

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-233

Approval Letter

FEB 24 2000

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 21, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Estradiol Transdermal System, 0.05 mg/day, (Once-a-Week formulation).

Reference is also made to your amendments dated March 12 and October 28, 1998; and April 14, July 26, September 3, and October 27, 1999.

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 Estradiol Transdermal System, 0.05 mg/day to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Climara® Transdermal System, 0.05 mg/day of Berlex Laboratories, Inc.).

The dissolution testing should be incorporated into your manufacturing controls and stability program. The "interim" dissolution test and tolerances are:

The dissolution testing should be conducted in 500 mL of 0.3% sodium lauryl sulfate in 0.005N NaH₂ PO₄, pH 5.5, at 32° C using USP 23 apparatus 5 (paddle over disk) at 100 rpm. These percentages of the labeled amount of estradiol in the dosage form should be released within the following time periods:

1 hour	15 - 40%
4 hours	45 - 70%
8 hours	70 - 90%
24 hours	Not Less Than 80%

The "interim" dissolution test and tolerances should be finalized by submitting dissolution data for the first three production size batches in a supplemental application. The supplemental application should be submitted under Section 505(j) of the Act as a "Changes Being Effected (CBE-0)" supplement when there are no revisions to the interim specifications or when the final specifications are tighter than the interim specifications. In all other instances the supplement should be submitted under Section 505(j) of the Act as a prior approval supplement.

We note that the listed drug (RLD) referenced in your application, Climara Transdermal System of Berlex Laboratories, is subject to a period of patent protection which expires on June 29, 2010, (U.S. Patent No. 5,223,261). Your application contains a patent certification 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 of an abbreviated application shall be made effective immediately, unless an infringement action is brought against you before the expiration of forty-five days from the date of the notice provided under paragraph (2)(B)(I). You have notified FDA that Mylan Technologies, Inc. (Mylan) has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Mylan within the statutory forty-five day period.

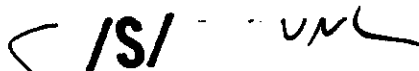
Under Section 506(A) of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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 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) which 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,

Handwritten signature consisting of the letters 'JW' in a stylized, cursive font.

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-233

FINAL PRINTED LABELING

"SPECIMEN"

Estradiol Transdermal System (Once a Week Formulation) Continuous Delivery for Once-Weekly Application

R
only

INFORMATION FOR THE PATIENT

INTRODUCTION

The Estradiol Transdermal System (once a week formulation) that your doctor has prescribed for you releases small amounts of estradiol through the skin in a continuous way. Estradiol is the same hormone that your ovaries produce abundantly before menopause. The dose of estradiol you require will depend upon your individual response. The dose is adjusted by the size of the Estradiol Transdermal System (once a week formulation) used; the systems are available in two sizes.

This leaflet describes when and how to use estrogens, and the risks and benefits of estrogen treatment.

Estrogens have important benefits but also some risks. You must decide, with your doctor, whether the risks to you of estrogen use are acceptable because of their benefits. If you use estrogens, check with your doctor to be sure you are using the lowest possible dose that works, and that you don't use them longer than necessary. How long you need to use estrogens will depend on the reason for use.

1. ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE ("CHANGE OF LIFE").

If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

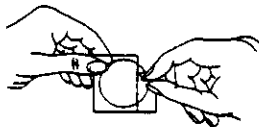
Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.

INFORMATION ABOUT ESTRADIOL TRANSDERMAL SYSTEM (ONCE A WEEK FORMULATION)

How The Estradiol Transdermal System (Once a Week Formulation) Works
The Estradiol Transdermal System (once a week formulation) contains 17 β -estradiol. When applied to the skin as directed below, the Estradiol Transdermal System (once a week formulation) releases 17 β -estradiol, which flows through the skin into the bloodstream.

How and Where to Apply the Estradiol Transdermal System (Once a Week Formulation)

Each Estradiol Transdermal System (once a week formulation) is individually sealed in a protective pouch. Tear open this pouch at the indentation (do not use scissors) and remove the system.



A protective liner covers the adhesive side of the system - the side that will be placed against your skin. This liner must be removed before applying the system. Remove the protective liner and discard it. Try to avoid touching the adhesive. Apply the adhesive side of the system to a clean, dry area of the skin on the abdomen. Do not apply the Estradiol Transdermal System (once a week formulation) to your breasts.

The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site on the abdomen or the upper quadrant of the buttock. The area selected should not be oily, damaged, or irritated. Avoid the waistline, since light clothing may rub and remove the system. Application to areas where sitting would dislodge the system should be avoided. Apply the system immediately after opening the pouch and removing the protective liner. Press the system firmly in place with the fingers for about 10 seconds, making sure there is a good contact, especially



around the edges.

The Estradiol Transdermal System (once a week formulation) should be worn continuously for one week. You may wish to experiment with different locations when applying a new system, to find ones that are most comfortable for you and where clothing will not rub on the system.

When to Apply the Estradiol Transdermal System (Once a Week Formulation)

The Estradiol Transdermal System (once a week formulation) should be changed once weekly. When changing the system, remove the used Estradiol Transdermal System (once a week formulation) and discard it. Any adhesive that might remain on your skin can be easily rubbed off. Then place the new Estradiol Transdermal System (once a week formulation) on a different skin site. (The same skin site should not be used again for at least 1 week after removal of the system.)

Contact with water when you are bathing, swimming, or showering may affect the system. In the unlikely event that a system should fall off, a new system should be applied for the remainder of the 7-day dosing interval.

USES OF ESTROGEN

(Not every estrogen drug is approved for every use listed in this section. If you want to know which of these possible uses are approved for the medicine prescribed for you, ask your doctor or pharmacist to show you the professional labeling. You can also look up the specific estrogen product in a book called the "Physicians' Desk Reference", which is available in many book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.)

- To reduce moderate or severe menopausal symptoms. Estrogens are hormones made by the ovaries of normal women. Between ages 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels which causes the "change of life" or menopause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden drop in estrogen levels causes "surgical menopause". When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. Most women have only mild menopausal symptoms or none at all and do not need to use estrogen drugs for these symptoms. Others may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. The majority of women do not need estrogen replacement for longer than six months for these symptoms.
- To treat vaginal and vaginal atrophy (itching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause.
- To treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.
- To treat certain types of abnormal vaginal bleeding due to hormonal imbalance when your doctor has found no serious cause of the bleeding.
- To treat certain cancers in special situations, in men and women.
- To prevent thinning of bones.

Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists and hips break most often in osteoporosis. Both men and women start to lose bone mass after about age 40, but women lose bone mass faster after the menopause. Using estrogens after the menopause slows down bone thinning and may prevent bones from breaking. Lifelong adequate calcium intake, either in the diet (such as dairy products) or by calcium supplements (to reach a total daily intake of 1000 milligrams per day before menopause or 1500 milligrams per day after menopause), may help to prevent osteoporosis. Regular weight-bearing exercise (like walking and running for an hour, two or three times a week) may also help to prevent osteoporosis. Before you change your calcium intake or exercise habits, it is important to discuss these lifestyle changes with your doctor to find out if they are safe for you.

Since estrogen use has some risks, only women who are likely to develop osteoporosis should use estrogens for prevention. Women who are likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, sister, or aunt. Women who have relatively early menopause, often because their ovaries were removed during an operation ("surgical menopause"), are more likely to develop osteoporosis than women whose menopause happens at the average age.

WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:



- **During pregnancy (see Based Warning).**
If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.
- **If you have unusual vaginal bleeding which has not been evaluated by your doctor (see Based Warning).**
Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.
- **If you have had cancer.**
Since estrogens increase the risk of certain types of cancer, you should not use estrogens if you have ever had cancer of the breast or uterus, unless your doctor recommends that the drug may help in the cancer treatment. (For certain patients with breast or prostate cancer, estrogens may help).
- **If you have any circulation problems.**
Estrogen drugs should not be used except in unusually special situations in which your doctor judges that you need estrogen therapy so much that the risks are acceptable. Men and women with abnormal blood clotting conditions should avoid estrogen use (see DANGERS OF ESTROGENS, below).
- **When they do not work.**
During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims and such long-term estrogen use may have serious risks.
- **After childbirth or when breastfeeding a baby.**
Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see DANGERS OF ESTROGENS, below).
If you are breastfeeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your health care provider.

DANGERS OF ESTROGENS

- **Cancer of the uterus.**
Your risk of developing cancer of the uterus gets higher the longer you use estrogens and the larger doses you use. One study showed that after women stop taking estrogens, this higher cancer risk quickly returns to the usual level of risk (as if you had never used estrogen therapy). Three other studies showed that the cancer risk stayed high for 8 to more than 15 years after stopping estrogen treatment. Because of this risk, **IT IS IMPORTANT TO TAKE THE LOWEST DOSE THAT WORKS AND TO TAKE IT ONLY AS LONG AS YOU NEED IT.**
Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (but see OTHER INFORMATION below).
If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.
- **Cancer of the breast.**
Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used higher doses for shorter time periods.
Regular breast examinations by a health professional and monthly self-examination are recommended for all women.
- **Gallbladder disease.**
Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.
- **Abnormal blood clotting.**
Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting off blood to the heart), a pulmonary embolus (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long-term disability. However, most studies of low dose estrogen usage by women do not show an increased risk of these complications.

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

- Nausea and vomiting.
- Breast tenderness or enlargement.
- Enlargement of benign tumors ("fibroids") of the uterus.
- Retention of excess fluid. This may make some conditions worsen such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- A spotty darkening of the skin, particularly on the face.

REDUCING RISK OF ESTROGEN USE

- If you use estrogens, you can reduce your risks by doing these things:
- **See your doctor regularly.**
While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal

- mammogram (breast x-ray), you may need to have more frequent breast examinations.
- **Remember your need for estrogens.**
You and your doctor should reevaluate whether or not you still need estrogens at least every six months.
- **Be alert for signs of trouble.**
If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:
Abnormal bleeding from the vagina (possible uterine cancer)
Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)
Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye)
Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly)
Yellowing of the skin or eyes (possible liver problem)
Pain, swelling, or tenderness in the abdomen (possible gallbladder problem).

OTHER INFORMATION

1. Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctors may prescribe a progestin for you to take together with your estrogen.
You should know, however, that taking estrogens with progestins may have additional risks. These include:
 - unhealthy effects on blood fats (especially a lowering of HDL blood cholesterol, the "good" blood fat which protects against heart disease);
 - unhealthy effects on blood sugar (which might make a diabetic condition worse); and
 - a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

Some research has shown that estrogens taken without progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

- You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatments as they affect you personally.
2. Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.
 3. If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about how much to take.
 4. Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.
 5. This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physicians' Desk Reference," which is available in book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

HOW SUPPLIED

Descriptions

Estradiol Transdermal System (once a week formulation), is designed to release 17 β -estradiol continuously upon application to intact skin. Two (15.5 and 31 sq cm active area) systems are available to provide nominal *in vivo* delivery of 0.05 or 0.1 mg respectively of estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 15.5 or 31 sq cm, and contains 1.94 or 3.88 mg of estradiol USP respectively.

