CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-073

Approval Letter

ANDA 75-073 (0.2 mg/hr)
75-075 (0.4 mg/hr)
75-076 (0.1 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 applications dated February 7, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Nitroglycerin Transdermal Systems.

Reference is also made to your amendments dated October 17, December 15, and December 22, 1997; April 16, and August 28 (75-073), 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 applications contain 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 these drug products 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 these applications.

We have completed the review of these abbreviated applications and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the applications are approved. The Division of Bioequivalence has determined your Nitroglycerin Transdermal Systems, 0.2 mg/hr, 0.4 mg/hr, and 0.1 mg/hr, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug [Nitro-Dur® Transdermal Infusion Systems, 0.2 mg/hr, 0.4 mg/hr and 0.1 mg/hr, respectively, of Key Pharmaceuticals, Inc.]. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your applications.

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

Post-marketing reporting requirements for these abbreviated applications 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 campaigns. 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/ 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 75-073

FINAL PRINTED LABELING

BLACK 160 BROWN DIE-LINE

Nitroglycerin Transdermal System 0.2 mg/hr

Each 7.5 cm² system contains 21 mg of nitroglycerin. The inactive components are acrylic adhesive, polyolefin film, a polyester release liner coated on one side with silicone and white ink containing titanium dioxide.

MYLAN PHARMACEUTICALS INC. Morgantown, WV 26505

NDC 0378-8422-93

℞ only

MYLAN®

NITROGLYCERIN TRANSDERMAL SYSTEM

0.2 mg/hr (7.5 cm²)

30 Systems

Each system contains 21 mg of nitroglycerin in an acrylic pressure sensitive adhesive with a cross-linking agent.

Rated release *in vivo* 0.2 mg/hr.

Patient: See instructions on back panel.

FOR TRANSDERMAL USE ONLY

N 3 0378-8422-93 5

LOT

EXP

M8422-93-30C:R1

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.

STORE AT CONTROLLED ROOM TEMPERATURE 15° AND 30°C (59° AND 86°F). DO NOT REFRIGERATE.

2

NDC 0378-8422-93

NITROGLYCERIN TRANSDERMAL SYSTEM

0.2 mg/hr (7.5 cm²)

Instructions for Application

1. Open 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.

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.

"SPECIMEN"

MYLAN TECHNOLOGIES INC.

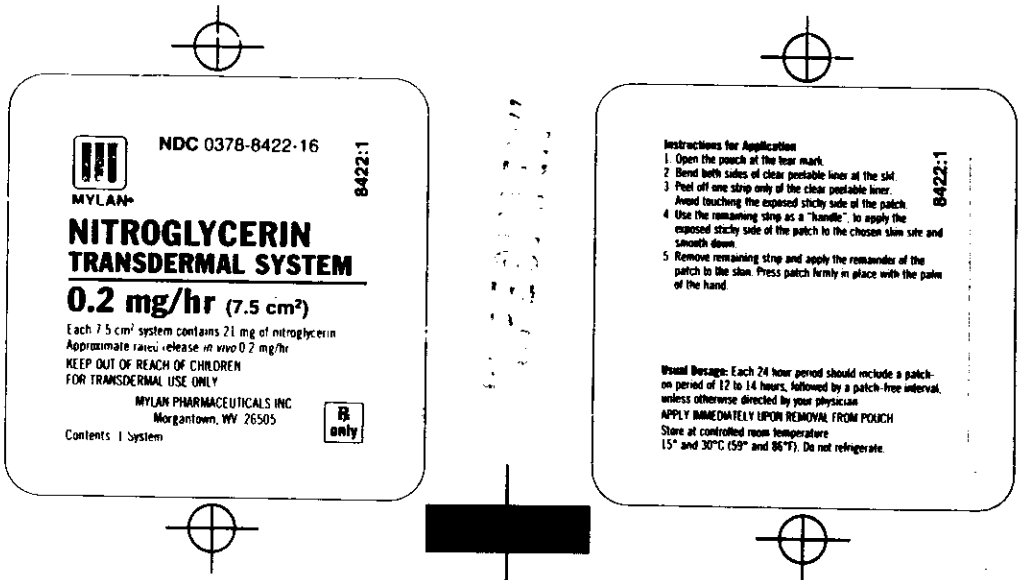
NITROGLYCERIN TRANSDERMAL SYSTEM, 0.2 mg/hr

ANDA 75-073

MYLAN TECHNOLOGIES INC.

NITROGLYCERIN TRANSDERMAL SYSTEM, 0.2 mg/hr

ANDA 75-073



Pouch Face prints
PMS 160 Brown and Black

Pouch Back prints Black

N 12

SYSTEM, 0.2 mg/hr

SPECIMEN

How to use NITROGLYCERIN TRANSDERMAL PATCH for the prevention of angina

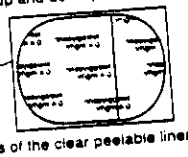
The Nitroglycerin Transdermal Patch is easy to use – it has a clear peelable liner, and a special adhesive that keeps the patch firmly in place.

Where to place the Nitroglycerin Transdermal Patch

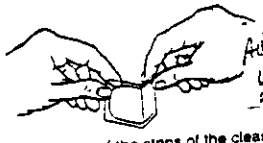
Select any area of skin on the body, EXCEPT the extremities below the knee or elbow. The chest is the preferred site. The area should be clean, dry, and hairless. If hair is likely to interfere with patch adhesion or removal, it can be clipped but *not* shaved. Take care to avoid areas with cuts or irritations. 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

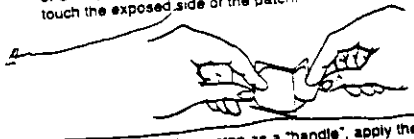
1. Each Nitroglycerin Transdermal Patch is individually sealed in a protective package. Open the pouch at the tear mark. Carefully remove the patch. The patch is printed with the wording '**Nitroglycerin**' and the amount of nitroglycerin delivered each hour. The patch is attached to a clear peelable 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.

