CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 201675 Orig1s000

Generic or Proper Name:	Estradiol transdermal system
Sponsor:	Mylan Pharmaceuticals Inc.
Approval Date:	December 19, 2014
Indication:	Estradiol transdermal system (twice-weekly) is an estrogen indicated for: • Treatment of moderate to severe vasomotor symptoms due to menopause (1.1) • Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause (1.2) Limitation of Use: When prescribing solely for the treatment of moderate to severe vaginal atrophy, topical vaginal products should be considered. • Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure (1.3) • Prevention of postmenopausal osteoporosis (1.4) Limitation of Use: When prescribing solely for the treatment of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201675Orig1s000

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Reviews / Information Included in this Review	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201675Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 201675

ANDA APPROVAL

Mylan Technologies Inc.
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated April 26, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Estradiol Transdermal System USP, Each system delivers 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice Weekly Application).

Reference is also made to the Complete Response letter issued by this office on April 3, 2014, and to your amendments dated June 23, August 19, August 22, September 18, and September 26, 2014.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice Weekly), to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Vivelle-Dot 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day, respectively, (Twice Weekly), of Novartis Pharmaceuticals Corporation.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

Dissolution Testing should be conducted in:

Apparatus:	USP VI (cylinder, modified- Attach the patch on the cylinder using double-sided tape, release side facing away from the cylinder. The release side should not be covered by a membrane)
Speed:	50 rpm
Medium:	Water
Volume:	500 mL for 0.025 mg/day and 0.0375 mg/day; 900 mL for 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day

Temperature: 32°C ± 0.5°C

The test product should meet the following specifications:

Time (hours)	Percent Dissolved
2	20-40
6	48-68
12	70-90

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement – Changes Being Effected" if there are no revisions to be made to the "interim" specifications or if the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

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

Postmarketing reporting requirements for this ANDA 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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not

met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

Robert L. West -S

Digitally signed by Robert L. West -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Robert L. West -S, 0.9.2342.19200300.100.1.1=1300009131
Date: 2014.12.19 10:30:59 -05'00'

For Carol A. Holquist, R.Ph.
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201675Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 201675

COMPLETE RESPONSE

Mylan Technologies, Inc.
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs
110 Lake St.
St. Albans, VT 05478

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated April 26, 2010, received April 27, 2010, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice-Weekly).

We acknowledge receipt of your amendments dated May 25, and September 10, 2010; January 4, July 28, and December 2, 2011; and April 25, and June 15, 2012.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The deficiencies presented below are minor deficiencies:

A. Deficiencies

1. It appears that (b) (4) is not used in the drug product. Please clarify why DMF (b) (4) is referenced.

2. Please tighten the limit of viscosity range for Estradiol Blend so that it's more representative of the test results of the exhibit batch and R&D lots.

3. The following deficiency is based on comments from initial consult to FDA's Pharmacology/Toxicology division: Please submit toxicology data or a justification as to

why the limits for [redacted] should be considered acceptable.

4. Please scientifically justify your claim that shear test is unsuitable for pressure sensitive adhesive emulsion blend, with data on your product. We also ask that you provide comparative cold flow data on your product and RLD batches close to expiry.

5. Please discuss the emulsion system in more details including: which adhesive is dispersed phase; where the API is dissolved in the emulsion (i.e. in dispersed phase or dispersion medium); droplet size; how the emulsion system is stabilized; what are the controls and data to suggest that the emulsion will not break during shelf life.

6. Please tighten the release and stability acceptance criteria of Oleyl Alcohol and Dipropylene Glycol in the drug product specification based on exhibit batch data.

7. The Agency requires evidence that the formulation of a generic product is not less safe than the RLD. We acknowledge that it is possible that different transdermal formulations of the same drug may have different responses to heat and/or under other "in-use conditions". The RLD labeling states that "Contact with water while bathing, swimming or showering will not affect the patch". To ensure that the RLD labeling with respect to heat and/or other in-use conditions are applicable to the ANDA product, the ANDA applicant should provide information about the formulation performance to ensure that the sensitivity to heat (or other "stress conditions") of the generic product is not more pronounced than that of the RLD. You may design and provide an in vitro study (e.g., skin flux permeation study with "heat" or other "stressed" conditions to mimic certain in-use conditions) to compare in vitro skin permeation flux data to the RLD at normal and elevated temperatures. If the generic product was not more sensitive than the RLD, it would be acceptable. Such in vitro data would assure that the proposed generic TDDS product would not create a greater risk when exposed to heat (or under in-use conditions) than the RLD. Please refer to the FDA response to the CP 2012-P-0932 (see link below) for additional information.

   http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0932-0003

BIOEQUIVALENCE

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

It was noticed that you performed the drug release testing using the test lots of [redacted]. As a result, the DB I **tentatively** accepts the drug release method and specifications below. Please submit drug release data from 12 units from each of at least three [redacted] lots for each strength of the test product, when available, to confirm and verify the tentative dissolution method and specifications that the DB I is recommending.

These lots should be manufactured using the FDA-approved manufacturing site, process, equipment, formulation, and specifications.

Apparatus:	USP VI (cylinder, modified- Attach the patch on the cylinder using double-sided tape, release side facing away from the cylinder. The release side should not be covered by a membrane)
Speed:	50 rpm
Medium:	Water
Volume:	500 mL for 0.025 mg/day and 0.0375 mg/day; 900 mL for 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day
Temperature:	32ºC ± 0.5ºC

The test product should meet the following specifications:

2 hr: 20-40%;
6 hr: 48-68%;
12 hr: 70-90%

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

CLINICAL

The Division of Clinical Review has completed its review of your skin irritation, sensitization, and adhesion data and has identified the following deficiencies:

1. You have not provided adequate data to ensure that the adhesive performance of your product is at least as good as that of the RLD and that the irritation potential of your product is non-inferior to the RLD.

   In the skin irritation, sensitization and adhesion study (**EDOT-0908)**, your product was statistically significantly less adhesive than the reference product and failed to show that it is no more irritating than the RLD .

2. There are still outstanding issues related to the specification limits of certain excipients that must be resolved. Comments will be forthcoming from the OGD Chemistry Division.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. These comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or

regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

LABELING

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated (April 25, 2012).