Estradiol Transdermal System, 0.05 mg/day (Once a Week Formulation) - each 15.5 sq cm system contains 1.94 mg of estradiol USP.....NDC 0378-3350-99

Individual Carton of 4 systems

Estradiol Transdermal System, 0.1 mg/day (Once a Week Formulation) - each 31 sq cm system contains 3.88 mg of estradiol USP.....NDC 0378-3352-99

Individual Carton of 4 systems

Store at 15° - 30°C (59° - 86°F). Do not store unpouched. Apply immediately upon removal from the protective pouch.



MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505

REVISED MAY 1999
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APPROVED

Estradiol Transdermal System
0.05 mg/day (15.5 cm²)

FEB 24 2000

"SPECIMEN"

*Estradiol Transdermal System,
0.05 mg/day (Once a Week Formulation)*



MYLAN®

NDC 0378-3350-99

*Estradiol
Transdermal System,
0.05 mg/day
(Once a Week Formulation)*

B
only

4 Systems

Contents: Each 15.5 cm² system contains 1.94 mg estradiol USP to provide 0.05 mg of estradiol per day. The inactive ingredients are propylene glycol, povidone, anhydrous colloidal silicon dioxide, pressure sensitive acrylic adhesive, copolymer foam, polyester film, and brown ink (yellow iron oxide pigment, red iron oxide pigment and carbon black pigment.)

FOR TRANSDERMAL USE ONLY.

Keep this and all drugs out of the reach of children.

*Estradiol Transdermal System,
0.05 mg/day (Once a Week Formulation)*

*Estradiol Transdermal System,
0.05 mg/day (Once a Week Formulation)*

NDC 0378-3350-99

Do not store unpouched. Store at 15°-30°C (59°-86°F).

Usual Dosage: See attached prescribing information. Apply immediately upon removal from pouch.

Each Estradiol Transdermal System (Once a Week Formulation) is intended to be worn for 7 days.

MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505



3 0378-3350-99 8

Lot

Exp

M3350-99-4C.R1

BLACK

200 RED

"SPECIMEN"

⊕


NDC 0378-3350-16
R only
3350:1

MYLAN
Estradiol **APPROVED**
Transdermal System
0.05 mg/day
(Once a Week Formulation) [FEB 24 2009]

Contents:
 One 15.5 cm² system containing 1.94 mg estradiol USP to provide 0.05 mg of estradiol per day. The inactive components are propylene glycol, povidone, anhydrous colloidal silicon dioxide, pressure sensitive acrylic adhesive, copolymer foam, polyester film, and brown ink (yellow iron oxide pigment, red iron oxide pigment and carbon black pigment.) Do not store unpouched. Store at 15°-30°C (59°-86°F).

MYLAN PHARMACEUTICALS INC.
 Morgantown, WV 26505

⊕

⊕

3350:1

Usual Dosage: See patient instructions for application. Apply immediately upon removal from pouch.
 Each system is intended to be worn for 7 days.
 Keep this and all drugs out of the reach of children.

⊕

Face prints PMS 306 Blue, PMS 200 Red, and Black.
 92 mm x 92 mm - 6 mm Heat Seal.
 Keylines and Heat Seal do not print.

Back prints Black.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-233

MEDICAL REVIEW(S)

ATTACHMENT 2

MEDICAL OFFICER REVIEW

May 7, 1999

ANDA 75-182
75-233

Drug Product: Estradiol Transdermal System, 0.1 mg/day and 0.05 mg/day
Sponsor: Bertek Inc.

Reference Listed Drug: Climara Estradiol Transdermal System (Berlex, Inc.)

Regulatory History

In correspondence dated February 24, 1998, the Office of Generic Drugs recommended that Mylan/Bertek conduct a 21-day cumulative irritation study on this product. This was the usual requirement for transdermal products and was particularly important because the Bertek product contains a greater amount of propylene glycol than was present in other transdermal products. Bertek sent an amendment to their original application on May 28, 1998. This amendment included two studies: a primary dermal irritation study (test vs. reference for a single application) and a repeat insult study (test vs. placebo for 21 days with subsequent evaluation for contact sensitization). These studies were found to establish similar patterns of adhesion of the test and reference products and acceptable contact sensitization for the test product. The requirement for cumulative skin irritation comparing test vs. reference was not addressed adequately, however. The sponsor was in touch with the Office of Generic Drugs to discuss this in April 1999. They had completed a 21-day skin irritation study that compared test vs. reference, and they wanted to know if it would be necessary to submit it. It was agreed that they would submit it for review to complete the requirements for skin irritation studies.

Title

A 21-Day Evaluation of Cumulative Skin Irritation Potential in Humans for a 0.05 mg/day Estradiol Transdermal Patch

CRO: c.

Study Objective

To evaluate the cumulative irritation potential of Estradiol Transdermal Systems, manufactured by Bertek, Inc., relative to that of the reference product, Climara (Berlex, Inc.) following repetitive topical application over a 21-day period.

Study Design

This was a blinded (to scorer) study comparing the skin irritation of three test articles:

1. Estradiol Transdermal System 0.05 mg/day
2. Climara Transdermal System 0.05 mg/day
3. Estradiol Transdermal System placebo

The transdermal patches were applied for 7 days each for a total of 3 consecutive applications. Scoring for irritation was done prior to re-application of a new patch and after removal of the last patch. Any site reaching maximum irritation (score of 3 or greater) was not re-patched but it continued to be scored until the end of the study. The study

enrollment was set to have 25 "completers" – subjects who satisfied all entry criteria and completed all required visits. Patients who withdrew were not replaced.

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Females, 18 years of age or older.
2. Absence of menses for one year for post-menopausal subjects, or at least 6 weeks for oophorectomized subjects. For oophorectomized subjects, an operative report documenting bilateral oophorectomy and a surgical pathology report documenting the absence of malignant disease must be available for review.
3. Signed informed consent.
4. Minor deviations in normal medical history, physical examination and clinical laboratory results, considered to be clinically insignificant by the Investigator/Sub-Investigator and the Mylan monitor will be permitted.
5. Baseline 17-beta-estradiol plasma serum level \leq 20 pg/ml.
6. Baseline FSH serum levels $>$ 40 mIU/ml.

Exclusion Criteria

1. Male; premenopausal, perimenopausal or pregnant, lactating females.
2. History of any significant chronic disease or medical condition which, in the Investigator's judgement, makes the subject ineligible or places the subject at undue risk as determined by a prestudy medical evaluation performed within 14 days of the initial dose of study medication:
 - a. Physical examination
 - b. Breast examination
 - c. Pelvic examination consistent with hypoestrogenism
 - d. Mammogram – if not done in the last 12 months
 - e. Papanicolaou smear – if not done in the last 12 months
 - f. Clinical laboratory evaluation (chemistry/hematology/urinalysis)
 - g. 12-lead EKG
3. Active clinically significant skin diseases which may contraindicate participation, including eczema, psoriasis and atopic dermatitis.
4. Any acute illness or surgery within the past four weeks.
5. Participation in a patch test for irritation or sensitization within the last 30 days.
6. Topical drugs used at patch site.
7. Damaged skin in or around test sites which include sunburn, uneven skin tones, tattoos, scars or other disfiguration of the test site.
8. Allergy or hypersensitivity to any of the components of the transdermal system (i.e., adhesive dressings, medical tape, band-aids), estradiol or other hormonal products.
9. History of drug and/or alcohol abuse.
10. Subjects who have received an investigational drug within the last 30 days of the initiation of this study or who are currently participating in or plan to enter a clinical study.
11. Use of any systemic antibiotic, estrogens, or hormone within a minimum of 4 weeks prior to the initial dose of study medication.
12. Unwillingness or inability to sign consent.
13. Known or suspected breast cancer.
14. Known or suspected estrogen-dependent neoplasia.
15. Active thrombophlebitis or thromboembolic disorders.
16. Any undiagnosed vaginal bleeding.
17. Insulin-dependent diabetes.
18. Asthma that requires prescribed medication.
19. Immunological disorders such as HIV positive, AIDS and systemic lupus erythematosus.
20. Use of any prescribed anti-inflammatory drug, immunosuppressive drugs or prescription or non prescription antihistamine medication (steroid nose drops and/or eye drops are permitted) within 14 days of dosing and

throughout the study. Any over-the-counter pain medication that is ingested in quantities exceeding label instructions within 14-days of dosing and throughout the study.

Study Conduct

Sixty-six individuals were screened. A medical history, physical examination, and laboratory testing was completed and subjects' eligibility was determined according to the inclusion/exclusion criteria listed above. Thirty subjects were enrolled in the study and 29 completed the study. Transdermal patches were applied to the abdomen at the same site for the duration of the study unless the maximum allowable irritation limit was reached (a score of 3 or greater or a letter grade of F, G, or H).

The primary measurement was the evaluation of irritation using a validated scoring system. Skin evaluations were conducted 30 minutes after removal of the first, second, and third patch by trained blinded scorers. Scoring was done by trained individuals. The protocol states that all attempts would be made to have a single individual do all the scoring but the final report does not specify if this was the case or not. The scorer was blinded to the treatment assignments and all prior scores. The following scale was used to quantify irritation:

- 0 = No evidence of irritation
- 1 = Minimal erythema, barely perceptible
- 2 = Definite erythema, readily visible; or minimal edema; or minimal papular response
- 3 = Erythema and papules
- 4 = Definite edema
- 5 = Erythema, edema and papules
- 6 = Vesicular eruption
- 7 = Strong reaction spreading beyond the test site

Effects on the superficial layers of the skin were scored as follows:

- A = Slight glazed appearance
- B = Marked glazing
- C = Glazing with peeling and cracking
- F = Glazing with fissures
- G = Film of dried serous exudate covering all or portion of patch site
- H = Small petechial erosions and/or scabs

Several maximum limits were defined for these scores. When a numerical score of 3, 4, 5, 6, or 7 was reached or any numerical score was appended with the letter grade of F, G, or H, no further applications of test material were made. However, this site continued to be scored to the end of the 21-day study period. In this situation, a score of 3 was entered for all scores through the remainder of the study. The letter grades were converted to numerical scores as follows: A = 0, B = 1, C = 2, and F, G, and H = 3. These numerical equivalents were considered additive to the numerical score (e.g., 2C = 2 + 2 = 4). They were added in the calculation of the total irritancy score for the entire cohort. The upper limit individual score selected was 3. All scores were calculated and those above this were entered as 3 in order to maintain the focus on evaluation of mild irritation expected for these products. Statistical analysis was carried out on the total irritation for each test day and overall, ranked within each subject, and analyzed using the Friedman rank sum method. The hypotheses for this test were as follows:

Ho: The rank sums of the three test articles are identical.