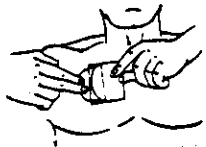


3. Slowly peel off only one of the strips of the clear liner. Do not touch the exposed side of the patch.



4. Using the remaining strip as a "handle", apply the 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. Once the patch is in place, do not test the adhesion by pulling on it.



When 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 skin 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 CONTROLLED ROOM TEMPERATURE 15°- 30°C (59° - 86°F). DO NOT REFRIGERATE.

Do not store unpouched. Apply immediately upon removal from [illegible] pouch.

Manufactured By: BERTEK INC.
St. Albans, VT 05478

Manufactured For: MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505

REVISED MAY 1996
NTG:R3

"Underline the word "not".

Replace with the milligrams strength for each. Add it or print "mg/hr" without indicating strength.

Add the word "sticky"

Add the word "exposed".

Aid the word "peelable"

Delete the word "Controlled"

APPROVED

AUG 30 1996

CENTER FOR DRUG EVALUATION AND RESARCH

Application Number 75-073

MEDICAL REVIEW(S)

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 75-073

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMISTRY REVIEW NO. 2 **Addendum**

2. ANDA # 75-073, 75-075, 75-076

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

4. LEGAL BASIS FOR SUBMISSION
Nitro-Dur® Nitroglycerin Transdermal System, 0.2 mg/hr
Key Pharmaceuticals, Inc.
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

The firm filed Paragraph IV Certification, July 23, 1997, with respect to Patent 5,186,938 for the innovator product, and submitted evidence of notification October 17, 1997. In response to notification of Bertek's Paragraph IV patent certification, Key Pharmaceuticals brought action against Bertek on 8/11/97 for patent infringement.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Nitroglycerin Transdermal System

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

9. AMENDMENTS AND OTHER DATES:
Firm:
2/7/97 - Original submission.
6/9/97 - Amendment - Response to Agency's Refusal to File letter of 3/28/97.
10/17/97- Amendment - Paragraph IV Certification Notification.
11/30/97- Bioequivalency Amendment.
12/15/97- Bioequivalency Amendment.
12/22/97- Notification of Paragraph IV Lawsuit.
4/16/98 - Bioequivalency Amendment.

8/28/98 - Bioequivalency Amendment.
9/17/98 - Amendment - Response to Agency's Letter of **3/27/98.**
2/19/99 - NC from Schering-Plough (Patent issue).
3/22/99 - NC from Schering-Plough (Patent issue).
9/16/99 - Amendment (Addressing outstanding issues for companion ANDA 74-992).

FDA:
3/28/97 - Refusal to File letter issued.
7/2/97 - Receipt Acknowledged - Accepted for Filing letter issued.
3/27/98 - Issuance of Not Approvable Letter.
7/26/99 - Information letter.

10. PHARMACOLOGICAL CATEGORY
Antianginal and Corony Artery Disease

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Transdermal delivery system

14. POTENCIES
ANDA 75-073 - 0.2 mg/hr
ANDA 75-075 - 0.4 mg/hr
ANDA 75-076 - 0.1 mg/hr

15. CHEMICAL NAME AND STRUCTURE
1,2,3-Propanetriol trinitrate (See USP for structure).
Molecular Formula: $C_3H_5N_3O_9$
Molecular Wt.: 227.09

16. RECORDS AND REPORTS
N/A.

17. COMMENTS
ANDA's **75-073, 75-075** and **75-076** are companion jackets to ANDA **74-992**, submitted by Mylan née Bertek **10/25/96.** Initial review of ANDA **74-992** was conducted by U.V.

Venkataram, **4/31/97**,. with deficiencies noted. Review of the three companion applications was conducted with reference to ANDA **74-992** to ensure consistency in the review process.

The firm had resolved all issues concerning the chemistry, manufacturing, and controls sections of the ANDA's **75-073**, **75-075**, and **75-076** at the time of Review # 2.

Our **6/3/99**, NA FAX to ANDA **74-992** addressed the remaining issues for the ANDA.

Our **7/26/99**, Information letter to ANDA's **75-073**, **75-075**, and **75-076** notified the applicant that the Div. of Chemistry had no further questions at that time, and we await response to our **6/3/99**, NA FAX to ANDA 74-992.

9/16/99, Amendment: This was sent to all 4 ANDA's, and addresses the outstanding issues for ANDA 74-992. The applicant notifies the file of a name change from Bertek Inc. to MYLAN TECHNOLOGIES.

10/28/97 - Bioequivalence review, A. Jackson.
1/16/98 - Chemistry review #1, G.J. Smith.
2/23/98 - Labeling review, J. White.
4/13/98 - Bioequivalence review, A. Jackson.
12/10/98 - Labeling review, A. Vezza.
1/4/99 - Bioequivalence review, A. Jackson.
3/19/99 - Chemistry Review # 2, G.J. Smith.
10/07/99 - Chemistry Review # 2 Addendum of **9/16/99**, **Amendment**, R.C. Permisohn.

1. CMC - Satisfactory.
2. Labels/labeling - Satisfactory per A. Vezza review dated **9/24/99**.
3. BIO - Satisfactory per A. Jackson review dated **1/4/99**.
4. EER - Acceptable per 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.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend Approval.

19. REVIEWER: DATE COMPLETED:
Robert C. Permisohn 10/6/99
/S/ 10/26/99

Page(s) 14

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Review #2

10/26/99

Page(s) 1

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

7/26/99

Chemistry Review

#3P

Page(s) 2

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

3/27/98
Chemistry Review

#38

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-073

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-075
75-073
75-076

APPLICANT: Bertek, Inc.