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a MINOR AMENDMENT. The designation as a **RESUBMISSION/AFTER ACTION – MINOR COMPLETE RESPONSE AMENDMENT** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Product Quality (CMC), Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dose forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to

import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Esther Chuh, Pharm.D., Regulatory Project Manager, at (240) 276-8530.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

05/28/2013

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 201675

COMPLETE RESPONSE

Mylan Technologies Inc.
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated April 26, 2010, received April 27, 2010, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice Weekly).

We acknowledge receipt of your amendments dated August 15 and December 30, 2013.

The August 15, 2013, submission constituted a complete response to our May 28, 2013, action letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The deficiencies presented below are MINOR deficiencies:

A. Deficiencies

1. In your response to Comment 3, a limit of (b) (4) in the finished product was proposed, but the limit is found to be (b) (4) in the revised Finished Product Specifications. Please revise.

2. Please analyze release and stability samples of your products for shear against RLD to assure your estradiol product is comparable to RLD with respect to this property.

3. Please tighten the release and stability specifications for known related substances namely 17 alpha-Estradiol and 1-methylestradiol.

4. Oleyl alcohol is [redacted] (b) (4). We note that oleyl alcohol decreases by ~10% at 24 month time point in long term stability studies. Please provide in vitro skin permeation data on drug product containing oleyl alcohol near the lower specification limit. Using appropriate statistical analysis, please demonstrate equivalence to the drug product lot containing the target amount.

BIOEQUIVALENCE

The Division of Bioequivalence has completed its review and has no further questions at this time. The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

CLINICAL

The Division of Clinical Review has completed its review and the following deficiencies have been identified:

You have not provided adequate data to ensure that the irritation potential of your product is non-inferior to the RLD.

The information you provided in your amendment dated 12/30/2013 is not adequate.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. These comments are subject to revision if additional concerns are raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

LABELING

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated August 15, 2013.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic

Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

FACILITY INSPECTIONS

Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
CHEMISTRY / CLINICAL

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those

responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Surjit Basi, Regulatory Project Manager, at (240) 276-8570.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

04/03/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201675Orig1s000

LABELING

ETSTW R5

060105

Estradiol Transdermal System, USP (Twice-Weekly)

H GHL GHTS OF PRESCRIBING NFORMATION
These high ights do not include a l the info mation needed to use ESTRADIOL tran dermal sy tem (twice week ly) safely and effec ively See full pre c ibing information for ESTRADIOL transdermal system twice weekly)
ESTRADIOL tran de mal system USP twice weekly)
Initial U S Approval 1996

WARN NG ENDOMETRIAL CANCER CARD OVASCULAR DISORDERS BREAST CANCER AND PROBABLE DEMEN IA
See full p e cribing information for complete boxed warning

E t Al Th

- **There is an increased isk of endometrial cancer in a woman wi h a uterus who uses unoppo ed est o gens 5 2)**
- **Est ogen alone herapy hou d not be used for the pre en ion of cardiovascular disease or dementia (5 1 5 3)**
- **The Women's Heal h In tiative (WHI) estrogen alone substudy reported increased risks of st oke and deep vein hrombosis (DVT) (5 1)**
- **The WHI Memo y Study (WH MS) est ogen alone anc llary study of WHI reported an increased isk of developing p obable dementia in postmenopausal women 65 years of age or older (5 3)**

E t Pl P i Th

- **Est ogen plus progestin therapy should not be used for he preven ion of cardiovascular disease or demen ia (5 1 5 3)**
- **The WHI estrogen plus p oge tin substudy reported inc eased risks of DVT pulmonary embolism (PE) st oke and myocardial infa ction (MI) (5 1)**
- **The WHI estrogen plus progestin substudy eported increased risks of invasive breast cancer (5 2)**
- **The WHIMS estrogen plus p ogestin anci lary study of WHI reported an increased risk of developing probable demen ia in postmenopau al women 65 years of age or o der (5 3)**

IND CA IONS AND USAGE
Estradiol transd rmal s stem twice wee ly) is an est ogen indicated for
- Tr atment of moderate to sev re vasomotor symptoms due to menopause (1 1)
- Tr atment of moderate to sev re symptoms of vulvar and vaginal atrophy due to menopause (1 2)

Lim ta ion of U e When presc ibing solely for the treatment of m derate to seve e vaginal at ophy topical vaginal p oducts should be onside ed
- Tr atment of hyp estr genism due to hypogonadism castration or primary ova ian fa lure (1 3)
- Prev n ion of postmenopausal osteoporo is (1 4)

Lim ta ion of Use When presc ibing solely for he t eatment of p stm nopausal osteopo osis therapy shou d only be conside ed for women at ignifi ant risk f osteoporo is and non est ogen medica ions should be carefully c n ide ed

DOSAGE AND ADM NISTRATION
- Sta t herapy with est adiol transde mal system (twice weekly) 0 0375 mg day Dosage adjustment should be guided by the linical r sponse 2 1 2 2 2 3)
- For the preven ion of po tmen pau al oste porosis start the apy with estradiol t ansdermal system twice wee ly) 0 025 mg day (2 4)
- Estradi l transde mal system (twice weekly) should be placed on a clean d y a ea on the lower abdomen or buttocks Estradi l transde mal s stem (twice wee ly) shou d not be applied to he br asts (2)

DOSAGE FORMS AND S RENGTHS
Transde mal sy tem 0 025 mg/day 0 0375 mg/day 0 05 mg/day 0 075 mg/day and 0 1 mg day 3)

CONTRAINDICA IONS
- Undiagn sed abno mal gen tal ble ding 4 5 2)
- Known suspected or history of breast cancer 4 5 2)
- Known r su pected est ogen dependent neoplasia (4 5 2)
- Ac ive DVT PE or a history of these cond ti ns 4 5 1)
- Ac ive art rial hromboembo ic di ease for example stroke and M) or a histo y f hese condi ions (4 5 1)
- Known anaph lac ic reac ion or angi edema or hype sensi iv ty wi h estradiol tran dermal system (twi e week ly) (4 5 15)
- Known iv r impairment or disease (4 5 10)
- Known p otein C pr tein S or ant thr mbin deficiency or oth r known th omboph lic disorde s 4)
- Known r su pected pregnancy (4 8 1)

WARN NGS AND PRECAU IONS
- Estrogens inc ease he isk of gal bladder disease (5 4)
- Di continue estrogen if seve e hype cal emia loss of vision seve e hype trigl cer demia or cholesta ic jaundice o curs (5 5 5 6 5 9 5 10)
- Monitor thy oid function in women on thy oid replacem nt herapy (5 11 5 18)