Ho: At least two of the rank sums differ.

Fisher's LSD test was performed if significant differences ($p < 0.05$) were observed with the Friedman rank sum test.

Concomitant medications and adverse events were recorded at each visit. The Investigator determined the severity and relatedness of adverse events to the test material.

Study Results

All primary data was provided by the Applicant and reviewed by the Medical Officer in tandem with review of the mean and cumulative data presented by the Applicant.

Thirty subjects were enrolled and patched between July 7, 1998 and July 28, 1998. One subject withdrew from the study because they were "going out town". There were 11 protocol violations. In 4 subjects the patch contact time of 8 patches at one application was reduced to 15, 36, 49, 76, and 167 hours. This involved 2 Estradiol, 3 Climara, and 3 placebo patches. Three subjects had laboratory values that were slightly out of the range specified in the Inclusion criteria (FSH level of 39.1 instead of >40 mIU/ml, FSH level of 38.3 instead of >40 mIU/ml, and Estradiol level of 21 instead of <= 20 pg/ml). In three subjects patches were reapplied after being "lost". This occurred on Day 2 (1) and Day 4 (2), patches were reapplied within 11 to 18 hours, and all three patches applied per subject were involved. One subject was erroneously patched using the incorrect randomization scheme.

Demographics

Twenty-six subjects (87%) were Caucasian and four were African-American (13%). The age distribution of the Caucasian subjects was 45 to 81 and the African-American subjects ranged in age from 52 to 74 years old.

Concomitant Medications

Twenty subjects who had not had a hysterectomy were also treated with Provera 10 mg following the final patch to minimize the risks of unopposed estradiol administration. In addition, 7 subjects took concomitant medications for hypertension, blood thinning, reduction of cholesterol, arthritis pain (Advil), yeast infection, kidney infection and associated pain, and headache. None of these medications were forbidden by the study protocol.

Adverse Events

Thirteen subjects experienced 27 events involving 18 different adverse events. Of these, 8 events in 9 subjects were determined to have a Possible, Probable, or Highly Probable relationship to the study drug. Only one of these events was a local reaction to the transdermal patch and/or its active drug product. These events are presented in the Table below.

Table I
Adverse events with a Possible, Probable, or Highly Probable relationship to the study drug.

	# of subjects	Mild	Moderate	Severe	# of occurrences
Highly Probable					
Itching on site B	1	0	1	0	1
Probable					
Breast Tenderness	2	1	1	0	2
Breast Soreness	3	2	2	0	4
Soreness in Nipples	3	1	3	0	4
Possible	# of subjects	Mild	Moderate	Severe	# of occurrences
Moodiness	1	0	0	1	1
Headache	1	0	1	0	1
Cramping (intermittent)	1	0	1	0	1
Cramping	1	1	0	0	1

Mean Irritation Scores

The mean scores for each evaluation day were calculated. Cumulative irritation was noted for all the patch types characterized as minimal to definite erythema. The mean scores are summarized in the table below (Table II).

Table II
Mean Irritation Scores

Test Article	Day 8 (n=29)	Day 15 (n=28)	Day 22 (n=29)	Overall (n=28)
Estradiol	0.793	0.964	1.172	2.857
Climara	0.862	0.821	1.000	2.750
Placebo	0.621	0.643	0.966	2.214
p-values	0.1935	0.0121	0.2050	0.0222
Significant LSD comparisons	None	Estradiol vs. placebo	None	Estradiol vs. placebo

The Estradiol transdermal system was significantly more irritating overall and at Day 15 than its placebo indicating that the active drug product contributed to the irritation. The mean scores did not differ on Day 22 and the scores for Estradiol and Climara were similar at all evaluations. Letter scores were assigned to one subject in each group: glazing and fissures, Estradiol and Placebo patches and papules, Climara patch.

Total Cumulative Irritation

Total cumulative irritation was similar for the two active patches and a little less in the placebo patch group. These figures were adjusted because of differences in sample size in each group at each visit to a base of 10 subjects. These results are similar to overall cumulative irritation and are displayed in Table III.

Table III
Cumulative Irritation Scores

	Cumulative Irritation	Base 10 Cumulative Irritation
Estradiol	87	30
Climara	77	27
Placebo	65	22

The distribution of scores at each evaluation day is shown in Table IV below. The majority of the scores for all groups were 1+. One-third of subjects in the placebo group had with scores of 0 throughout the application period.

Table IV
Proportion of subjects with individual scores of 0, 1+, 2+, and 3+ at each evaluation time

Score	Day 8			Day 15			Day 22		
	E	C	P	E	C	P	E	C	P
0	8	9	13	3	7	13	2	5	13
1	19	16	14	23	20	14	21	20	21
2	2	3	2	3	0	2	6	3	3
3	0	1	0	0	1	0	0	1	0

E - Estradiol C - Climara P - Placebo

0 = No evidence of irritation

1 = Minimal erythema, barely perceptible

2 = Definite erythema, readily visible; or minimal edema; or minimal papular response

3 = Erythema and papules

Only three subjects required patch site changes because of irritation: Day 8, Climara, score 3+; Day 15, Estradiol, score 2F (glazing and fissures); Day 15, Placebo, score 2F (glazing and fissures).

Conclusion

There was no significant difference in the mean or cumulative irritation scores of the Bertek Estradiol transdermal patch and the Climara patch. The Estradiol patch was found to be more irritating than its placebo patch at the Day 15 evaluation and overall. One subject experienced moderate itching on one occasion at the site of the Climara patch. There were no other patch site adverse events reported.

In combination with the studies reviewed previously that found similar patterns of adhesion of the test and reference products and acceptable contact sensitization for the test product, this study confirms that the test and reference products are similar in their skin irritation potential.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-233

CHEMISTRY REVIEW(S)

1. CHEMIST's REVIEW #5
2. ANDA 75-182
ANDA 75-233
3. APPLICANT, Name/Address/Telephone/Fax:
Mylan Technologies, Inc. (formerly Bertek, Inc.)
Attention: Elizabeth Ash
110 Lake Street
St. Albans, VT 05478
☎802 527-7792/fax 802 527-0486
4. LEGAL BASIS FOR ANDA SUBMISSION: 505(j)
5. Supplement: n/a
6. PROPRIETARY NAME: ncne
7. Non-PROPRIETARY NAME: Estradiol Transdermal System (TDS)

Innovator's Product Name: Climara® Estradiol Transdermal System (Berlex Labs)
8. Supplement Provides For: n/a
9. AMENDMENTS & Other DATES.
 - A. FIRM:
 - 08-06-97 Orig. application (75-182)
 - 10-21-97 Orig. application (75-233)
 - 07-26-99 Minor amendment
 - 07-29-99 new correspondance
 - B. FDA:
 - 06-07-99 labeling review (sat.)
 - 06-15-99 BIOEQUIVALENCY status sat. (Located in vol. 5.1) *see 75-182*
 - 09-02-99 telacon between Ms Ash and Drs. Rudman & Trimmer.
 - 09-03-99 tel amendment
10. PHARMACOLOGICAL CATEGORY: treatment of moderate to severe vasomotor symptoms associated with menopause, treatment of vulval & vaginal atrophy, treatment of hypoestrogenism, treatment of abnormal uterine bleeding.
11. Rx or OTC: Rx
12. RELATED ANDA's: none
13. DOSAGE Form: transdermal patches

14. POTENCY: 75-182 0.1 mg/day
75-233 0.05 "

15. CHEMICAL Name: Estradiol

16. Records & Reports: n/a

17. COMMENTS.

A. General Comments:

Not a USP drug product but is a USP drug substance.
MV sat. EER sat. Bio sat. CMC sat. DMF adequate.

18. CONCLUSIONS & RECOMMENDATIONS:
For approval

19. Reviewer/Branch Chief:

Robert W. Trimmer, Ph.D.
BRANCH IV, DIV. OF CHEMISTRY I, OGD

Davinder S. Gill, Ph.D.
TEAM LEADER

Date Started: 08-25-99
Date Completed: 08-26-99
revised: 09-08-99

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

Chemistry Review # 5
8/26/99

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-233

STATISTICAL REVIEW(S)

ATTACHMENT 1

Statistical Review: ANDA 75-182, Estradiol Transdermal System, 0.1 mg/day, Bertek, Inc.

Material reviewed: 1. One red-colored volume of ANDA 75-182, volume 5.1.

6. Original statistical review of ANDA 75-182, dated June 17, 1998, by Stella G. Machado, Ph.D., QMR staff, HFD-705.

Data for my analyses were provided on diskette in data files included with volume 5.1.

Stella G. Machado, Ph.D. carried out the original statistical review, dated June 17, 1998, of this bioequivalence study. Lin Whei Chuang, Ph.D. is the Division of Bioequivalence reviewer for this submission.

The issues in this review involve the sponsor's response to points made by the agency in correspondence dated July 15, 1998. Of the seven deficiencies listed in that correspondence, the first three will be the subject of this statistical review. These deficiencies, plus the sponsor's responses are as follows:

FDA DEFICIENCY 1: Please conduct statistical analysis (with and without carryover effects) on the total estrone data; because the method of calculation from which the concentration of estrone sulfate was derived, i.e. subtracting free estrone concentration from total estrone concentration, involved two sets (total estrone and of free estrone) of intra-subject variabilities.

BERTEK RESPONSE 1: The presentation of data and pharmacokinetic analysis for baseline subtracted total estrone (with a non-specific sulfatase incubation) can be found in Attachment 1A. The mean concentration versus time profiles are illustrated graphically in Attachment 1A, Section C. Mean plasma profiles are similar between Bertek estradiol transdermal system and Climara® (Berlex) estradiol transdermal system.

Attachment 1B provides statistical analysis and 90% confidence intervals using the model with and without carryover effects in the model on the baseline subtracted total estrone. For the model with residual 1 and treatment*residual 1 in the model, the 90% confidence intervals are 88% to 104%, 91% to 124%, and 84% to 104% for LNAUCL, LNAUCI, and LNCPEAK, respectively. For the model without residual 1 and treatment*residual 1 in the model, the 90% confidence intervals are 92% to 107%, 96% to 121%, and 89% to 106% for LNAUCL, LNAUCI, and LNCPEAK, respectively.

The 90% confidence intervals calculated for all of the above-mentioned LN transformed pharmacokinetic parameters for baseline subtracted total estrone are within the bioequivalence limits of 80% to 125%.

FDA DEFICIENCY 2: Using the estrone sulfate data you submitted, the 90% confidence intervals of LNAUCT and LNCmax of estrone sulfate (108%-146% and 100%-144%, respectively), calculated by the statistician of the Agency using SAS mixed model with carryover due to treatment-by-residual effect in the model, are outside the acceptable limits of 80-125%.