DRUG PRODUCT: Nitroglycerin Transdermal Systems, 0.4 mg/hr, 0.2 mg/hr, 0.1 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. The dissolution testing conducted by Mylan Pharmaceutical on its transdermal nitroglycerin patches, Lot No. 26C011B, 0.4 mg/hr , Lot No. 26C001C, 0.2 mg/hr and Lot No. 26C006E, 0.1 mg/hr comparing them to Key Pharmaceuticals Nitro-Dur^{R} patches 0.4 mg/hr, 0.2 mg/hr and 0.1 mg/hr respectively, is acceptable. However, you have not conducted an acceptable in-vivo bioequivalence study on your 0.6 mg/hr versus Nitro-Dur 0.6 mg/hr. From the Bioequivalence point of view, the application is incomplete.

   The study which Mylan refers to in the introduction of this submission as a basis for waiver requests, is ANDA 74-559. The reference listed drug in ANDA 74-559, is Transderm-Nitro by Summit Pharmaceuticals. The patches in ANDA 74-559 are also of different sizes. The bioequivalence study in ANDA 74-992 is the appropriate biostudy for these waivers. The ANDA 74-992 has been found to be incomplete.

2. The dissolution testing should be incorporated into your manufacturing controls and stability progran. The dissolution testing should be conducted using apparatus (5)-Paddle over disk at 50 RPM in 600 ml water. The test product should meet the following specifications:

Sincerely yours,

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

Nitroglycerin Transdermal Patch
ANDA # 75-075-0.4 mg/hr
ANDA # 75-073-0.2 mg/hr
ANDA # 75-076-0.1 mg/hr
Reviewer: Andre J. Jackson
WP# 75075WD.697

Bertek Pharmaceuticals
Morgantown, West Va.
Submission Dated:
June 9, 1997

REVIEW OF A WAIVER REQUEST FOR NITROGLYCERIN TRANSDERMAL PATCH

Background

The firm is requesting a waiver for their manufacture of patches (3.5 cm2, 7.5 cm2 and 15 cm2) containing nitroglycerin with release rates of 0.1 mg/hr, 0.2 mg/ hour and 0.4 mg/hr. The product will be manufactured by Bertek Inc., The original submission for the bio-study ANDA # 74-992 was done by Mylan. However, the current waiver requests are under Bertek which is a wholly owned subsidiary of Mylan Laboratories Inc.[Note: The reference listed product is Key's Nitro-Dur Nitroglycerin Transdermal System].

The nitroglycerin patch which is the subject of this application has the same composition and manufacturing process as the Nitroglycerin Transdermal System contained in ANDA 74-559 which was approved on August 30, 1996 [The RLD was Ciba's Transderm-Nitro]. The only difference is in the 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.

Table 1. Comparative composition of 0.1 mg/hr, 0.2 mg/hr and 0.4 mg/hr nitroglycerin patches and the approved 0.6 mg/hr patch.

ACTIVE	THEORETICAL **mg/PATCH (3.75 cm2)**	THEORETICAL **mg/PATCH (22.5 cm2)**
Nitroglycerin(0.1 mg/hr)	10.50[1]	63.0[1]
INACTIVE		
Range		
CARRIER SYSTEM		

IMPRINTING INK

ACTIVE	THEORETICAL mg/PATCH (7.5 cm2)	THEORETICAL mg/PATCH (22.5 cm2)
Nitroglycerin(0.2mg/hr)	21.0[1]	63.0[1]

INACTIVE

CARRIER SYSTEM	cm2/PATCH	cm2/PATCH

ACTIVE	THEORETICAL mg/PATCH (15 cm2)	THEORETICAL mg/PATCH (22.5 cm2)
Nitroglycerin(0.4 mg/hr)	42.0[1]	63.0[1]

INACTIVE

CARRIER SYSTEM	cm2/PATCH	cm2/PATCH

IMPRINTING INK

[1] Nitroglycerin content is targeted at a constant per square meter.
[2] Based upon targets of content in the a target potency of per square meter

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)

Assay:

The results are presented in Table 2.

Comments:

1. 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.

2. The 0.4mg/hr, 0.2 mg/hr and 0.1 mg/hr formulations are compositionally proportional to the 0.6 mg/hr formulation.

Deficiency:

1. The study which Mylan refers to in the introduction is for their submission for which the reference

drug is Transderm-Nitro by Summit Pharmaceuticals. The patches in ANDA# 74-559 are also of different sizes. The bioequivalence study ANDA # 74-992 is the appropriate biostudy for these waivers. This ANDA#74-992 has been found to be incomplete.

Recommendation:

1. The dissolution testing conducted by Mylan Pharmaceutical on its transdermal nitroglycerin patches, Lot No. 26C011B,0.4 mg/hr , Lot No. 26C001C, 0.2 mg/hr and Lot No. 26C006E, 0.1 mg/hr comparing them to Key Pharmaceuticals Nitro-Dur^{R} patches 0.4 mg/hr, 0.2 mg/hr and 0.1 mg/hr respectively, is acceptable. However, the firm has not conducted an acceptable in-vivo bioequivalence study on its 0.6 mg/hr versus Nitro-Dur 0.6 mg/hr. From the Bioequivalence point of view, the application is incomplete.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability progran. The dissolution testing should be conducted using apparatus (5)-Paddle over disk at 50 RPM in 600 ml water. The test product should meet the following specifications:

/S/

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

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/

Date: 10/28/97

Concur: /S/

Date: 11/15/97

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

Table 2 . In Vitro Dissolution Testing

Drug (Generic Name):Nitroglycerin Transdermal System
Dose Strength:0.4 mg/hr, 0.2 mg/hr and 0.1 mg/hr
ANDA No.:75-075, 75-073 and 75-076
Firm:Bertek Pharmaceutical
Submission Date:June 9, 1997
File Name:75075DW.697

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[R]
Assay Methodology

Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 26C0011B Strength(mg) 0.4 mg/hr			Reference Product Lot # D5202411 Strength(mg) 0.4 mg/hr		
	Mean %	Range	%CV	Mean %	Range	%CV
30	61.0		2.0	47		2.0
60	81.0		1.0	66		0.8
120	90.0		1.1	81		0.8
240	96.0		1.1	85		1.2