ADVERSE REACT ONS
Most common adverse rea tions (≥ 10 percen) w th stradiol t ansdermal ystem twice we kly) a e h adache breast t nderness nas pha yng tis sinus tis sinus headache upper espi atory tract infection back pain dep es sion and i regular vaginal bleeding or sp tting (6 1)

To eport SUSPECTED ADVERSE REACTIONS contact Mylan Pharmaceu icals Inc at 1 877 446 3679 (1 877 4 INFO RX) or FDA at 1 800 FDA 1088 or www fda go /medwatch

DRUG INTERACTIONS
Induce s and/ r inhib to s of CYP3A4 may affe t strog n drug metabolism 7 1)

USE IN SPECIF C POPULATIONS
- Nursing Mothe s Estr g n administration to nur ing women has been shown to decrease the quantity and qua ity of breast m lk Det ctable amounts of est ogens have been d ntifi d in he b east mi k of women eceiving e trogens (8 3)
- Geriat ic Use An incr ased isk of probable d mentia in women over 65 ears of age was repo ted in the WH MS anc llary studies of he WHI (5 3 8 5)

See 17 for PA IENT COUNSELING NFORMATION and FDA appro ed patient labe ing

E STW R5 PL ETSTW R4
REVISED AUGUST 2014

FULL PRESCR B NG INFORM TION CONTENTS*
WARNING ENDOMETRIAL CANCER CARD OVASCULAR DISORDERS BREAST CANCER AND PROBABLE DEMENTIA

*Sections or subs cti ns omi ted from he full pr scr bing info ma ion are not li ted

FULL PRESCR B NG INFORMA ION

WARN NG ENDOMETRIAL CANCER CARD OVASCULAR D SORDERS BREAST CANCER AND PROBABLE DEMEN IA

Estrogen Alone Therapy

Endometrial Cancer

The e is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hype plasia which may be a precursor to endometrial cancer Adequate diagnostic measures including directed or andom en dometrial samp ing when indicated shou d be undertaken to rule out ma ignancy in postmenopausal women w th undiagnosed pe sistent or recur ing abnormal gen tal bleeding *[see Warnings and Precau ions (5 2)]*

Cardiovascular Di o ders and Probable Demen ia

Estrogen alone the apy shou d not be used for he preven ion of cardiovascular disease or demen ia *[see Warnings and P ecautions (5 1 5 3) and Clinical Studies (14 3 14 4)]*

The Women's Health In tia ive (WH) estrogen alone substudy repo ted increased isks of stroke and deep vein hrombosis (DVT) in postmenopausal women (50 to 79 years of age) du ing 7 1 ears of t eatment wi h da ly oral conjugated est ogens (CE) [0 625 mg] alone rela ive to placebo *[ee Wa nings and Precautions 5 1) and Clinical Studies (14 3]*

The WHI Memory Study (WHIMS) e trogen alone anc llary tudy of he WHI eported an increased isk of de veloping probable dementia in postmenopausal women 65 ea s of age or older during 5 2 yea s of treatment w th da ly CE (0 625 mg) alone relative to placebo It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions 5 3) Use in Specific Populations 8 5) and Clinical Studies (14 4)]*

In he absence of compa able data these risks shou d be as umed to be similar for o her doses of CE and o her dosage forms of estrogens

Estrogens w th or w thout progestins should be presc ibed at he lowe t e fective doses and for the shortest du ation consistent w th treatment goals and isks for the individual woman

Estrogen Plus Proge tin Therapy

Cardiovascular Di o ders and Probable Demen ia

Estrogen plus progestin herapy should not be used for the preven ion of ca diovascular disease or dementia *[see Warnings and P ecau ions (5 1 5 3) and Clinical Studies 14 3 14 4)]*

The WHI estrogen plus progestin substudy eported increased risks of DVT pulmonary embo i m (PE) stroke and myoca dial infarction M) in postmenopausal women (50 to 79 years of age) during 5 6 years of treat ment w th daily oral CE (0 625 mg) combined w th medroxyp ogesterone acetate (MPA) 2 5 mg] elative to placebo *[see Warnings and Precau ions (5 1) and C inical Studies (14 3)]*

The WHIMS estrogen plus progestin anc llary study of the WHI repo ted an increased isk of developing p obable dementia in postmenopausal women 65 ears of age or older during 4 years of treatment w th daily CE (0 625 mg) combined wi h MPA (2 5 mg) relati e to placebo It is unknown whether this finding applies to younger postmenopausal women *[see Wa nings and Precautions 5 3) Use in Specific Populations 8 5) and Clinical Studies 14 4]*

B east Cancer

The WHI est ogen plus progestin substudy also demon trated an increased risk of invasive breast cancer *[see Warnings and P ecau ions (5 2) and C inical Studies (14 3)]*

In he absence of comparable data these risks shou d be assumed to be similar for other doses of CE plus MPA and o her combinations and dosage forms of est ogens and p ogestins

Estrogens w th or w thout progestins should be presc ibed at he lowe t e fective doses and for the shortest du ation consistent w th treatment goals and isks for the individual woman

1 ND CATIONS AND USAGE
Estradiol t ansdermal syst m twi e weekl) is indi ated for
1 1 Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopau e
1 2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal At ophy Due to Menopause
Limita ion of Use When pres ribing s lely for the tr atm nt of moderate to s vere symptoms of vulvar and vaginal atrophy topical vaginal pr du ts should be con ider d
1 3 Treatment of Hypoestrogenism Due to Hypogonadism Castration or Primary Ovarian Fa lure
1 4 P e ention of Postmenopausal Osteoporosis
Limita ion of U e When presc ibing solely for the p evention of p stmenopausal oste p rosis the apy shou d nly be cons dered for women at sign ficant risk of osteopo osis and non estrogen medicati ns shou d be ca efully conside ed

2 DOSAGE AND ADMIN STRA ION
G nerally when estrogen is p escr bed for a postmenopausal woman w th a uterus a proges in h uld be con side ed to reduce the risk of endometrial cancer A woman wi hout a ute us does not n ed a p ogestin In ome cases however h ster ctomized women w th a history of endomet iosis may ne d a p ogestin *[see Warnings and Precautions (5 2 5 14)]*