BERTEK RESPONSE 2: Attachment 2A presents Bertek's statistical re-analysis, using SAS mixed model with carryover due to treatment-by-residual effect in the model as requested by the FDA reviewer, on the original baseline subtracted estrone sulfate data submitted in the original ANDA 75-182. The results indicate the treatment-by-residual carryover are not significant ($p=0.0704$ and 0.2510 for LNAUCL, and LNCPEAK, respectively). The 90% confidence intervals for LNAUCL, LNAUCI and LNCPEAK are 88% to 104%, 90% to 108%, and 84% to 105%, respectively. The confidence intervals are within bioequivalence limits of 80% to 125%. Bertek was unable to replicate the results obtained by the Agency statistician. Bertek is available to discuss the differences in the results with the Agency.

For the above-mentioned data, the samples were assayed from March 24, 1997 to May 30, 1997 at the Pharmacokinetics Laboratory of Mylan Pharmaceuticals, Inc. The method developed for the analysis of plasma estradiol, estrone, and total estrone was performed using a detection. For the analysis of total estrone, plasma samples were incubated with a non-specific

(Sigma Cat# S 9751) before being measured for estrone concentration. Thus, the total estrone may contain some estrone β -glucuronide in addition to free estrone and estrone sulfate. Likewise, the estrone sulfate defined in the original submission contained estrone β -glucuronide and estrone sulfate.

In this Amendment, we also include the most recent data using a _____ method for estrone sulfate assayed at _____. The samples were assayed from July 29, 1998 to August 21, 1998. For the analysis of estrone sulfate, a specific sulfatase _____ was used. Attachment 3A contains the analytical report for the estrone sulfate using the _____ Attachment 3B contains the validation report for the _____

The presentation of data and pharmacokinetic analysis for baseline subtracted estrone sulfate can be found in Attachment 2B. The mean concentration versus time profiles are illustrated graphically in Attachment 2B, Section C. Mean plasma profiles are similar between Bertek estradiol transdermal system and Climara® (Berlex) estradiol transdermal system.

Attachment 2C provides statistical analysis and 90% confidence intervals using the model with carryover due to treatment-by-residual effect in the model. The 90% confidence intervals for LNAUCL, LNAUCI, and LNCPEAK are 88% to 104%, 86% to 112%, and 83% to 104%, respectively.

Overall, no matter if we use the estrone sulfate data submitted in the original ANDA or the estrone sulfate currently assayed, the results indicate the 90% confidence intervals are similar for the above-mentioned LN transformed pharmacokinetic parameters and the 90% confidence intervals are within bioequivalence limits of 80% to 125%.

FDA DEFICIENCY 3: For the assay of total estrone, please address the issue of glucuronide conjugate, and if it was included in the total estrone or estrone sulfate you reported.

BERTEK RESPONSE 3: The assay for the original submission conducted was validated for Total Estrone, which includes the glucuronide conjugates. As it pertains to the Assay Method used for the original submission, Total Estrone is defined as a combination of free estrone, estrone sulfate and estrone β -glucuronide. The Estrone Sulfate reported in the original submission was a combination of estrone sulfate and estrone β -glucuronide.

However, in the analysis by _____ the assay was specific for estrone sulfate only. Please reference Attachment 3B, the validation report from _____, for results from cross reactivity experiments demonstrating the specific analysis for estrone sulfate.

The other four deficiencies relate to technical aspects of the assay method, and are not addressed here.

Study Design

The experimental design for this bioequivalence (BE) study was a two-treatment, four-sequence, three-period replicated-crossover design. 32 subjects (out of 34 subjects enrolled) completed the BE study.

The two treatments studied were:

Test Product (treatment B) - _____ Mylan Estradiol Transdermal System – 31 cm²

Reference Product (treatment A) - Climara® Estradiol Transdermal System – 25 cm² (Berlex)

The study was conducted in three groups of subjects. The experimental design and subject numbers for those subjects who completed the study are as follows:

week

	1	2	3	4	5	6	7	8	9
group 1 sequence 1	A				B			A	
sequence 2	B				A			B	
sequence 3	B				A			A	
sequence 4	A				B			B	
group 2 sequence 1			A			B			A
sequence 2			B			A			B
sequence 3			B			A			A
sequence 4			A			B			B
group 3 sequence 1				A			B		A
sequence 2				B			A		B
sequence 3				B			A		A
sequence 4				A			B		B

subject numbers:

group 1, sequence 1:	1 5
group 1, sequence 2:	2 6 11
group 1, sequence 3:	3 8 9
group 1, sequence 4:	4 7 10
group 2, sequence 1:	12
group 2, sequence 2:	14 17
group 2, sequence 3:	16
group 2, sequence 4:	13
group 3, sequence 1:	20 22 29 33
group 3, sequence 2:	21 26 30
group 3, sequence 3:	19 23 27 32
group 3, sequence 4:	18 24 28 31 34

Since the participation in the study by three groups of subjects overlaps in time, the possibility of Group-by-Treatment interaction (i.e. that the difference between the treatments depends in a systematic way on which group is considered) does not seem to be a reasonable concern.

Three PK parameters (AUCI, AUCinf, and Cpeak) were analyzed. All PK parameters were statistically analyzed after log-transformation. These log-transformed parameters are designated as LAUCL=ln(AUCI), LAUCINF=ln(AUCinf), and LCPEAK=ln(Cpeak).

Statistical Models

The statistical model assumed initially for the analyses was:

[The subscripts "T" and "R" in these cases refer to the Test product and Reference product, respectively.]

where Y_{ijklm} = the response (e.g. $\ln(\text{AUCI})$, $\ln(\text{Cpeak})$, or $\ln(\text{AUCinf})$) for subject k in group i , sequence j receiving treatment m in period l

μ_{ijkm} = the average response to treatment m for subject k in group i , sequence j

α_i = the effect of group i

β_j = the effect of sequence j

γ_{ij} = the interaction effect of group i and sequence j

$\delta_{(i)l}$ = the effect of period l in group i

ϵ_{ijklm} = the within-subject random error for subject k in group i , sequence j receiving treatment m in period l

Statistical analyses using this model were carried out using SAS PROC MIXED (SAS version 6.12). For analyses without carryover effects, the SAS statements used for LAUCL and LCPEAK were:

where $\langle y \rangle$ is the particular response (LAUCL, LCPEAK) being analyzed. These SAS statements allow for possible subject-by-treatment interaction and also allow the within-subject variances of T and R to differ.

In the case of LAUCINF, the dramatic number of missing observations (42 out of 96 observations were missing for estrone sulfate, 37 out of 96 observations were missing for total estrone) made it essentially impossible to estimate all of the parameters of this statistical model. For this reason, the following SAS statements were used to analyze LAUCINF

For analyses including carryover effects, additional terms were added to the CLASS and MODEL statements in the PROC MIXED runs to model the carryover effects. Only first-order carryover effects were considered. However, the possibility of Direct-by-Carryover interaction (i.e. the possibility that carryover effects depended both on the preceding treatment and on the treatment being preceded) was considered in modeling the carryover effects.

Summary of Findings from Dr. Machado's Original Review

Dr. Machado found no evidence of bias in the treatment difference estimate due to carryover effects in her analysis of Estrone (i.e. Free Estrone) and of Estradiol. The 90% confidence intervals she obtained in those cases all fell within the limits of 80% to 125% for all three PK parameters (LAUCL, LAUCINF, and LCPEAK).

In the case of Estrone Sulfate, Dr. Machado found statistical evidence ($p < 0.10$) of possible bias due to carryover effects for LAUCL and LCPEAK. The 90% confidence intervals she obtained for LAUCL and LCPEAK using a model that included carryover effects fell outside of the limits of 80% to 125%. These confidence intervals for

Estrone Sulfate were 108.16% to 146.43% for LAUCL and 99.62% to 143.88% for LCPEAK. The 90% confidence interval for LAUCINF using a model that did not include carryover effects fell within the limits of 80% to 125%.

These results for Estrone Sulfate have been rendered moot by the reassy of the plasma samples for estrone sulfate in response to FDA DEFICIENCY 3.

Dr. Machado was not asked to carry out an analysis of Total Estrone.

Comments on the Sponsor's Statistical Model and Analyses

There were a number of deficiencies in the statistical model used by the sponsor for their PROC MIXED analyses of the original Estrone Sulfate data and their PROC GLM analyses of the reassayed Estrone Sulfate and Total Estrone data:

7. The sponsor failed to include any factors in their model to allow for subject-by-treatment interaction. The variation due to the subject-by-treatment interaction random effect forms the basis for the estimated standard error of the estimated treatment difference in a replicated-treatment crossover study.
8. The sponsor's model does not allow the possibility that the period effects might be different in the three different groups of subjects. The three periods of the study fell in different weeks for the three groups.
9. For analyses with carryover effects, the sponsor has attempted to model the carryover effects by including a CLASS variable called "RESID1" which captures the simple first-order carryover effects, and by also including TREAT*RESID1 in their model. This is a valid way of doing the analysis with carryover if it is done correctly. However, the sponsor has not done it correctly.

The variable RESID1 appears to have the following definition:

RESID1	=	1	if the preceding treatment was A
	=	-1	if the preceding treatment was B
	=	0	if the observation is in the first period

It is necessary to define this third level, level "0", for RESID1 when using SAS, since each observation must have a level of the RESID1 variable. Since by definition there is no carryover effect in period 1, this "0" level of RESID1 is an indicator of period 1. The situation becomes more complicated when we include an interaction with the RESID1 variable. Including TREAT*RESID1 in the model causes SAS to define the following levels of TREAT*RESID1:

TREAT	RESID1	TREAT*RESID1
A	0	A 0
A	1	A 1
A	-1	A -1
B	0	B 0
B	1	B 1
B	-1	B -1

Since there is no carryover effect in period 1, the "A 0" level of TREAT*RESID1 is just an indicator for treatment A in period 1, and the "B 0" level of TREAT*RESID1 is just an indicator for treatment B in period 1. On the other hand, the levels "A 1", "A -1", "B 1", and "B -1" are true indicators of treatment-specific carryover effects.