Sampling Times (Minutes)	Test Product Lot # 26C001C Strength(mg) 0.2 mg/hr			Reference Product Lot # D5910212 Strength(mg) 0.2 mg/hr		
	Mean %	Range	%CV	Mean %	Range	%CV
30	63.0		2.1	53		2.5
60	83.0		1.0	70		1.9

120	92.0		0.8	90		1.6
240	101		0.8	95		1.2
Sampling Times (Minutes)	Test Product Lot # 26C006E Strength(mg) 0.1 mg/hr			Reference Product Lot # D4901117 Strength(mg) 0.1 mg/hr		
	Mean %	Range	%CV	Mean %	Range	%CV
30	63.0		2.1	49		2.0
60	81.0		1.3	70		0.8
120	94.0		2.7	88		0.8
240	99.0	97-102	1.4	97		1.2

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

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

JUN - 9 1998

Bertek, Inc.
Attention: Lamont M. Fulton

[illegible]

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

AUG 28 1998

BERTEK

NEW CORRESP

NC/B10

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, 0.1 mg/hr ANDA #75-076
NITROGLYCERIN TRANSDERMAL SYSTEM, 0.2 mg/hr ANDA #75-073
NITROGLYCERIN TRANSDERMAL SYSTEM, 0.4 mg/hr ANDA #75-075
Response to Agency Correspondence Dated February 27, 1998 & April 20, 1998

Dear Mr. Sporn:

Reference is made to the ANDA identified above, which is currently under review, and to the February 27, 1998 and April 20, 1998 correspondences 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. The Division reaffirmed the requirement for a skin irritation study in the April 20 correspondence. For the convenience of the reviewer, copies of the February 27, 1998 and April 20, 1998 correspondence are provided in Attachment 1.

In response to the Agency's correspondence of February 27, 1998, Bertek has conducted the required skin irritation study. The clinical final report of this study, entitled "Evaluation of Cumulative Irritation Potential in Humans 21-Day Test for Nitroglycerin Transdermal Patch", was submitted in the August 28, 1998 Bioequivalency Amendment to ANDA #74-992 for Nitroglycerin Transdermal Systems, 0.6 mg/hr and is incorporated herein by reference. This study was conducted pursuant to Protocol NITR9831 which was submitted to the Agency on April 16, 998. The Agency found this protocol to be acceptable as documented in a letter of Bertek dated June 15, 1998.

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

BERTEK ORIGINAL

APR 16 1998

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

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

c.1

FEB 27 1998

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

V2.1

Nitroglycerin Transdermal Patch
ANDA # 75-073-0.2 mg/hr
Reviewer: Andre Jackson
WP# 75073A.D97

Bertek Incorporated
St. Albans, Vt.
Submission Dated:
December 15, 1997

Review of Amendment

Background

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 and the study was found to be acceptable pending the outcome of a skin irritation study. The current study formulation has been shown to be proportional to ANDA # 74992 in a June 9, 1997 submission in which a waiver was requested for this formulation. However the waiver request for this submission was denied since the firm referenced the incorrect study (ANDA#74-559) and had not supplied skin irritation data for the appropriate study in which Key Nitro-Dur was the reference product (ie 74-992).
The current correspondence is the firm's amendment to the June 9th submission.

FDA COMMENT 1:

The dissolution testing conducted by Mylan Pharmaceutical on its transdermal nitroglycerin patches, Lot No. 26C011B, 0.4 mg/hr, Lot No. 26C001C, 0.2 mg/hr and Lot No. 26C006E, 0. 1 mg/hr comparing them to Key Pharmaceuticals Nitro-Dur patches 0.4 mg/hr, 0.2 mg/hr and 0. 1 mg/hr respectively, is acceptable. However, you have not conducted an acceptable in-vivo bioequivalence study on your 0.6 mg/hr versus Nitro-Dur 0.6 mg/hr. From the Bioequivalence point of view, the application is incomplete.

The study which Mylan refers to in the introduction of this submission as a basis for waiver requests, is ANDA 74-559. The reference listed drug in ANDA 74-559, is Transderm-Nitro by Summit Pharmaceuticals. The patches in ANDA 74-559 are also of

different sizes. The bioequivalence study in ANDA 74-992 is the appropriate biostudy for these waivers. The ANDA 74-992 has been found to be incomplete.

BERTEK RESPONSE:

As noted in the Introductions and Readers' Guide to the above referenced application (see Attachment 1) and provided for in our Biowaiver Request contained in Section VI of the original application (see Attachment 2), Bertek performed a single-dose bioequivalence study to compare the Nitroglycerin Transdermal System, 0.6 mg/hr to the reference listed drug, Nitro-Dur, 0.6 mg/hr. The results of this study are provided in ANDA 74-992, which Bertek references in its Biowaiver Request for the above referenced application.

ANDA 74-559 (versus Transderm-Nitro by Summit Pharmaceuticals) was referenced in the Introduction and Reader's Guide of the application for the following reasons:

1) As a point of reference, the intermediate coated laminate which is the subject of our current applications for which we are requesting approval is identical to that used to manufacture our approved nitroglycerin transdermal product (as approved under ANDA 74-559). The approved and proposed finished drug products are also identical with the exception of a minor variation in patch size. Bertek had hoped to facilitate the review of our current pending applications by indicating similarities between the approved product and those for which approval is being requested.

2) In addition to the bioequivalence study, wearability and irritation studies were performed on the approved product, under ANDA 74-559. As these studies are not size-relevant and are not used to demonstrate bioequivalence, they were not repeated for our pending applications. In our pending applications (ANDAs 74-992, 75-075, 75-073 and 75-076), Bertek referenced this supplemental data as an aid to the reviewer.

Bertek is currently in correspondence with the Agency to address the outstanding deficiencies with regard to ANDA 74-992. That information is being submitted under a separate cover.