U e of estrogen alone or in combination w th a proge tin hould be wi h he lowest effective d se and the shortest duration con ist nt w th treatment goals and risks for the individual woman Postmenopausal women shou d be reevaluated periodica ly as clinica ly approp iate to det rmine whe her treatment is s i l necessary

The adhesive s de of estradiol transdermal system twice wee ly) shou d be placed on a cl an d y a ea of the trunk of the body (including the abdomen or bu tock) *Est adiol t ansdermal s stem (twice weekly) should not be app ied to the breasts*

Estradiol transd rmal sy tem (twice weekly) should be replaced twice weekly The ites of applicati n must be rotated w th an interval of at least 1 week allowed between applications to a pa ticular site The ar a selected should not be o ly damaged or irr tat d The wai tline hould be avo ded sin e ight cl thing may rub the system off he s stem shou d be applied immediately a ter opening he pouch and emo ing the oversized prot ctive iner The s stem shou d be pressed firmly in place w th the palm of the hand for about 10 econds making su e here is good contact espe ially around he edg s In he e ent hat a system should fa l off he same s stem may be reapplied If he same s stem cannot be eapplied a new ystem shou d be applied to ano her location In ei her case the original t eatment schedule shou d be continued If a woman has fo gott n to apply a patch she should apply a new patch as soon as poss ble The new pat h shou d be appli d on the riginal tr atment sch dule The int rrup ion of t eatment in w men taking estradiol t ansdermal system (twice weekly) might inc ease the l kel hood of breakth ough bleeding p tting and recu rence of symptoms

2 1 Moderate to Severe Vasomotor Symptoms
Start herapy w th est adiol transde mal sy tem (twice weekly) 0 0375 mg per day applied to he s in twice weekly D sage adjustment shou d be gu ded by the linical response In wom n not curren ly taking oral estrogens or in women switching from another estradiol transdermal therapy treatment w th e tradiol transde mal system (twice weekly) may be ini iated at once In women who are cur ently taking oral estrogens treatment wi h estradiol transde mal s stem (twice wee ly) shou d be in tiated 1 week a ter wi hdrawal of oral hormone therapy or ooner if m nopausal symptoms reappear in less than 1 week Attempts to taper or discontinue he medi ati n shou d be made at 3 to 6 month intervals

Estradiol transde mal system (twice weekl) may be given continuously in pa ients who do not have an intact uterus In th se patients w th an intact uterus estradiol transde mal system (twice weekl) may be given on a cyc ic schedule (for example 3 weeks on drug followed by 1 week off d ug)

2 2 Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy
Start herapy w th est adiol transde mal sy tem (twice weekly) 0 0375 mg per day applied to he s in twice weekly D sage adju tment shou d be gu ded by the clinical r sponse Att mpts to taper or discon inue he medica ion shou d be made at 3 to 6 month intervals

In w men not cu ren ly taking o al e trog ns or in w men sw tching f om another estradi l transde mal the apy t eatment w th stradiol t ansdermal ystem twice w ekly) may be in tiated at n e In women who are curren ly taking o al est ogens t eatment w th est adiol transdermal system (twice weekly) should be ini iated 1 w ek a ter withd awal f ral hormone herapy r s oner if m nopausal symptoms reappear in less than 1 week

Est adiol t ansdermal s stem (twice weekly) may be gi en continuously in patients who do not have an intact ute us In hose pa ients wi h an intact ute us estradiol tran dermal s stem (twice weekly) may be given on a cyc ic schedule for example 3 w eks on drug fo lowed by 1 w ek o f drug)

2 3 Hypoestrogenism Due to Hypogonadism Castra ion or Primary O arian Failure

2 4 Prevention of Postmenopausal Osteoporosis
Sta t herapy wi h estradiol transde mal sy tem (twice weekly) 0 025 mg per day app ied to the skin twice weekly In w men not cu ren ly taking o al e trog ns or in w men sw tching f om another estradi l transde mal the apy t eatment w th stradiol t ansdermal ystem twice w ekly) may be in tiated at n e In women who are curren ly taking o al est ogens t eatment w th est adiol transdermal system (twice weekly) should be ini iated 1 w ek a ter withd awal f ral hormone herapy r s oner if m nopausal symptoms reappear in less than 1 week

Est adiol t ansdermal s stem (twice weekly) may be gi en continuously in patients who do not have an intact ute us In hose pa ients wi h an intact ute us estradiol tran dermal s stem (twice weekly) may be given on a cyc ic schedule for example 3 w eks on drug fo lowed by 1 w ek o f drug)

3 DOSAGE FORMS AND STRENGTHS
Transd rmal s stem 0 025 mg/day 0 0375 mg/day 0 05 mg/day 0 075 mg/day and 0 1 mg/day

4 CONTRA ND CA IONS
Est adiol transdermal system (twice weekly) is cont aindicated in women w th any of he f llowing c nditions
- Undiagnosed abnormal genital bleeding
- Known uspected or history of breast cancer
- Known or suspected estrogen dependent neoplasia
- Active DVT PE or a history of these cond tions
- Active a te ial th omboembolic disease (for example st oke and MI) r a history of these cond tions
- Known anaphyla tic reac ion or angioedema or hyper ensi iv ty w th estradiol t ansdermal s stem (twice w ekly)
- Known liver impai ment or disease
- Known protein C prot in S or an i hrombin d ficiency or other known hrombophi ic diso ders
- Known or suspected p egnancy

5 WARNINGS AND PRECAUTIONS
5 1 Cardiovascular Disorders
An increas d risk f stroke and DVT has been repo ted w th str g n alone the apy An increased risk of PE DVT st oke and MI has been eported wi h estrogen plus proges in the apy Should any f hese occur or be suspe ted est ogen w th or w thout prog stin the apy hould be discontinued immediately

Risk factors for arterial vascular disease (for e ample hypertension diabetes me l tus tobacco use hyperch les te olemia and obesity) and/or venous thromboemb lism VTE) (for example pe sonal history or fam ly history of VTE obes ty and systemic lupus e ythematosus) sh u d be manag d approp iately

Stroke In the WHI est ogen alone substudy a sta is ica ly sign ficant increased risk of st oke was eported in women 50 to 79 yea s of age r ceiving daily CE (0 625 mg) alone compa ed to women in the same age gr up rec iving pla ebo (45 versus 33 per 10 000 women ears) he in rease in isk was demonst ated in y ar 1 and persist d *[see Clinical Studies (14 3]* Should a stroke occur or be suspected est ogen al ne the apy hould be dis ontinu d imm diately