The goal of the analysis is to obtain an unbiased estimate of the difference between the treatment means. In particular, the estimate should be unbiased by carryover effects. Thus, the coefficients for levels of the carryover effect variables that represent true carryover effects should all be zero. The sponsor appears to have used an ESTIMATE statement of the form:

in their SAS PROC MIXED code, and a similar statement in their PROC GLM code, in order to obtain their estimate and confidence interval for the difference between the treatment means (the sponsor did not actually report their SAS code in this submission, but I was able to reproduce their analysis using the above ESTIMATE statement). Unfortunately, they did not specify coefficients for the levels of TREAT*RESID1, which is an interaction factor that “contains” TREAT (in the jargon of SAS). The SAS algorithm thus chose default coefficients for the levels of TREAT*RESID1 in order to obtain an estimable comparison, and unfortunately these default coefficients are not the appropriate ones for the objective of the analysis. The default coefficients for TREAT*RESID1 chosen by the SAS algorithm may be obtained by specifying the E option in the ESTIMATE statement. In the following table, I give the coefficients on the levels of TREAT, RESID1, and TREAT*RESID1 that produce the sponsor’s estimates, as well as the correct coefficients for obtaining an unbiased estimate of the treatment mean difference:

Effect	level	coefficients used by the sponsor	correct coefficients
TREAT	A	-1	-1
	B	1	1
RESID1	0	0	0
	1	0	0
	-1	0	0
TREAT*RESID1	A 0	-1/3	-1
	A 1	-1/3	0
	A -1	-1/3	0
	B 0	1/3	1
	B 1	1/3	0
	B -1	1/3	0

The non-zero coefficients on the “A 0” and “B 0” levels of TREAT*RESID1 in the “correct coefficients” column are necessary to make the comparison estimable. Because these levels of TREAT*RESID1 do not reflect carryover effects (because by definition there are no carryover effects in the first period of the study), they do not bias the treatment comparison.

An estimate using the correct coefficients could have been obtained by using an ESTIMATE statement of the form:

This assumes that the sort order of the levels of TREAT*RESID1 is A 0, A 1, A -1, B 0, B 1, and B -1, which in turn depends on the order in which the CLASS variables are listed in the CLASS statement.

The fact that the sponsor’s approach resulted in inappropriate coefficients for the levels of TREAT*RESID1 is the most important reason why the sponsor “was unable to replicate the results obtained by the Agency statistician”.

- In the sponsor’s “BERTEK RESPONSE 2”, referring to their PROC MIXED analysis of the original estrone sulfate data, they state “The results indicate the treatment-by-residual carryover are not significant ($p = 0.0704$ and 0.2510 for LNAUCL, and LNCPEAK, respectively).” It is our standard practice when testing for carryover to use a level of significance of $\alpha = 0.10$, rather than the more usual $\alpha = 0.05$, for purposes of deciding whether the carryover effects do or do not need to be included in the statistical model to be used for the final inference.

Under this criterion, the sponsor's result of $p = 0.0704$ is statistically significant. Also, due to the deficiencies in the sponsor's statistical model, as described in 1. and 2. above, the p-value for TREAT*RESID1 they obtained is questionable, and in fact would have been lower if a more appropriate statistical model had been used.

Our Analyses without Carryover Effects

We have carried out analyses of the reassayed estrone sulfate and total estrone data using the statistical models described above without carryover effects. The resulting 90% confidence intervals (in percentages) for the ratio of test product geometric mean response over reference product geometric mean response are:

	Estrone Sulfate	Total Estrone
LAUCL	94.24% , 110.02%	90.92% , 107.52%
LCPEAK	90.65% , 110.37%	87.49% , 107.52%
LAUCINF	84.62% , 111.83%	89.11% , 123.90%

In all cases, these 90% confidence intervals fall within the usual limits of 80% to 125%.

Our Analyses with Carryover Effects

We have carried out analyses of the reassayed estrone sulfate and total estrone data using the statistical models described above with the addition of carryover effects. The possibility of carryover effects in this study is a legitimate concern given the fact that it involves an endogenous substance.

If a treatment administered in a crossover study has an effect on the response to a treatment administered at a later period of the study, this is called a carryover effect. In bioequivalence studies, we have generally assumed that we only need to worry about first-order carryover effects – i.e. effects that a treatment has on the response to a treatment administered in the next period. However, we do need to consider the possibility that the carryover effect depends not only on the preceding treatment but also on the treatment being preceded. This is called Direct-by-Carryover interaction.

If these carryover effects are not all equal, then the estimate of the difference between the average response to T and the average response to R that we would obtain with no carryover effects in the model may be biased. It is possible to estimate this bias and test the hypothesis that the bias is zero. The p-values for the test of this bias are as follows:

	p-values for bias	
	Estrone Sulfate	Total Estrone
LAUCL	0.0007	0.0032
LCPEAK	0.0233	0.0170
LAUCINF	0.0044	0.1596

For technical reasons, I have also carried out the test for bias with an additional factor, SEQ*TREAT interaction, included in the model. The p-values for the test of bias with this model are as follows:

	p-values for bias	
	Estrone Sulfate	Total Estrone
LAUCL	0.0011	0.0071
LCPEAK	0.0170	0.0289
LAUCINF	0.0116	0.0445

In the analysis of bioequivalence studies where the possibility of unequal carryover needs to be considered, it has been the practice to test for bias due to carryover effects and to drop carryover effects from the statistical model if the p-value for such bias is greater than 0.10. If the p-value for bias is less than or equal to 0.10, carryover effects are retained in the statistical model used to make the final inference. In the above tables, the p-value for bias is less than 0.10 (indeed, it is less than 0.05) in all cases but one: LAUCINF for Total Estrone in the model without SEQ*TREAT. Thus, from a statistical point of view, we cannot justify dropping carryover effects from the model, with the possible exception of Total Estrone LAUCINF.

I have calculated the 90% confidence intervals resulting from analyses using a statistical model that includes carryover effects. These 90% confidence intervals are:

	Estrone Sulfate	Total Estrone
LAUCL	119.47% , 163.69%	108.38% , 144.95%
LCPEAK	105.64% , 160.38%	99.91% , 142.11%
LAUCINF	116.86% , 203.79%	96.46% , 184.17%

As may be seen, none of these 90% confidence intervals fall within the limits of 80% to 125%. I have also tried a number of alternate carryover models, and the conclusion is always the same: with carryover effects in the model, the 90% confidence intervals fail to fall within the limits of 80% to 125% by a wide margin, in all cases.

Summary

11. If a statistical model without carryover effects is used, the 90% confidence intervals for the ratio of the average response for treatment B (the Test product) over the average response for treatment A (the Reference product) fall within the usual bioequivalence limits of 80% to 125% for all three PK parameters (AUCI, Cpeak, and AUCinf), for both Estrone Sulfate and Total Estrone, as submitted by the sponsor after reassay of the plasma samples.
12. If a statistical model including carryover effects is used, the 90% confidence intervals fail to fall within the usual bioequivalence limits of 80% to 125% by a wide margin, for all three PK parameters (AUCI, Cpeak, and AUCinf) for both Estrone Sulfate and Total Estrone.
13. Potential bias due to carryover effects was statistically significant (p considerably less than 0.10) for all three PK parameters in the case of Estrone Sulfate and for LAUCL and LCPEAK in the case of Total Estrone. The test was ambiguous in the case of Total Estrone LAUCINF.
14. Because Estrone is an endogenous substance, Estrone Sulfate and Total Estrone do not meet the usual criteria that would lead us to discount the possibility of carryover effects. It is clear that this study does not meet the usual bioequivalence criteria for Estrone Sulfate or Total Estrone unless the possibility of carryover effects may be discounted.
15. Results for Estrone (i.e. Free Estrone) and Estradiol were reported in Dr. Machado's original Statistical Review.

Donald J. Schuirmann
Expert Mathematical Statistician
Quantitative Methods & Research staff

Concur: Stella Green Machado, Ph.D.
Director, Quantitative Methods & Research staff

cc:

Original ANDA 75-182

HFD-652	Lin Whei Chuang
HFD-652	Yih Chain Huang
HFD-651	Rabindra N. Patnaik
HFD-650	Dale P. Conner
HFD-600	Douglas L. Sporn
HFD-615	Harvey A. Greenberg
HFD-705	QMR Chron
HFD-705	Stella G. Machado

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-233

BIOEQUIVALENCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE

ANDA #: 75-182 & 75-233

SPONSOR: Bertek, Inc.

DRUG AND DOSAGE FORM: Estradiol Transdermal System

STRENGTHS: 0.1 mg/day & 0.05 mg/day

TYPES OF STUDIES: Single-Dose, Fasting and Waiver Request

CLINICAL STUDY SITE: Clinical & Pharmacologic Research, Inc. Morgantown, WV

ANALYTICAL SITE: Pharmacokinetics Laboratories of Mylan Pharmaceuticals Inc.

STUDY SUMMARY: Acceptable

WAIVER REQUEST: Granted

DISSOLUTION: Acceptable with Revised Specification

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
YES		
First Generic <u>Yes</u>	Inspection requested: (date)	
New facility <u>Yes</u> (Analytical)	Inspection completed: (date)	
For cause <u>No</u>		
Other _____		

PRIMARY REVIEWER: Lin-Whei Chuang BRANCH: I

INITIAL: /S/ DATE: 6/7/99

TEAM LEADER: Yih-Chain Huang, Ph.D. BRANCH: I

INITIAL: /S/ DATE: 6/7/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.

INITIAL: /S/ DATE: 6/15/99

Estradiol
Transdermal System,
ANDA #75-182 (0.1 mg/day)
ANDA #75-233 (0.05 mg/day)
Reviewer : Lin-Whei Chuang

Bertek, Inc.
St. Albans, VT

Submission Date:
October 28, 1998

Review of an Amendment to a Bioequivalence Study

The bioequivalence study conducted on the 0.1 mg/day strength submitted on 8/6/97 under ANDA #75-182 was reviewed within the Division of Bioequivalence and by the mathematical statistician of QMR staff. It was found to be incomplete due to 7 deficiencies (see review of 7/10/98 and 6/5/98).

As noted in the review of 6/8/98 by the QMR staff, using SAS PROC MIXED model with carryover effects, the data of non-conjugated estradiol and non-conjugated estrone supported bioequivalence between the test and reference drugs. However, using the same SAS model, bioequivalence was not supported by the estrone sulfate data since the 90% confidence intervals for LNAUCT and LNCMAX fail to fall within the acceptable range.

The firm's response to these deficiencies are reviewed below. Response to deficiencies 1-3 are also reviewed by the expert mathematical statistician of QMR staff (Attachment 1).

#1. Please conduct statistical analysis (with and without carryover effects) on the total estrone data; because the method of calculation from which the concentration of estrone sulfate was derived, i.e. subtracting free estrone concentration from total estrone concentration, involved two sets (total estrone and of free estrone) of intra-subject variabilities.

Firm's Response:

a. Total estrone data are presented in Figure 1 and Tables 1-2.