FDA Reply:

The firm was sent a letter dated February 25, 1998 relating to them that the skin irritation study for ANDA # 74-559 was not sufficient by today's standards to be used for ANDAs 74-992, 75-075, 75-073 and 75-076. Therefore they will have to complete a new study for approval of these products.

FDA COMMENT 2:

The dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted using apparatus (5) -Paddle over disk at 50 RPM in 600 ml water. **The test product** should meet the following specification:

5
95

BERTEK RESPONSE:

As requested, Bertek has revised the Nitroglycerin Transdermal System specifications to those listed above. Attachment 3 contains copies of both the revised drug product specifications and the post-approval stability protocol which were 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.)

For ease of review, a copy of the Agency's correspondence, dated November 30, 1997, is provided in Attachment 4.

FDA Reply:

The firm's response is acceptable.

Deficiency:

1. The firm is required to complete a skin irritation study on the lowest dosage strength, 0.1 mg/hr, before the request for waiver of ANDA # 75-073 can be considered.

Recommendation

The dissolution testing data conducted by Bertek Incorporated on its 0.2 mg/hr transdermal nitroglycerin patch, lot no. 26C001C, comparing it to Key Pharmaceuticals Nitro-Dur 0.2 mg/hr patch Lot No. D5910212 has been previously found to be acceptable by the Division of Bioequivalence. The firm however, has not conducted an acceptable in vivo skin irritation study. From the Bioequivalence point of view, the application is incomplete.

/S/

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

RD INITIALED YCHUANG /S/
FT INITIALED YCHUANG

Date: 4/14/98

Concur: /S/ Date: 4/14/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-073, 75-075, 75-076
APPLICANT:Bertek Incorporated

DRUG PRODUCT:Nitroglycerin Transdermal System
0.2 mg/hr, 0.4 mg/hr, 0.1 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. Your application is still deficient. You must complete a skin irritation study on the lowest dosage strength 0.1 mg/hr before the request for waivers of ANDA # 75-073, 75-075 and 75-076 can be considered.

Sincerely yours,

/S/

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

APR 20 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-073, 75-075, 75-076
APPLICANT:Bertek Incorporated

DRUG PRODUCT:Nitroglycerin Transdermal System
0.2 mg/hr, 0.4 mg/hr, 0.1 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. Your application is still deficient. You must complete a skin irritation study on the lowest dosage strength 0.1 mg/hr before the request for waivers of ANDA # 75-073, 75-075 and 75-076 can be considered.

Sincerely yours,

/S/

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

BERTEK

DEC 15 1997

NDA

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)

N/A

Re: 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 November 30, 1997

Dear Mr. Sporn,

Reference is made to the Abbreviated New Drug Application highlighted above and to the Agency's correspondence submitted by facsimile on November 30, 1997 which contained deficiencies with regard to the bioequivalence information submitted in the application. In response to the November 30, 1997 letter, Bertek wishes to amend this application with the following:

FDA COMMENT 1:

The dissolution testing conducted by Mylan Pharmaceutical on its transdermal nitroglycerin patches, Lot No. 26C011B, 0.4 mg/hr, Lot No. 26C001C, 0.2 mg/hr and Lot No. 26C006E, 0.1 mg/hr comparing them to Key Pharmaceuticals Nitro-Dur^R patches 0.4 mg/hr, 0.2 mg/hr and 0.1 mg/hr respectively, is acceptable. However, you have not conducted an acceptable in-vivo bioequivalence study on your 0.6 mg/hr versus Nitro-Dur^R 0.6 mg/hr. From the Bioequivalence point of view, the application is incomplete.

The study which Mylan refers to in the introduction of this submission as a basis for waiver requests, is ANDA 74-559. The reference listed drug in ANDA 74-559, is Transderm-Nitro by Summit Pharmaceuticals. The patches in ANDA 74-559 are also of different sizes. The bioequivalence study in ANDA 74-992 is the appropriate biostudy for these waivers. The ANDA 74-992 has been found to be incomplete.

RECEIVED
DEC 16 1997
GENERIC DRUGS

BERTEK RESPONSE:

As noted in the Introductions and Readers' Guide to the above referenced application (see Attachment 1) and provided for in our Biowaiver Request contained in Section VI of the original application (see Attachment 2), Bertek performed a single-dose bioequivalence study to compare the Nitroglycerin Transdermal System, 0.6 mg/hr to the reference listed drug, Nitro-Dur^R, 0.6 mg/hr. The results of this study are provided in ANDA 74-992, which Bertek references in its Biowaiver Request for the above referenced application.

ANDA 74-559 (versus Transderm-Nitro^R by Summit Pharmaceuticals) was referenced in the Introduction and Reader's Guide of the application for the following reasons:

1) As a point of reference, the intermediate coated laminate which is the subject of our current applications for which we are requesting approval is identical to that used to manufacture our approved nitroglycerin transdermal product (as approved under ANDA 74-559). The approved and proposed finished drug products are also identical with the exception of a minor variation in patch size. Bertek had hoped to facilitate the review of our current pending applications by indicating similarities between the approved product and those for which approval is being requested.

2) In addition to the bioequivalence study, wearability and irritation studies were performed on the approved product, under ANDA 74-559. As these studies are not size-relevant and are not used to demonstrate bioequivalence, they were not repeated for our pending applications. In our pending applications (ANDAs 74-992, 75-075, 75-07[illegible] and 75-076), Bertek referenced this supplemental data as an aid to the reviewer.

Bertek is currently in correspondence with the Agency to address the outstanding deficiencies with regard to ANDA 74-992. That information is being submitted under a separate cover.

FDA COMMENT 2:

The dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted using apparatus (5) -Paddle over disk at 50 RPM in 600 ml water. The test product should meet the following specification:

BERTEK RESPONSE:

As requested, Bertek has revised the Nitroglycerin Transdermal System specifications to those listed above. Attachment 3 contains copies of both the revised drug product specifications and the post-approval stability protocol which were 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.)

For ease of review, a copy of the Agency's correspondence , dated November 30, 1997, is provided in Attachment 4.