Subgroup analys s of women 50 to 59 years of age sugge t no inc eased risk of st oke for those women receiving CE 0 625 mg) alone versus those r ceiving placebo (18 v rsus 21 per 10 000 women ears) [1]

In the WHI est ogen plus prog stin substudy a statistically ignifi ant increased risk of st oke was eported in women 50 to 79 yea s of age eceiving CE (0 625 mg) plus MPA (2 5 mg) compared to wom n in the ame age group receiving pla ebo 33 ve sus 25 per 10 000 women yea s) *[see Clinical Studies (14 3]* The inc ease in isk was demonst ated aft r he fi st year and persisted Shou d a st oke ccur or be su pected estrogen plus prog stin the apy sh uld be discontinued immediately

Coronary Hea t Disease In the WHI est ogen al ne substudy no ove all e fect on co onary heart di ease CHD) events defined as nonfatal MI silent MI or CHD dea h) was repo ted in w men receiving est ogen alone ompar d to plac bo[2] *[see C inical Studies 14 3)]*

Subgroup analys s of women 50 to 59 years of age sugg st a sta is ica ly nonsignificant reduc ion in CHD events repo ted in women ecei ing da ly CE (0 625 mg) alone c mpared to placebo in women less than 10 years since men pau e 8 ve sus 16 per 10 000 women yea s) [1]

In the WHI estrogen plus proges in substudy here was a statistically nonsign ficant incr ased isk of CHD events repo ted in women r ceiving da ly CE (0 625 mg) plus MPA (2 5 mg) compared to women r ceiving placebo 41 ver us 34 per 10 000 women yea s) [1] An inc ease in ela ive risk was demonstrated in year 1 and a tr nd towa d decr asing relative risk was repo ted in years 2 hrough 5 *[see C inical Studi s 14 3)]*

In postmenopausal women with documented heart dis a e (n 2 763 a erage 66 7 ears of age) in a ontro l d clini al trial of secondary pr vention of ca diovas ular disea e H a t and Estrogen/P ogestin Replacement Study HERS) tr atment wi h daily CE (0 625 mg) plus MPA (2 5 mg) demonstrat d no ca diovas ular benefit During an ave age follow up of 4 1 years treatment w th CE plus MPA did n t educe he ove all rate of CHD events in postmenopausal women w th e tablished CHD There we e more CHD ev nts in the CE plus MPA treated gr up than in the placebo group in year 1 but not during the subsequent yea s Two th usand th ee hund ed twenty one (2 321) women f om the o iginal HERS trial ag eed to par icipate in an p n label extension of HERS HERS II Average fo l w up in HERS I was an add tional 2 7 years for a total of 6 8 yea s o era l Rates of CHD events were comparable among women in the CE plus MPA gr up and he placebo group in he HERS the HERS I and overa l

Venous Th omboembo ism In the WHI est ogen alone substudy the ri k of VTE DVT and PE) was increased for women rec iving da ly CE 0 625 mg) alone compared to placebo (30 ver us 22 per 10 000 w men ears) alth ugh only he increas d risk of DVT eached statistical sign ficance (23 versus 15 per 10 000 women y ars) he increase in VTE risk was d monst ated du ing the fi st 2 years[3] *[see Clinical Studies 14 3)]* Shou d a VTE occur or be suspected est ogen alone herapy should be discon inued immediately

In the WHI estrogen plus p ogestin sub tudy a tatistically significant 2 fold greater ate of VTE was eported in women receiving daily CE (0 625 mg) plus MPA 2 5 mg) compared to women ecei ing placebo (35 ersus 17 per 10 000 women years) Sta is ica ly significant increases in risk for bo h DVT (26 versus 13 per 10 000 w men ears) and PE (18 versus 8 p r 10 000 women yea s) w re also demonstrated The increase in VTE risk was demonstrat d during he fi st year and pe sisted[4] *[see Clinical Studies (14 3)]* Shou d a VTE occur or be uspected e trogen plus proge tin the apy sh uld be discontinued immediately

If feasible est ogens shou d be disc ntinued at least 4 to 6 we ks before surgery of the type associated w th an inc eased ri k of th ombo mbo ism or during periods f p olong d imm bi iza ion

5 2 Ma ignant Neoplasms
Endometrial Cancer An increased risk of endometrial cancer has been eported w th the use of un pp sed strog n the apy in a woman w th a uterus The repo ted endometrial cancer risk among unopp sed estrogen users is about 2 to 12 imes g eater than in n nu ers and appea s dependent on duration of t eatment and on estrogen dose Most tudies show no sign ficant inc eased isk associated w th he use of estr gens f r less than one year The greatest risk appears to be a sociated w th prolonged use w th inc eased risks f 15 fo d to 24 fo d f r 5 to 10 years or mo e and his risk has been hown to persist for at l ast 8 to 15 ears after e trogen the apy is discon inued

Clinical su vei lance of all women using e trogen alone or est ogen plus p ogestin herapy is important Adequate diagno tic measures including directed or andom endom trial samp ing when indicated should be und rtak n to rule ut malignancy in postmenopausal women w th undiagnosed persist nt r recur ing abnormal genital bl eding

There is no eviden e that he use of natural strog ns r sults in a d fferent endomet ial risk profile than synth tic est ogens of quivalent strog n dose Adding a p ogestin to estrogen the apy has been shown to reduce the isk of endom trial hyperplasia which may be a p ecurs r to endomet ial canc r

Breast Cancer The most important andomized linical t ial pr viding information about breast canc r in estro gen alone use s is he WHI ubstudy of da ly CE 0 625 mg) alone In the WHI estrogen alone sub tudy after an average fo low up of 7 1 ears da ly CE (0 625 mg) alone was not ass ciat d wi h an increased risk of invasive breast canc r (relative isk [RR] 0 80)[5] *[see C inical Studies 14 3)]*

The most impo tant randomized c ini al trial prov ding informa ion about breast canc r in e trogen plus prog stin users is the WHI substudy of da ly CE (0 625 mg) plus MPA (2 5 mg) After a mean follow up of 5 6 ears the est ogen plus p ogestin substudy r p rted an in reased ri k of invasive b east cancer in women who took da ly CE plus MPA