FIGURE 1: PLASMA LEVELS OF TOTAL ESTRONE

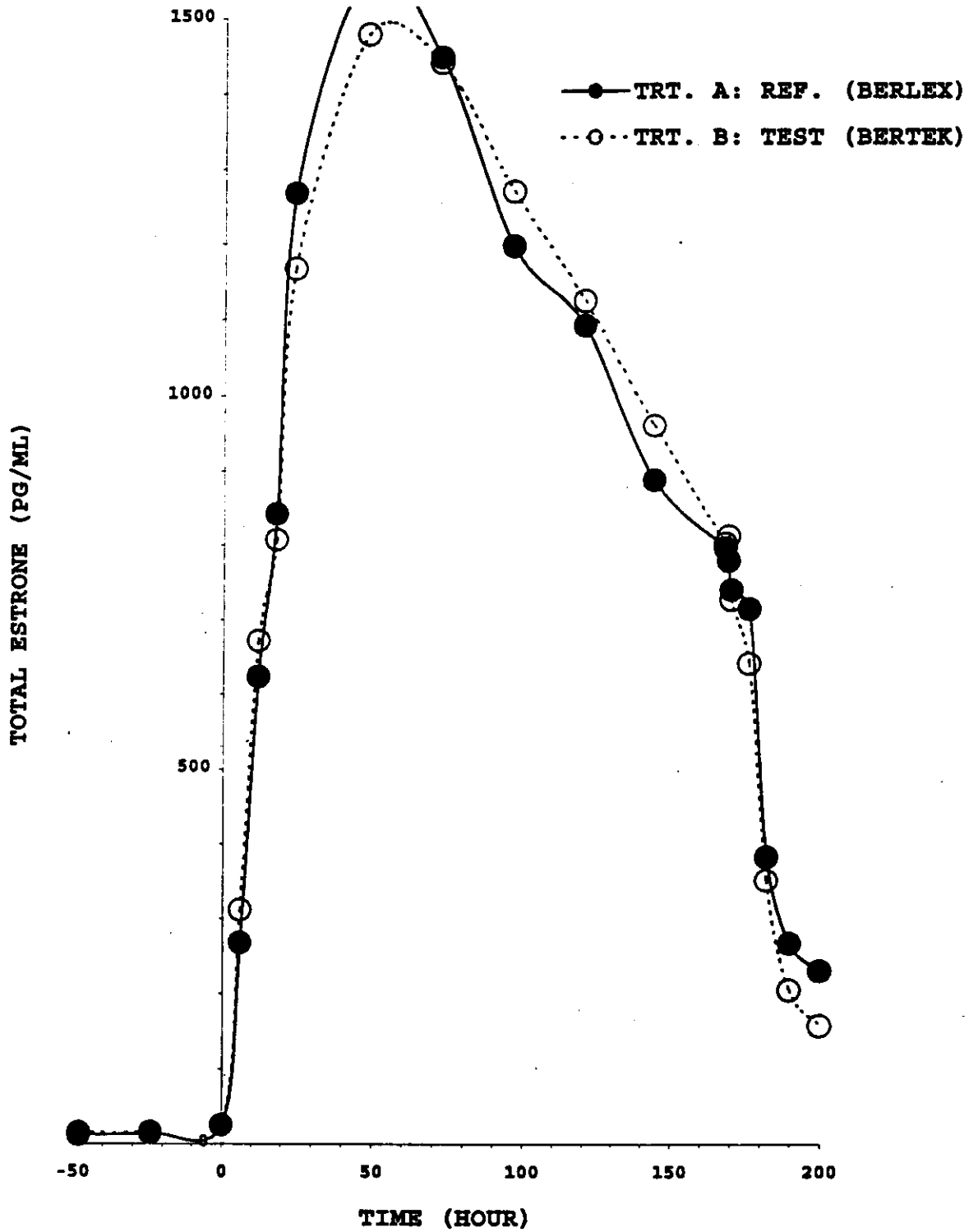


TABLE 1: MEAN PLASMA CONCENTRATIONS OF TOTAL ESTRONE

TIME	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
TIME HR					
-48	14.28	41.13	7.14	24.69	2.00
-24	7.22	15.03	8.14	24.56	0.89
0	18.47	39.63	16.22	30.90	1.14
6	255.02	182.58	277.60	272.63	0.92
12	536.15	266.19	551.00	271.00	0.97
18	673.16	389.80	730.51	377.40	0.92
24	979.33	571.40	1120.22	691.72	0.87
48	1261.36	766.14	1346.63	907.01	0.94
72	1260.24	876.13	1255.81	823.76	1.00
96	1155.39	915.15	1088.46	761.25	1.06
120	975.40	719.70	1003.06	767.80	0.97
144	806.28	541.83	809.16	648.37	1.00
168	678.08	495.32	694.72	496.03	0.98
169	638.67	475.83	659.90	480.77	0.97
170	610.45	448.55	639.35	411.45	0.95
176	508.29	401.11	553.44	438.08	0.92
182	293.54	279.97	358.37	311.22	0.82
190	187.54	186.77	240.76	258.53	0.78
200	137.46	146.92	216.45	276.61	0.64

TABLE 2: ARITHMETIC MEANS OF PK PARAMETERS OF TOTAL ESTRONE

	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
PARAMETER					
AUCI	200348.39	128746.40	177610.10	89296.17	1.13
AUCT	173187.54	108649.08	178859.74	116764.78	0.97
C _{MAX}	1492.42	952.76	1538.94	891.29	0.97
KE	0.09	0.11	0.07	0.08	1.22
LAUCI	11.114809	0.61	11.954930	0.55	1.07a
LAUCT	11.883914	0.61	11.924549	0.60	0.96a
LC _{MAX}	7.146000	0.56	7.205984	0.52	0.94a
THALF	16.34	21.11	15.16	8.75	1.08
T _{MAX}	72.45	40.31	62.30	29.46	1.16

a = RATIO OF GEOMETRIC MEANS

- b. ANOVA was conducted on the above data using SAS PROC GLM model with and without carryover effect. No significant effect for the factor of "treatment*residual 1" at alpha level of 0.05 was found by the firm. The p value of this factor for LNAUCL was 0.0766. Following are results obtained by the firm with various SAS models.

TABLE 3: STATISTICAL ANALYSIS OF TOTAL ESTRONE - USING SAS PROC GLM									
	WITH FULL CARRYOVER			WITH RESIDUAL 1 ONLY			WITHOUT CARRYOVER		
	TEST LSM	REF. LSM	90% CI	TEST LSM	REF. LSM	90% CI	TEST LSM	REF. LSM	90% CI
AUCT	168281	177481	0.84- 1.05	176790	175057	0.91- 1.11	175738	176153	0.90- 1.09
AUCI	193397	186995	0.85- 1.21	193820	183948	0.89- 1.21	194955	183613	0.91- 1.21
C _{MAX}	1465.9	1533.5	0.83- 1.08	1526.9	1503.0	0.90- 1.14	1513.0	1517.5	0.88- 1.10
LNAUCT	11.88	11.92	0.88- 1.04	11.90	11.90	0.92- 1.09	11.90	11.91	0.92- 1.07
LNAUCI	12.05	11.99	0.91- 1.23	12.03	11.96	0.93- 1.22	12.03	11.96	0.94- 1.21
LNC _{MAX}	7.15	7.21	0.84- 1.04	7.16	7.19	0.88- 1.08	7.16	7.19	0.89- 1.06

Reviewer's Comments:

- a. The firm's calculation of PK parameters has been confirmed by the reviewer.
 - b. Statistical analysis with carryover effect have been reviewed by the QMR staff (see attached review of 4/20/99). It was concluded that, using SAS PROC MIXED model and without carryover effects, the 90% confidence intervals for all pivotal parameters fall within 80-125% for total estrone. However, if the statistical model (PROC MIXED) including carryover effects is used, the 90% confidence intervals of all pivotal parameters fail to fall within 80-125% by a wide margin for total estrone.
- #2.** Using the estrone sulfate data you submitted, the 90% confidence intervals of LNAUCT and LNC_{max} of estrone sulfate (108-146% and 100-144%, respectively), calculated by the statistician of the Agency using SAS mixed model with carryover due to treatment-by-residual effect in the model, are outside the acceptable limits of 80-125%.

Two types of carryover were estimated, first-order residual effects and treatment-by-residual effects. It was concluded that data you submitted supported the bioequivalence of the test and reference treatments for the components estradiol and estrone, but the bioequivalence of estrone sulfate was not supported. This was due to the significant treatment-by-residual carryover on the LNAUCT and LNC_{max} of estrone sulfate ($p = 0.0047$ and 0.0281 respectively) and resulted in above mentioned out-of-limit 90% confidence intervals.

Firm's Response:

- a. The data was re-analyzed by the firm using SAS mixed model with carryover effect in the model. The firm, however, was unable to replicate the results obtained by the Agency statistician.

- b. In addition, the study samples were re-analyzed for estrone sulfate using specific aliquots of plasma sample with added internal standard (for determination of recovery) was extracted with organic solvent (mixture of _____ and _____ to remove unconjugated estrone. Plasma portion was then incubated for 16 hours with _____ and extracted with the organic solvent. After evaporation and reconstitution, estrone was separated by the

The _____ involved the addition _____ and assay antibody _____) to samples, non-specific binding tubes, and calibration standards; incubation at room temperature for 14 hours; and addition of 2nd antibody and

Amount of _____ in the precipitate was measured to determine the amount of I¹²⁵ estrone bound to the antibody. Recovery of each sample was determined by the _____ from the internal standard in the reconstituted plasma samples before the addition of antigen.

The standard curve response in the _____ is linearized by using LOGIT-LOG function of the percentage of bound versus the mass of the unlabelled standards.

The results of pre- and during-study validation are presented below in Table 4:

Parameter	Pre-Study	During-Study
Sensitivity/LOQ (pg/mL)	40 (1.25)	40 (1.25/
Quality Control Conc. (pg/mL) (Lo, Med, Hi)	100, 700, 4200	128, 1359, 3383
Linear Range (pg/mL)	40-4900 (spiked plasma samples)	1.25-80
Linearity	R ² ≥ 0.99706 (based on curves of 1.25-80	R ² ≥ 0.99720

Intra-run Precision (%CV)	2.0 - 7.3	N/A
Intra-run Accuracy (%Actual)	96.5 - 108	N/A
Inter-run Precision (%CV)	2.5 - 14.4	3.53-12.41
Inter-run Accuracy (%CV)	92.0 - 104.2	95.5 - 105.4
Selectivity	cross-reaction <3%	N/A
Stability (%)		
a) Plasma Sample @ Room Temp. for 48 hours	<u>Hi</u> <u>Lo</u> 101.0 82.6	N/A
b) Plasma Sample after 5 freeze-thaw cycles	<u>Hi</u> <u>Lo</u> 101.8 103.9	
c) Plasma Sample at -15°C for 24 months	<u>Hi</u> <u>Lo</u> 91.4 86.9	
Percent Recovery of internal standard in the QCs & LOQ	<u>Hi</u> <u>Med</u> <u>Lo</u> <u>LOQ</u> 59.2 64.5 58.5 58.3	N/A

c. Estrone sulfate data obtained from the above analysis are presented below in Tables 5-6 and Figure 2.