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

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-075
75-073
75-076

APPLICANT: Bertek, Inc.

DRUG PRODUCT: Nitroglycerin Transdermal Systems, 0.4 mg/hr, 0.2 mg/hr, 0.1 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. The dissolution testing conducted by Mylan Pharmaceutical on its transdermal nitroglycerin patches, Lot No. 26C011B, 0.4 mg/hr , Lot No. 26C001C, 0.2 mg/hr and Lot No. 26C006E, 0.1 mg/hr comparing them to Key Pharmaceuticals Nitro-Dur® patches 0.4 mg/hr, 0.2 mg/hr and 0.1 mg/hr respectively, is acceptable. However, you have not conducted an acceptable in-vivo bioequivalence study on your 0.6 mg/hr versus Nitro-Dur 0.6 mg/hr. From the Bioequivalence point of view, the application is incomplete.

   The study which Mylan refers to in the introduction of this submission as a basis for waiver requests, is ANDA 74-559. The reference listed drug in ANDA 74-559, is Transderm-Nitro by Summit Pharmaceuticals. The patches in ANDA 74-559 are also of different sizes. The bioequivalence study in ANDA 74-992 is the appropriate biostudy for these waivers. The ANDA 74-992 has been found to be incomplete.

2. The dissolution testing should be incorporated into your manufacturing controls and stability progran. The dissolution testing should be conducted using apparatus (5)-Paddle over disk at 50 RPM in 600 ml water. The test product should meet the following specifications:

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 # 75-075-0.4 mg/hr
ANDA # 75-073-0.2 mg/hr
ANDA # 75-076-0.1 mg/hr
Reviewer: Andre J. Jackson
WP# 75075WD.697

Bertek Pharmaceuticals
Morgantown, West Va.
Submission Dated:
June 9, 1997

REVIEW OF A WAIVER REQUEST FOR NITROGLYCERIN TRANSDERMAL PATCH

Background

The firm is requesting a waiver for their manufacture of patches (3.5 cm2, 7.5 cm2 and 15 cm2) containing nitroglycerin with release rates of 0.1 mg/hr, 0.2 mg/ hour and 0.4 mg/hr. The product will be manufactured by Bertek Inc.. . The original submission for the bio-study ANDA # 74-992 was done by Mylan. However, the current waiver requests are under Bertek which is a wholly owned subsidiary of Mylan Laboratories Inc.[Note: The reference listed product is Key's Nitro-Dur Nitroglycerin Transdermal System].

The nitroglycerin patch which is the subject of this application has the same composition and manufacturing process as the Nitroglycerin Transdermal System contained in ANDA 74-559 which was approved on August 30, 1996 [The RLD was Ciba's Transderm-Nitro]. 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.

Table 1. Comparative composition of 0.1 mg/hr, 0.2 mg/hr and 0.4 mg/hr nitroglycerin patches and the approved 0.6 mg/hr patch.

ACTIVE	THEORETICAL **mg/PATCH (3.75 cm2)**	THEORETICAL **mg/PATCH (22.5 cm2)**
Nitroglycerin(0.1 mg/hr)	10.50[1]	63.0[1]
INACTIVE		

ACTIVE	THEORETICAL mg/PATCH (7.5 cm2)	THEORETICAL mg/PATCH (22.5 cm2)
Nitroglycerin(0.2mg/hr)	21.0[1]	63.0[1]

INACTIVE

Range

I

ACTIVE	THEORETICAL mg/PATCH (15 cm2)	THEORETICAL mg/PATCH (22.5 cm2)
Nitroglycerin(0.4 mg/hr)	42.0[1]	63.0[1]

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)

Assay:

The results are presented in Table 2.

Comments:

1. 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.

2. The 0.4mg/hr, 0.2 mg/hr and 0.1 mg/hr formulations are compositionally proportional to the 0.6 mg/hr formulation.

Deficiency:

1. The study which Mylan refers to in the introduction is for their submission for which the reference

drug is Transderm-Nitro by Summit Pharmaceuticals. The patches in ANDA# 74-559 are also of different sizes. The bioequivalence study ANDA # 74-992 is the appropriate biostudy for these waivers. This ANDA#74-992 has been found to be incomplete.

Recommendation:

1. The dissolution testing conducted by Mylan Pharmaceutical on its transdermal nitroglycerin patches, Lot No. 26C011B,0.4 mg/hr , Lot No. 26C001C, 0.2 mg/hr and Lot No. 26C006E, 0.1 mg/hr comparing them to Key Pharmaceuticals Nitro-Dur® patches 0.4 mg/hr, 0.2 mg/hr and 0.1 mg/hr respectively, is acceptable. However, the firm has not conducted an acceptable in-vivo bioequivalence study on its 0.6 mg/hr versus Nitro-Dur 0.6 mg/hr. From the Bioequivalence point of view, the application is incomplete.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability progran. The dissolution testing should be conducted using apparatus (5)-Paddle over disk at 50 RPM in 600 ml water. The test product should meet the following specifications:

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

/S/

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/

Date: 10/28/97

Concur:

Date: 11/18/97

/S/

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

Table 2 . In Vitro Dissolution Testing

Drug (Generic Name):Nitroglycerin Transdermal System
Dose Strength:0.4 mg/hr, 0.2 mg/hr and 0.1 mg/hr
ANDA No.:75-075, 75-073 and 75-076
Firm:Bertek Pharmaceutical
Submission Date:June 9, 1997
File Name:75075DW.697

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[R]
Assay Methodology

Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 26C0011B Strength(mg) 0.4 mg/hr			Reference Product Lot # D5202411 Strength(mg) 0.4 mg/hr		
	Mean %	Range	%CV	Mean %	Range	%CV
30	61.0		2.0	47		2.0
60	81.0		1.0	66		0.8
120	90.0		1.1	81		0.8
240	96.0	94-97	1.1	85	[illegible]	1.2

Sampling Times (Minutes)	Test Product Lot # 26C001C Strength(mg) 0.2 mg/hr			Reference Product Lot # D5910212 Strength(mg) 0.2 mg/hr		
	Mean %	Range	%CV	Mean %	Range	%CV
30	63.0		2.1	53		2.5
60	83.0		1.0	70		1.9

120	92.0		0.8	90		1.6
240	101		0.8	95		1.2

Sampling Times (Minutes)	Test Product Lot # 26C006E Strength(mg) 0.1 mg/hr			Reference Product Lot # D4901117 Strength(mg) 0.1 mg/hr		
	Mean %	Range	%CV	Mean %	Range	%CV
30	63.0		2.1	49		2.0
60	81.0		1.3	70		0.8
120	94.0		2.7	88		0.8
240	99.0		1.4	97		1.2

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-073

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 75-075

Date of Submission: June 9, 1997

Applicant's Name: Bertek, Inc.