In this substudy prior use of estrogen alone or est ogen plus pr gestin th rapy was repo ted by 26 percent of the women The relati e risk f invasive breast cancer was 1 24 and the absolute risk was 41 ve sus 33 a es per 10 000 w men ears for CE plus MPA ompar d with plac bo Among women who eported p ior use of ho mone the apy the rela ive risk of invasive breast cancer was 1 86 and the absolute risk was 46 ver us 25 ca es per 10 000 women years for CE plus MPA compa ed w th placebo [6] Among women who rep rted no pri r use of ho mone the apy the rela ive risk of invasive breast cancer was 1 09 and the absolute risk was 40 ver us 36 ca es per 10 000 women ears for CE plus MPA compar d wi h placebo In the same substudy invasive breast cance s were la ger we e more l kely to be node pos ti e and were diagnosed at a m re advanced tage in the CE (0 625 mg) plus MPA (2 5 mg) g oup compared w th the placebo group M tasta ic disea e was are wi h no appa ent difference between the two g oups Other pr gn stic fa tors uch as histologic ubtype g ade and hormone receptor status did not di fer between the groups *[see Clinical Studies (14 3)]*

Consi tent with the WHI c inical trial obs rvational studies ha e also eport d an increa ed risk of breast cancer for estrogen plus proge tin the apy and a sma ler increased risk for est ogen alone herapy a ter seve al years of use The risk increased with dura ion of use and appear d to return to ba eline ov r about 5 years after stopping t eatment (only he obs rvational studies have substantial data n risk after stopping) Observa ional studies also suggest that the ri k of breast cancer was greater and became appa ent ea lier wi h est ogen plus pr gestin herapy as c mpared to est ogen alone herapy However these studies ha e not found significant variation in he isk of breast cancer among d ff rent est ogen plus p ogestin ombinations doses or routes of administ ation

The use of estrogen alone and strogen plus proges in has been r ported to resu t in an increase in abn rmal mammograms requiring fu ther evaluation All women should receive yearly b east examinations by a hea thca e p ovider and perform monthly b east se f examina ions In add tion mammog aphy examinations h uld be sch d uled based on pa ient age isk factors and pri r mammogram r sults

Ovarian Cancer The WHI estrogen plus p ogestin substudy eported a statistically nonsignificant increased risk of ova ian canc r After an a erage follow up of 5 6 years he r lative isk for ovarian cancer f r CE plus MPA ve sus placebo was 1 58 95 pe cent CI 0 77 to 3 24) The abs lute risk for CE plus MPA versus placebo was 4 ve sus 3 cases per 10 000 women yea s [7] In some epid mi logic studies he use of estr gen plus prog stin and estrogen only products in pa ticular for 5 or more years has been asso iat d with an increased risk of ovarian cancer However he du ation of expo ure a sociated w th increa ed isk is not consistent ac oss a l ep d miologic studies and some report no association

5 3 Probable Demen ia
In the WH MS estrogen alone anc llary study of WHI a population of 2 947 hysterectomized women 65 to 79 yea s of age was randomi ed to da ly CE (0 625 mg) alone or placebo

A ter an average fo low up of 5 2 years 28 women in the est ogen al ne group and 19 women in he placebo g oup were diagno ed wi h p obable demen ia The relative isk of probable dementia for CE alone versus placebo was 1 49 95 perc nt CI 0 83 to 2 66) The abs lute risk of p obable demen ia for CE alone versus plac bo was 37 versus 25 ca es per 10 000 women years[8] *[see Use in Specific Populati ns (8 5) and Clinical Studies (14 4]*

In the WH MS estrogen plus proges in anc llary study of WHI a population of 4 532 postmenopausal wom n 65 to 79 years was andomized to da ly CE 0 625 mg) plus MPA (2 5 mg) or placebo

A ter an ave age f llow up of 4 yea s 40 women in the CE plus MPA g oup and 21 women in he placebo g oup were diagnos d wi h probable dementia he r lative isk of probable dementia for CE plus MPA ve sus placebo was 2 05 (95 pe cent CI 1 21 to 3 48) The absolute isk of probable demen ia for CE plus MPA ersus placebo was 45 versus 22 ca es per 10 000 women years[8] *[see Use in Specific Populati ns (8 5) and Clinical Studies (14 4]*

When data f om the two popula ions in the WHIMS e trogen alone and estrogen plus p ogestin anc llary studies were pooled as planned in he WH MS protocol he eported ove all relative isk for probable dementia was 1 76 95 perc nt CI 1 19 to 2 60) Since both anci la y studies were onducted in women aged 65 to 79 y ars f age t is unkn wn whe her these findings apply to younger postmenopausal w men[8] *[see Use in Spec fic Populations 8 5) and Clinical Studies (14 4]*

5 4 Gal bladder Disease
A 2 fo d to 4 fo d increase in the risk of ga lbladder disease r quiring su gery in postmenopausal wom n r ceiving estrogens has b en r port d

5 5 Hypercalcemia
Estrogen administ ation may lead to sev re h percalcemia in women wi h brea t canc r and bone metastases If hype cal emia occu s u e of the drug shou d be stopped and approp iate measu es taken to r du e the serum calcium level

5 6 Visual Abno ma ities
Re inal vascular thrombosis has been eported in women eceiving e trog ns Discon inue medication pending ex amination if the e is sudden pa tial or complete lo s of visi n or a sudden onset of p optosis diplopia or mig aine f examination eveals papi led ma r etinal vascular lesi ns est ogens sh uld be permanently discon inued

5 7 Addi ion of a Proges in When a Woman Has Not Had a Hysterectomy
Studies of the addi ion of a proges in for 10 or mo e da s of a cycle of est ogen administ ation or daily w th est ogen in a continuous egimen have eported a lowered inc dence of endometrial h perpla ia than wou d be induced by estrogen tr atm nt alone Endom trial hyperplasia may be a pre ursor to endom trial cancer Th re a e however poss ble risks that may be asso iated w th he use of p ogestins with est ogens compared to estrogen alone egimens These include an inc eased isk of breast canc r

5 8 Ele ated Blood Pressu e
In a mall number of ase eports ub tantial inc eases in blood p essure have been attributed to diosyn ratic eactions to estrogens In a large andomized placebo cont olled c inical t ial a genera iz d effect of est ogens on blood pres ure was not seen

5 9 Hypertriglycer demia
In women w th preexisting hype trigl cer demia e trogen the apy may be a sociated wi h elevations of plasma triglyce ides leading to panc eat tis C nsider discontinuati n of t eatment if pancrea i is occurs