TABLE 5: MEAN PLASMA CONCENTRATIONS OF ESTRONE SULFATE

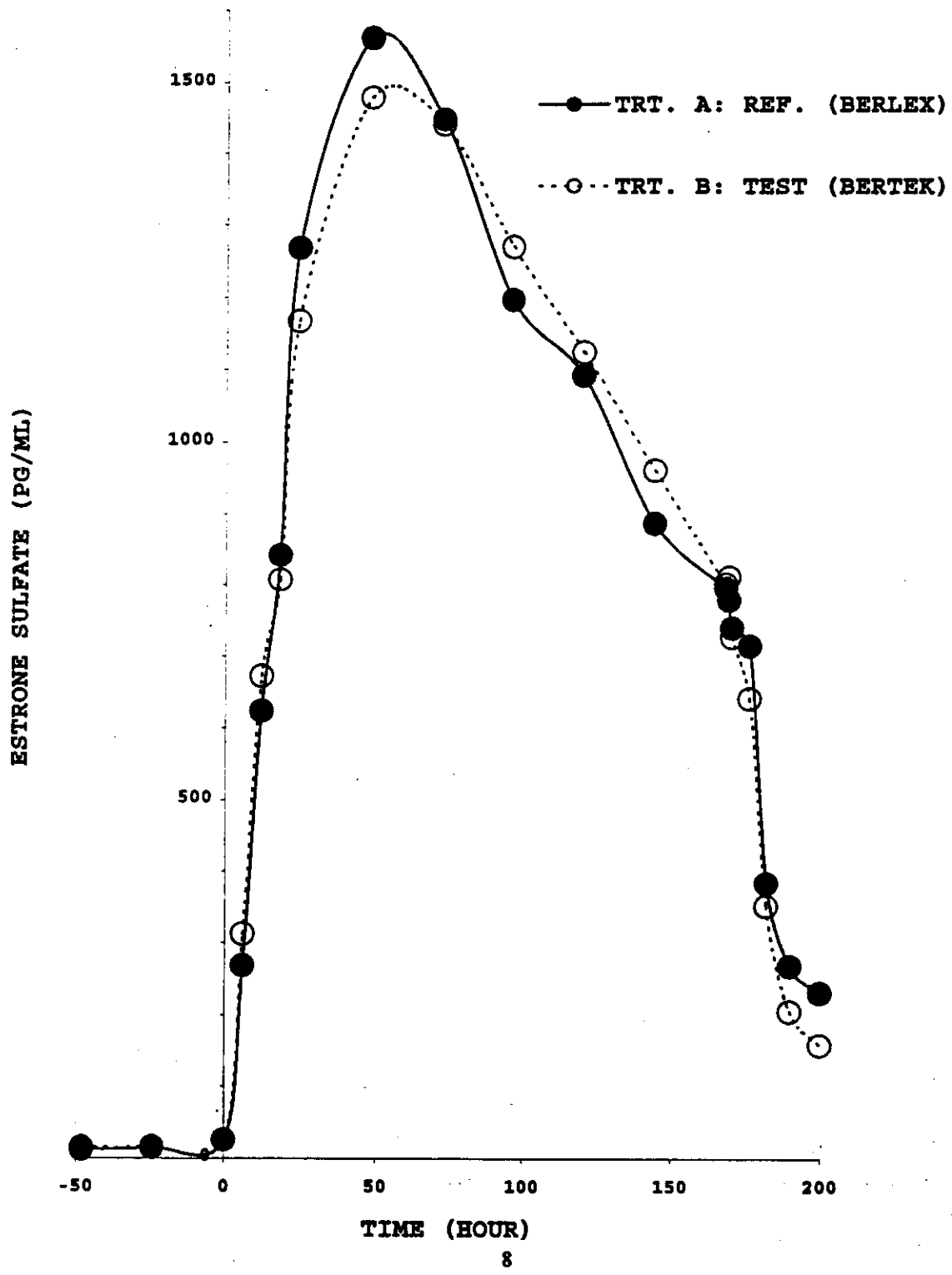
	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
TIME HR					
-48	15.54	47.23	12.01	28.46	1.29
-24	16.22	33.60	14.59	25.85	1.11
0	25.62	40.62	25.46	46.39	1.01
6	311.57	235.33	267.71	211.14	1.16
12	671.80	440.28	623.23	316.66	1.08
18	806.76	499.15	841.79	441.50	0.96
24	1167.00	640.19	1267.57	727.54	0.92
48	1478.16	804.79	1561.53	957.10	0.95
72	1439.76	927.52	1447.11	845.97	0.99
96	1269.20	905.50	1196.23	841.14	1.06
120	1123.41	825.83	1090.91	785.84	1.03
144	958.82	605.96	885.70	620.60	1.08
168	800.76	565.22	794.57	514.47	1.01
169	810.65	672.76	777.68	505.82	1.04
170	725.88	513.82	738.94	468.31	0.98
176	639.94	508.53	713.74	554.00	0.90
182	350.99	345.74	382.47	316.01	0.92

TABLE 6: ARITHMETIC MEANS OF PK PARAMETERS OF ESTRONE SULFATE

	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
PARAMETER					
AUCI	216186.33	132267.65	220744.01	113849.59	0.98
AUCT	201019.62	114199.93	201621.44	116517.63	1.00
C _{MAX}	1805.71	985.49	1818.40	937.42	0.99
KE	0.07	0.04	0.08	0.06	0.88
LAUCI	12.078305	0.69	12.161532	0.58	0.92 ^a
LAUCT	12.047281	0.60	12.060282	0.58	0.99 ^a
LC _{MAX}	7.352030	0.56	7.385454	0.51	0.97 ^a
THALF	12.59	5.68	13.84	8.64	0.91
T _{MAX}	73.12	44.82	61.28	34.60	1.19

^a = RATIOS OF GEOMETRIC MEANS

FIGURE 2: PLASMA LEVELS OF ESTRONE SULFATE



- d. ANOVA of the above data was conducted by the firm using PROC GLM with carryover effect ("residual 1" and "treatment*residual 1" were both included in the model). The p value of the factor "treatment*residual 1" was 0.0089 for LNAUCL and 0.0825 for LNCMAX. Results obtained by the firm with carryover effect in its SAS model indicate 90% intervals of all 3 pivotal PK parameters are within the acceptable range of 80-125%.

PARAMETER	TEST LSM	REF. LSM	90% CI
AUCT	193689.37	204480.30	0.854 - 1.040
AUCI	190642.97	203853.60	0.822 - 1.048
C _{MAX}	1745.04	1877.06	0.822 - 1.037
LNAUCT	12.03	12.08	0.878 - 1.043
LNAUCI	12.00	12.03	0.852 - 1.123
LNC _{MAX}	7.34	7.42	0.827 - 1.036

Reviewer's Comments:

- a. The analytical method conducted by the firm using specific to measure plasma concentration of estrone sulfate is acceptable.
- b. The firm's calculation of PK parameters was confirmed by the reviewer.
- c. Statistical analysis with carryover effect have been reviewed by the QMR staff in comments 1-3 of the attached review of 4/20/99. The Agency's conclusion is different from the firm's results in Table 7. It was concluded by the agency that, using SAS PROC MIXED and without carryover effects, the 90% confidence intervals of all pivotal parameters fall within 80-125% for estrone sulfate. However, if the statistical model (PROC MIXED) including carryover effects is used, the 90% confidence intervals of all pivotal parameters fail to fall within 80-125% by a wide margin for estrone sulfate.
- #3.** For the assay of total estrone, please address the issue of glucuronide conjugate, and if it was included in the total estrone or estrone sulfate you reported.

Firm's Response:

The firm indicates that the total estrone reported in the original submission did include the glucuronide and sulfate conjugates; and the estrone sulfate reported in the original

submission was a combination of estrone sulfate and estrone beta-glucuronide.

In addition, the study samples were re-analyzed for estrone sulfate using specific :
Results of this re-analysis were reviewed and commented in deficiency #2 (see reviewer's comments a-c of #2).

Reviewer's Comment:

The firm's response is adequate.

#4. For the assay of estrone sulfate, please clarify if standards and QC samples were prepared by spiking plasma samples with free estrone or with estrone sulfate.

The preferred method to prepare standards and QC samples for the analysis of estrone sulfate would be to spike plasma with sulfate ester.

Firm's Response:

Free estrone was used in the original assay to prepare both standards and QC samples. This practice was supported by the fact that the assay was validated to show complete hydrolysis of the estrone conjugates to free estrone.

However, the new assay method conducted for the re-analysis of estrone sulfate did use to prepare the standard curve and QC samples; and was used as internal standard.

Reviewer's Comment:

The firm's explanation is acceptable.

#5. Please define the enzymatic activities of , which was used to the plasma sample with internal standard to indicated if they include the activity of

Firm's Response:

The original assay had both and activities.

However, for the new assay method conducted for the re-analysis of estrone sulfate, a specific was used which had mostly and very little

Reviewer's Comment:

The firm's explanation is acceptable.

#6. Please report whether estrone or estrone sulfate was used in the studies during analytical method validation for total estrone.

Firm's Response:

was used in both the studies. It was also used in the new report submitted in this amendment. conducted for

Reviewer's Comment:

The firm's explanation is acceptable.

#7. Please submit adequate stability data for total estrone since the maximum number of days for samples storage during the analysis of total estrone was reported to be 153 days, yet the stability of frozen samples was documented for only 106 days.

Firm's Responses:

- a. Frozen stability (109.1%) of estrone sulfated in human plasma was extended to 174 days (ending 7/29/97, about 6 months after the study).
- b. In addition, frozen stability (86.9-91.4%) of 24 months (ending 2/3/98, about 25 months after the study) was documented, which is longer than maximal possible time period of 604 days for analysis by which was conducted during 7/29-8/21/98.

Reviewer's Comment:

The stability data submitted by the firm is acceptable.

Overall Comments:

1. The firm has satisfactorily addressed all the deficiencies except when the statistical model (PROC MIXED) including carryover effects is used, the 90% confidence intervals of all pivotal parameters fail to fall within 80-125% by a wide margin for estrone sulfate and total estrone.

2. However, as commented in earlier review of 6/10/98, at this point in time, the Division is not enforcing testing for carryover in the statistical model.
3. Using the correct statistical model and without carryover effects, the 90% confidence interval falls within the acceptable range of 80-125% for LNAUCT, LNAUCI and LNCMAX of all 4 analytes: non-conjugated estradiol, non-conjugated estrone, estrone sulfate, and total estrone.
4. In addition, the firm has conducted "A 21-day Evaluation of Cumulative Skin Irritation Potential In Humans for a 0.05 mg/day Estradiol Transdermal Patch". It was reviewed by the medical officer (see Attachment 2), and concluded the test and reference products are similar in their skin irritation potential.
5. The comparative formulations show proportionality between the 0.1 mg/day strength and 0.05 mg/day strength for the active and inactive ingredients in both test and reference drugs.