Established Name: Nitroglycerin Transdermal System 0.4 mg/hr

Labeling Deficiencies:

1. General Comments

   a. Revise "Nitroglycerin Delivery System" to read "Nitroglycerin Transdermal System" on all labels and labeling.

   b. Delete the terminal zero following the decimal point on your labels and labeling. [i.e., "42 mg" instead of "42.0 mg"]

   c. We note your application has been transferred to Bertek, Inc. If necessary, please revise your labels accordingly or comment.

   d. Replace the "Caution: Federal law ..." statement with "℞ Only" where it appears on your labels and labeling. We refer you to Section 126 of the FDA Modernization Act of 1997 for guidance.

2. IMMEDIATE PATCH

   Satisfactory in draft.

3. CONTAINER (Pouch)

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

   b. Front panel

      i. To be consistent with your carton and insert

labeling, we encourage you to revise "unit" to read "system" on your container labels.

ii. Add the following statements:

A) Contents: 1 system

B) FOR TRANSDERMAL USE ONLY

iii. We encourage you to add the text, "KEEP OUT OF REACH OF CHILDREN".

c. Back panel

i. Instruction for Application

Revise to read as follows:

1. Open the pouch at the tear mark.

2. Bend both ... liner at the slit.

3. Peel ... 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 ... skin site and smooth down.

5. Remove remaining strip and apply the remainder of the patch to the skin. Press patch firmly ... hand.

ii. Add the statement "APPLY IMMEDIATELY UPON REMOVAL FROM POUCH".

iii. We encourage you to add the "Usual Dosage: Each 24 hour ... physician" statement following Instruction for Application #5.

iv. We encourage you to add the storage recommendation statement.

4. CARTON: 30s and 100s

a. See comment 3(a) under CONTAINER.

b. Center panel

i. Add the statement, "FOR TRANSDERMAL USE ONLY".

ii. Revise the first sentence to read, "Each system contains 42 mg of nitroglycerin in an acrylic pressure sensitive adhesive with a cross-linking agent".

c. Back panel

See comment 3(b)(ii)(B) under CONTAINER.

5. PATIENT PACKAGE INSERT LABELING:

Revise your patient package insert labeling to be in accord with the enclosed mocked up copy of your approved patient package insert labeling for ANDA 74-607 [Nitroglycerin Transdermal System, approved 8/30/96 and revised 5/95].

6. PROFESSIONAL PACKAGE INSERT

a. DESCRIPTION

i. In the last sentence of the third paragraph. delete the text, "in an acrylic pressure sensitive adhesive".

ii. 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".

iii. 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.

iv. In your list of inactive ingredients include any dyes in the imprinting ink used on the transdermal system.

v. 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)...

b. CLINICAL PHARMACOLOGY (Clinical Trials)

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.

c. PRECAUTIONS

i. Information for Patients

Add the following as the last sentence of the last paragraph:

> ... systems. See Patient Information Leaflet at the end of the insert.

ii. Drug Interactions

A) In the first and last sentence revise "addictive" to read "additive".

B) Add the following as the last paragraph 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.

iii. Carcinogenesis, Mutagenesis, Impairment of Fertility:

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 incidence 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.

d. ADVERSE REACTIONS

i. 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.

ii. In the third paragraph, revise "...this diagnosis" to read "... its diagnosis".

e. 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.

Please revise your labels and labeling, as instructed above, and submit in 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 and the enclosed patient package insert with

all differences annotated and explained.

/S/

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

Enclosure: Mylan's Nitroglycerin Transdermal System Patient Package Insert [ANDA 74-607], approved 8/30/96 and revised 5/95]

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-073

CORRESPONDENCE

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

NDA ORIG AMENDMENT

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) 4

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

9/16/99

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,

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

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.

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

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

NAI The Judgment is applicable only to Hercon — NA → to Babel (Wheeler)

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.

FEB 2 ... GENERIC DRUGS

Nadine 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

NDA ORIG AMENDMENT
N/Ac

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

SEP 17 1998

labeling review
drafted 11/30/98
AVzjw

MAJOR AMENDMENT

Re: 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 March 27, 1998

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Applications identified above and to the Agency's comments submitted via facsimile on March 27, 1998. 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:

REGARDING CHEMISTRY ISSUES:

Page(s) 3

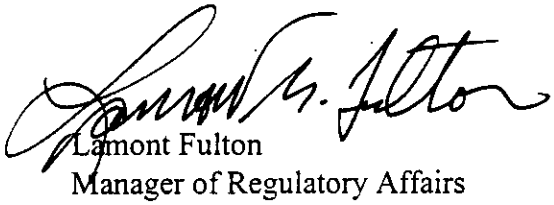
Contain Trade Secret, Commercial/Confidential Information and are not releasable.

9/17/98

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

NAF
N. Mallek
11/18/97

BERTEK

October 17, 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

RE: NITROGLYCERIN DELIVERY SYSTEM,
0.2 MG/HR
ANDA NO. 75-073

Dear Mr. Sporn:

Pursuant to 21 CFR 314.95(e), Bertek hereby amends the above referenced application with documentation of receipt of the notice required by 21 CFR 314.95(a). I have enclosed documentation of receipt by the owner of the patents, and the holder of the application for the listed drug claimed by said patents. Proof of delivery by Registered Mail, Return Receipt evidences receipt by Key Pharmaceuticals and Schering Corporation on July 23, 1997.