5 10 Hepatic Impai ment and/or Past History of Chole tatic Jaundice
Estrogens may be poorly metabolized in women w th impaired iver fun ti n For w men w th a histo y of chole tatic jaundice associated wi h past est ogen use or w th p egnancy caution shou d be exercised and in the case of ecurr nce medication sh u d be di continued

5 11 Hypothy oidism
Estrogen administra ion leads to increased hyro d binding globulin (TBG) levels Women wi h normal hyro d functi n can c mpensate for the inc eased BG by making more th roid hormone thus maintaining f ee T_4 and T_3 se um oncent ati ns in the normal range Women dependent on thyr id h rm ne r placement therapy who a e also ecei ing e trogens may require inc eased dos s of their thyr id eplac ment the apy These women shou d have their thy oid func ion mon to ed in o der to maintain their free th ro d ho mone lev ls in an acceptable range

5 12 Flu d Retention
Estrogens may cause some deg ee of fluid ret n ion Women w th onditions that might be influenced by this factor such as ardiac or renal impairment warrant ca eful obse vation when str gen alone is pr scr bed

5 13 Hypocalcemia
Estrogen therapy shou d be used with caution in women w th h poparath ro dism as strog n induced hypocal cemia may occur

5 14 Exacerba ion of Endometriosis
A few cases of ma ignant t ansfo mation of esidual endometrial implants have been eport d in women treated post hysterectomy with est ogen alone herapy For women known to have esidual endomet iosis p st hy terec tomy he add tion of pr gestin shou d be cons dered

5 15 Severe Anaphylac ic/Anaphylacto d Reactions and Angioedema
Cases of anaphylac ic/anaphylactoid reac ions which developed anytime during the course of est adiol transder mal ystem twice weekly) t eatm nt and equi ed emergency medical management have be n repo ted in he postma keting se ting Involvement of skin (hives p u itus swollen ips tongue face) and e ther respiratory tract (respirato y comp omise) or gastrointe tinal tract (abdominal pain vom ting) has been noted

Angioedema in olving e e/ey l d face larynx pha ynx tongue and extremity hands legs an les and fingers) w th or wi hout urticaria equi ing medical interven ion has oc urred in the postmarke ing experience of using est adiol transdermal system (twi e weekl) If angioedema involves the tongue glo tis or lar nx airway obst uction may oc ur Patients who dev lop angioedema an time during the cou se of treatment wi h estradiol transd rmal ystem twice we kly) shou d not ecei e t again

Ex genous estrogens may exa erbate symptoms of angioedema in women wi h hered tary angioedema

5 16 Exacerba ion of O her Cond tions
Estrogen the apy may cause an exac rbation of a thma diabetes mel itus epilepsy migraines po phyria systemic lupus e ythematosus and hepatic hemangiomas and shou d be used w th caution in women w th hese condi ions

5 17 Laboratory Tests
Se um fo licle stimulating hormone (FSH) and e tradiol l vels have not been shown to be useful in he managem nt of moderate to seve e asomotor symptoms and moderate to s vere symptoms of vulvar and vaginal atrophy

Labo ato y pa ameters may be useful in gu ding dosage for he treatment of hypo strog nism due to hypogonadism castration and prima y o arian fa lure

5 18 Drug Labo atory Test Inte actions
- Accelerated p oth ombin time partial th omboplastin ime and platelet aggrega ion time increased platel t count incr ased fa tors II VII an igen V II antigen VI I coagulant ac iv ty X X XI V I X complex I VII X complex and beta thromboglobu in de reased levels f an i factor Xa and ant thr mbin I I de reased an t th ombin II activ ty increased le els of fibrin gen and fibrinog n activ ty increased plasminogen antigen and a ti ity
- Increased thy oid binding globu in TBG) leading to increa ed circula ing total hyro d ho mone levels as measured by p otein bound iodine PB) T_4 levels (by column or by adioimmunoassay) or T_3 l vels by radio immun assay T_3 resin uptake is dec eased refl cting the ele ated BG F ee T_4 and free T_3 concent ations are unaltered Wom n on thy oid replacement th rapy may require higher doses of thy oid hormone
- Other binding p oteins may be levated in serum for example co ti oste oid binding globu in CBG) ex hormone binding globulin SHBG) leading to increa ed total ci culating co ticoste oids and sex ste oids re pectively F ee ho mone concent ations such as testosterone and est adiol may be decreas d Oth r pla ma proteins may be increased (angiotensinogen/ enin subst ate alpha 1 ant t ypsin ce uloplasmin)
- Increased plasma high density ip protein HD) and HDL_2 cholest rol subf action conc ntra ions educed low density ipop otein LDL) cholesterol c ncentra ion increas d t iglyce ides lev ls
- Impai ed glucose tolerance

6 ADVERSE REACTIONS
The fo lowing se ious adverse r acti ns are discussed elsewhe e in labeling
- Cardiovascular Disorde s *[see Bo ed Warning Wa nings and Pre autions (5 1)]*
- Malignant Neoplasms *[ee Box d Warning Warnings and Precau ions (5 2)]*

6 1 Clinical T ial Experience
Because c inical t ials a e c nducted under w dely va ying cond tions adve se eaction rates obse ved in the clinical trials f a drug ann t be di ectly ompar d to rates in the c ini al trials of another drug and may not refle t he ates obser ed in p actice There were no clinical trials conducted wi h he evi ed formulation of est adiol transder mal system (twice weekly) The r vised fo mulati n of estradiol tran dermal system twi e weekl) is bioequival nt to the original f rmulation of estradiol transde mal system (twice weekl) The following adverse reac ions have been repo ted w th the original f rmulation of estradiol transd rmal s stem twice wee ly) herapy

Table 1 Summary of Most Frequently Reported Adver e Reactions Regardless of Rela ionship Reported at a F equency ≥ 5 Percent

