1996

DATE OF RECEIPT: October 28, 1996

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) 594-0305

Sincerely yours,

/S/ for 1/3/97

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

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

OCT 25 1996

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
ELECTRONIC DATA ENCLOSED

RE: Nitroglycerin Delivery System, 0.6 mg/hr

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: Nitroglycerin Delivery System, 0.6 mg/hr

This application consists of a total of 23 volumes:
Archival Copy - 10 volumes.
Review Copy - 11 volumes.
Technical Section For Chemistry - 3 volumes.
Technical Section For Pharmacokinetics - 8 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 study.

This application provides for the manufacture of patches (22.5 cm^2) containing nitroglycerin with a release rate of 0.6 mg per hour. This product will be manufactured for Mylan Pharmaceuticals Inc. by Bertek Inc, 110 Lake Street, St. Albans, VT 04578. Bertek is a wholly owned subsidiary of Mylan Laboratories Inc.

The nitroglycerin patch which is the subject of this application has the same composition and manufacturing process as the Nitroglycerin Transdermal Delivery System contained in ANDA 74-559, which was approved on August 30, 1996. The only difference is in the die cutting process to obtain the correct size patch. Based on these similarities the human and animal studies designed to evaluate wearability and irritation potential of the nitroglycerin patch have not been repeated for this application. The original studies conducted and submitted in ANDA 74-559 are considered applicable to this application and are therefore incorporated by reference as noted in Section XXI.

Department	Fax Number				
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		

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 Boston District Office.

For more detailed information regarding the organization of this ANDA, please refer to the Introduction, Reader's Guide and Master Table of Contents following this letter.

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 [FAX No. (304) 285-6407, Phone No. (304) 599-2595].

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

enclosures

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