Sincerely,

Lamont M. Fulton
Manager, Regulatory Affairs

Amend 11-23-97

RECEIVED
OCT 20 1997
GENERIC DRUGS

BERTEK INC. 11710 LAKE STREET ST. ALBANS, VT 05478 800-421-7792 FAX 802 527-0486 TELEX 11 210-991-8483

BERTEK

NEW CORRESP

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

December 22, 1997

Re: NITROGLYCERIN DELIVERY SYSTEM, 0.1 mg/hr ANDA # 75-076
NITROGLYCERIN DELIVERY SYSTEM, 0.2 mg/hr ANDA # 75-073
NITROGLYCERIN DELIVERY SYSTEM, 0.4 mg/hr ANDA # 75-075
NITROGLYCERIN DELIVERY SYSTEM, 0.6 mg/hr ANDA # 74-992

Dear Mr. Sporn:

Bertek confirms that it was sued by Key Pharmaceuticals, Inc. with respect to the above-referenced product. Said lawsuit was filed on August 11, 1997 in the United States District Court for the Western District of Pennsylvania. Bertek amended this ANDA on October 17, 1997, and provided documentation of receipt of the notice required by 21 CFR §314.95(a).

Sincerely,

Lamont M. Fulton
Manager of Regulatory Affairs

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

ANDA 75-073

Bertek, Inc.
Attention: Lamont Fulton

JUL 2

Dear Sir:

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

Reference is also made to our "Refuse to File" letter dated March 28, 1997, and your amendment dated June 9, 1997.

NAME OF DRUG: Nitroglycerin Transdermal Delivery System, 0.2 mg/hr

DATE OF APPLICATION: February 7, 1997

DATE OF RECEIPT: February 10, 1997

DATE ACCEPTABLE FOR FILING: June 10, 1997

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

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

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

Jerry Phillips 7/2/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

e

ate 7/2/97
ate

BERTEK

ANDA - 75-073

June 9, 1997

NDA ORIG AMENDMENT
Ac

Office of Generic Drugs
Mr. Douglas Sporn, Director
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

RE: Refusal to File Amendment

Dear Mr. Sporn:

This is in reference to our abbreviated new drug application (ANDA) dated February 7, 1997, submitted pursuant to section 505 (j) of the Federal FD&C Act, and the subsequent refusal to file dated March 28, 1997 under 21 CFR 314.101 (d) (3) for the Nitroglycerin Transdermal Delivery System, 0.2 mg/hr.

:rtek has reviewed your comments and will provide the following:

- Copies of a transfer of ownership letter from Mylan to Bertek.
- Copies of the acceptance of the ownership letter from Bertek.

The required in vivo bioequivalence data submitted in ANDA 74-992 can now be correctly referenced in support of our ANDA.

Sincerely,

Lamont Mike Fulton
Manager, Regulatory Affairs

LMF/slc

Enclosures

cc: S. Govil
B. Ash

RECEIVED
JUN 10 1997
GENERIC DRUGS

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

REF: K:\REGULATO\FDA\SPORNLT2.609

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

April 22, 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

CORRESPONDENCE

RE: NITROGLYCERIN DELIVERY SYSTEM, 0.6 MG/HR
ANDA 74-992
TRANSFER OF OWNERSHIP

Dear Mr. Sporn:

On October 25, 1996, Mylan Pharmaceuticals Inc. submitted an Abbreviated New Drug Application for the following transdermal nitroglycerin product:

Nitroglycerin Delivery System, 0.6 mg/hr.

This application was received by the Agency on October 28,1996 and assigned ANDA # 74-992.

By way of this letter and in accordance with the regulations set forth in 21 CFR 314.72, Mylan is transferring ownership of this application to Bertek Inc., located at
Bertek Inc. is a wholly owned subsidiary of Mylan Laboratories Inc. and is the manufacturer of the nitroglycerin product which is the subject of this application. All rights to ANDA 74-992 are hereby transferred to Bertek Inc. The contact person at Bertek is Lamont Fulton, Manager of Regulatory Affairs.

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

This correspondence is submitted in duplicate.

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

/maa

Department—Fax Numbers

Accounting	(304) 598-5403	Information Systems	(304) 598-5404	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) 598-5409
Human Resources	(304) 598-5406	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
		Medical Unit	(304) 598-5445		

BERTEK

April 23, 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

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 [redacted] k, 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

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

ANDA 75-073

Bertek, Inc.
Attention: Lamont Fulton

MAR 28 1997

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated February 7, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Nitroglycerin Transdermal Delivery System, 0.2 mg/hr.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> The information submitted to support approval of your application should include the required *in vivo* bioequivalence data. Cross-referencing *in vivo* bioequivalence studies submitted by another applicant is not permitted.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

If you have any questions please call:

Harvey Greenberg
Project Manager
(301) 594-0315

Sincerely yours,

/S/

Jerry Phillips 3/28/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BERTEK

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

RE: Nitroglycerin Delivery System, 0.2 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, 0.2 mg/hr

This application consists of a total of 10 volumes:

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

This application provides for the manufacture of patches (7.5 cm^2) containing nitroglycerin with a release rate of 0.2 mg per hour. The product will be manufactured by Bertek Inc.,
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 System contained in ANDA 74-559, which was approved on August 30, 1996. The only difference is in the rocess 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.

1997

BERTEK INC. 100 LAKE STREET ST. ALBANS, VT 05478 802-527-7792 FAX 802-527-0486 TELEX 4-710-931-8483

As required by 21 CFR 314.94(d)(5) we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Boston District Office.

For more detailed information regrading 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 Bertek Inc.,
Phone No.].

Sincerely,

Lamont Fulton
Manager
Regulatory Affairs