Recommendations:

1. The single-dose, fasted bioequivalence study conducted by Bertek, Inc. on its estradiol transdermal system, 0.1 mg/day, lot #26C001L, comparing it to Climara^R transdermal system, lot #P50169, has been found acceptable by the Division of Bioequivalence. The firm's estradiol transdermal system, 0.1 mg/day is deemed bioequivalent to Climara^R transdermal system, 0.1 mg/day, when administered under fasting conditions.
2. The dissolution testing conducted by Bertek, Inc. on its Estradiol transdermal system, 0.05 mg/day and 0.1 mg/day, lot #26C001L & #26D011D, respectively, comparing them to Climara^R transdermal system, 0.1 mg/day and 0.05 mg/day, respectively, has been found acceptable by the Division of Bioequivalence. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 500 mL of 0.3% sodium lauryl sulfate in 0.005 N NaH₂PO₄, pH 5.5, at 32° C using USP 23 apparatus 5 (paddle over disk) at 100 rpm. The test products should meet the following specifications: ✓

3. Waiver of the in vivo bioequivalence testing requirements for Bertek's estradiol transdermal system, 0.05 mg/day, is granted per 21 CFR 320.24(b)(6). The firm's estradiol transdermal system, 0.05 mg/day is deemed bioequivalent to Climara^R transdermal system, 0.05 mg/day.

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Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG

6/7/99

Concur:

ISI

Date: 6/15/99

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-182 (0.1 mg/day) APPLICANT: Bertek, Inc.
75-233 (0.05 mg/day)

DRUG PRODUCT: Estradiol Transdermal System

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 500 mL of 0.3% sodium lauryl sulfate in 0.005 N NaH_2PO_4 , pH 5.5, at 32° C using USP 23 apparatus 5 (paddle over disk) at 100 rpm. The test products should meet the following specifications:

1

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,

131

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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-233

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 75-233 Date of Submission: June 2, 1999

Applicant's Name: Bertek Inc.

Established Name: Estradiol Transdermal System
0.05 mg/day

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes

Patch Labels: Satisfactory as of June 2, 1999 submission. ✓

Pouch Labeling: (1 patch per pouch) Satisfactory as of April 30, 1999 submission. ✓

Carton Labeling: (4's) Satisfactory as of April 30, 1999 submission. ✓

Professional Package Insert Labeling: Satisfactory as of June 2, 1999 submission. ✓

Patient Package Insert Labeling: Satisfactory as of June 2, 1999 submission. ✓

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Climara® (Estradiol Transdermal System)

NDA Number: 20-375/S-013

NDA Drug Name: Climara® (Estradiol Transdermal System)

NDA Firm: Berlex Pharmaceuticals

Date of Approval of NDA Insert and supplement #: May 20, 1999

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison labels submitted in jacket.

Basis of Approval for the Carton Labeling: Side-by-side comparison labeling submitted in jacket.

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? Estradiol Film, extended-release Transdermal.	X		
If not USP, has the product name been proposed in the FT?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FT, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FT.	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	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			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	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FT: 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 ANSP guidelines)		X	

Labeling(continued)	Yes	No	N.A.
Does NLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
SCORING: Describe scoring configuration of NLD and applicant (page #) in the FTR			
Is the scoring configuration different than the NLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacods, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)	X		
USP ISSUES: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , F 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Climara®; NDA#20-375/S-013 Approved May 20, 1999) and the Class Labeling Guidance for Estrogen Drug Products.

2. Patent/ Exclusivities:

There one patent that exists for this product. 5223261 - Expires June 29, 2010. This patent is for the adhesive material of the patch. The generic has filed a paragraph IV certification. There are two exclusivities that pertain to this drug product.

D-26 - One weekly application. This expired on December 22, 1997.

I-254- Expires March 5, 2002 - Prevention of Postmenopausal Osteoporosis (Loss of Bone Mass). The applicant has not included this in their insert.

3. Storage/Dispensing Conditions:

NDA: Do not store above 86°F (30°F). Do not store unpouched. Apply immediately upon removal from the protective pouch.

ANDA: Store at 15° - 30°C (59° - 86°F). Do not store unpouched. Apply immediately upon removal from the protective pouch.

USP: Not a monograph in the USP nor purposed the PF.

4. Product Line:

The innovator markets their product in 0.05 mg/day (12.5 sq cm) patch and a 0.1 mg/day (25 sq cm) patch. The patches are contained in pouches then placed in cartons of 4 and 6. The innovator also has a physician sample size of 1.

The applicant proposes to market their product in a 0.1 mg/day (31 sq cm) patch and a 0.05 mg/day (15.5 sq cm). The patch is contained in a pouch then placed in a cartons of 4s.

NOTE: Prevention of osteoporosis is covered by exclusivity, however, the reference to use in osteoporosis appeared in the patient package insert prior to the granting of exclusivity. It was decided that it should remain in the patient insert only for reference.

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert does not appear to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 365, 366, and 368 Vol. 1.2. The dyes in the "brown ink" are not listed and see note to chemist regarding adhesives.

6. All manufacturing will be performed by Burtek. Burtek is a wholly owned subsidiary of Mylan Pharmaceuticals. All outside firms are utilized for testing. See pages 561 and 555, Vol. 1.2.

7. Container/Closure:

The patch is heat sealed between 2 layers of pouching material. Laminate of white paper on one side and dull silver on the other. See page 741 and 746, Vol. 1.2.

8. There are several differences which exist between the RLD and this generic product.

a. The NDA is a 3 layer system that consists of a film backing, Drug/Adhesive Layer/Protective Layer. The ANDA has a 4 layer system that consists of foam backing with adhesive layer, polyester film, acrylate adhesive matrix and a protective liner.

b. The NDA patch size is 12.5 sq cm and the ANDAs patch size is 15.5 sq cm.

c. The CLINICAL PHARMACOLOGY, Pharmacokinetics subsection was revised to reflect the delivery rate rather than the surface area. See FTR in file folder regarding this entire section.

Date of Review: June 7, 1999

Date of Submission: June 2, 1999

Reviewer:

Date: 6/7/99

Team Leader:

Date: 4/8/1999

cc: //

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-233

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

ORIG AMENDMENT

AM

September 3, 1999

**TELEPHONE AMENDMENT
(CMC INFORMATION ENCLOSED)**

Re: ESTRADIOL TRANSDERMAL SYSTEM, 0.1 mg/day ANDA 75-182
ESTRADIOL TRANSDERMAL SYSTEM, 0.05 mg/day ANDA 75-233
Response to Agency Telephone Request for Information on September 2, 1999

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Applications identified above and to the Agency's comments received via telephone on September 2, 1999. A copy of MYLAN TECHNOLOGIES, INC.'s telephone log is provided in Attachment A for the reviewer's convenience.

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

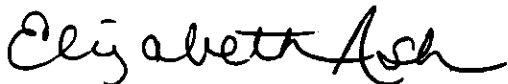
MYLAN TECHNOLOGIES, INC. hereby commits to revising its Estradiol, USP raw material specifications based upon our interpretation of the "Other Impurities" General Notice in USP 24 (page 7) as follows:

PREVIOUS SPECIFICATIONS (EFFECTIVE DATE JULY 26, 1999)

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,

A handwritten signature in cursive script that reads "Elizabeth Ash".

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

FDA TELEPHONE REPORT

CALL DATE: September 2, 1999

TIME: 5:30 pm

FROM: Alan Rudman, Deputy Director Division I Chemistry Review, OGD, FDA
Robert Trimmer, Chemistry Review, OGD, FDA

TO: Elizabeth Ash, Regulatory Manager, CMC

PRODUCT: Estradiol Transdermal System, 0.1 mg/hr ANDA 75-182
Estradiol Transdermal System, 0.05 mg/hr ANDA 75-233

DESCRIPTION: Dr. Rudman and Dr. Trimmer telephoned to request clarification on issues surrounding MTI's Estradiol, USP raw material specifications. Per our amendment dated, September 29, 1998, MTI committed to testing for "Other Impurities" for Estradiol, USP raw material. Upon review of our July 29, 1999 amended raw material specifications, Dr. Rudman said that the Agency saw no evidence of the requested testing in our revised specifications and asked if there had been an oversight to explain this fact. He stated that a letter of commitment to do the requested testing would be sufficient and could be sent via facsimile to him directly as well as submitted in hard copy.

At 6:00 pm, Michael Sturm, Director of Quality, and I called Dr. Rudman back to request further clarification of his concerns. MTI had reviewed its specifications and believed the specifications to be in compliance with Supplement 10 to the USP, currently in effect. Dr. Rudman said that the Agency did not consider the specifications to be in compliance with the current USP and requested revisions based upon the USP 24 General Notice entitled, "Other Impurities," as found on page 7 of the referenced USP. Mr. Sturm and I assured Dr. Rudman that MTI would revise its specifications accordingly.

ACTION: The Estradiol, USP raw material specifications were reworded using the appropriate compendial terminology in order to incorporate the Agency's request. A letter of commitment is to be sent to Dr. Rugman's attention today, September 3, 1999 as well as via a hard copy telephone amendment.

ORIGINATOR:

Elizabeth Ash
Elizabeth Ash, M.S., RAC
Regulatory Manager, CMC

DATE:

9/3/99

cc: M. Costigan, L. DeBone, J. Fauteux, M. Friedly, S. Govil, J. O'Donnell, F. Sisto, M. Sturm, F. Tackett



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

NEW CORRESP
NC

July 29, 1999

CORRESPONDENCE

Re: ESTRADIOL TRANSDERMAL SYSTEM, 0.1 mg/day ANDA 75-182
~~ESTRADIOL TRANSDERMAL SYSTEM, 0.05 mg/day ANDA 75-233~~ ✓

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Application identified above. MYLAN TECHNOLOGIES, INC. wishes to amend this application with the following:

- A copy of correspondence regarding the referenced applications from Dr. John O'Donnell of Mylan Pharmaceuticals, Inc. to Mr. Douglas Sporn, Director, Office of Generic Drugs, CDER, FDA

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, M.S., RAC
Regulatory Associate
MYLAN TECHNOLOGIES, INC.
110 Lake Street
St. Albans, VT 05478



ORIG AMENDMENT
NFM



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

**MINOR AMENDMENT
(CMC INFORMATION ENCLOSED)**

Re: ESTRADIOL TRANSDERMAL SYSTEM, 0.1 mg/day ANDA 75-182
 ESTRADIOL TRANSDERMAL SYSTEM, 0.05 mg/day ANDA 75-233 ✓
 Response to Agency Correspondence Dated July 14, 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 July 14, 1999. A copy of the Agency correspondence is 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:

Chemistry Deficiencies:

Page (s) _____

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

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,

A handwritten signature in cursive script that reads "Elizabeth Ash".

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