	Estradiol Transdermal System Twice Weekly)					Placebo
	0 025 mg/da † (N 47) N %)	0 0375 mg day† N 130) N %)	0 05 mg/day† (N 103) N (%)	0 075 mg/day† N 46) N (%)	0 1 mg/da † (N 132) N %)	(N 157) N (%)
Gastrointestinal diso ders						
Constipation	2 (4 3)	5 (3 8)	4 (3 9)	3 6 5)	2 (1 5)	4 (2 5)
Dyspepsia	4 (8 5)	12 (9 2)	3 (2 9)	2 4 3)	0	10 (6 4)
Nausea	2 (4 3)	8 (6 2)	4 (3 9)	0	7 (5 3)	5 (3 2)
Gene al disorde s and administration s te cond tions* **						
Influen a l ke i lne s	3 (6 4)	6 (4 6)	8 (7 8)	0	3 (2 3)	10 (6 4)
Pain NOS*	0	8 (6 2)	0	2 4 3)	7 (5 3)	7 (4 5)
Infec ions and infesta ions						
Influen a	4 (8 5)	4 (3 1)	6 (5 8)	0	10 (7 6)	14 (8 9)
Nasopharyng tis	3 (6 4)	16 (12 3)	10 (9 7)	9 (19 6)	11 (8 3)	24 (15 3)
Sinus tis NOS*	4 (8 5)	17 (13 1)	13 (12 6)	3 6 5)	7 (5 3)	16 (10 2)
Upper respirato y t act infe ti n NOS*	3 (6 4)	8 (6 2)	11 (10 7)	4 8 7)	6 (4 5)	9 (5 7)
Inves igations						
W ight inc eased	4 (8 5)	5 (3 8)	2 (1 9)	2 4 3)	0	3 (1 9)
Musculoskeletal and connective issue diso ders						
Ar hralgia	0	11 (8 5)	4 (3 9)	2 4 3)	5 (3 8)	9 (5 7)
Back pain	4 (8 5)	10 (7 7)	9 (8 7)	4 8 7)	14 (10 6)	10 (6 4)
Neck pain	3 (6 4)	4 (3 1)	4 (3 9)	0	6 (4 5)	2 (1 3)
Pain in limb	0	10 (7 7)	7 (6 8)	2 4 3)	6 (4 5)	9 (5 7)
Nervous ystem di orders						
Headache NOS*	7 14 9)	35 (26 9)	32 (31 1)	23 50 0)	34 (25 8)	37 (23 6)
Sinus headache	0	12 (9 2)	5 (4 9)	5 (10 9)	2 (1 5)	8 (5 1)
Psychiatric diso de s						
Anxiety NEC**	3 (6 4)	5 (3 8)	0	0	2 (1 5)	4 (2 5)
Depression	5 (10 6)	4 (3 1)	7 (6 8)	0	4 (3 0)	6 (3 8)
Ins mnia	3 (6 4)	6 (4 6)	4 (3 9)	2 4 3)	2 (1 5)	9 (5 7)
Rep oductive system and breast disorders						
Breast t nderness	8 (17 0)	10 (7 7)	8 (7 8)	3 (6 5)	17 (12 9)	0
Dysmenorrh a	0	0	0	3 6 5)	0	0
Intermenst ual ble ding	3 (6 4)	9 (6 9)	6 (5 8)	0	14 (10 6)	7 (4 5)
Respiratory tho acic and mediastinal diso ders						
Sinus conges ion	0	4 (3 1)	3 (2 9)	3 6 5)	6 (4 5)	7 (4 5)
Vascular diso ders						
Hot flushes NOS*	3 (6 4)	0	3 (2 9)	0	0	6 (3 8)
Hypertensi n NOS*	2 (4 3)	0	3 (2 9)	0	0	2 (1 3)

† Rep esen s mi ig ams of es radiol de i ered da ly by each sy tem
* NOS rep esen s n t othe wise sp cified
** NEC rep esen s ot el ewhere class fied
*** App ication ite e yth ma and ap lication i e ir i ation we e ob erv d in a sma l number of patien s 3 2% or less of pa ie ts acr ss rea ment group)

6 2 Postmarke ing Experience
The following add tional adverse rea tions have been dent fied du ing post app oval use of stradiol t ansdermal system twi e weekl) Because the e eactions a e eported olunta ily from a populati n of unce tain size t is not always p ssible to eliably es imate heir frequency or estab ish a au al rela ion hip to d ug e posure

Gen tourinary S stem Vaginal hemor hage and abno mal wi hd awal bleeding or fl w brea through bleeding spotting ut rine leiomyomata vagini is vaginal di charge ova ian cancer endometrial hype plasia dysmenorrh a
B east Enla gement pain nipple discha ge fibroc stic br a t hang s breast cancer
Ca diovascular Deep enous hrombosis pulmona y embo ism thrombophleb tis
Gastrointestinal Nausea vom ting abdominal cramps bloa ing chol li hiasis liver function t sts abno mal diar hea
Skin Application ite r a ti ns include lo ali ed bleeding b uising burning discomfo t dr ness ecz ma edema ery hema er thema mu tiforme ery hema nodosum inflamma ion irr tation pain papules and vesicl s O her skin reactions include pares hesia skin discoloration skin pigmentation urticaria swel ing lo s of scalp hair hirsu ism pru itus ash
E es Int le ance to contact lenses
Central Nervous System Migraine dizziness cho ea nerv u ness affect liabi ity ir itabi ity
Miscellaneous D crease in weight r duced ca bohydrate t le an e edema ar hralgias leg c amps changes in lib do purpu a hypers n itiv ty anaphylactic eaction anaphylactoid reac ion angioedema

7 DRUG N ERACT ONS
No drug interaction studi s have been onducted w th est adiol transdermal system (twice weekly)

7 1 Metabo ic Inte actions
In vit o and *in vivo* studies have shown hat strog ns a e metabo iz d par ia ly by cyt chrome P450 3A4 CYP3A4) Therefore inducers or inh bito s f CYP3A4 may aff ct str gen drug metabolism Inducers of CYP3A4 such as St John's wort *H pericum perf ratum*) prepara ions ph nobarbital ca bamazepine and r fampin may reduce plasma concent ati ns of estrogens poss bly r sulting in a decrease in the apeutic e fects and/or changes in the ute ine bleeding profile Inh bitors of CYP3A4 such as ery hromycin clar thromycin ketocona ole tra onazole itonavir and grapefru t juice may increase plasma oncent ations of estrogens and may esult in s de e fects

8 USE IN SPECIF C POPU ATIONS
8 1 Pregnancy
Estradiol t ansdermal system (twice weekly) shou d not be used during p egnancy *[see Cont aindicati ns 4)]* here app ars to be l ttle r no inc eased isk of bi th defects in chi dren born to women who have used est ogens and p oges ins as an oral contraceptive inadve tently during early pregnancy

8 3 Nur ing Mothe s
E tradiol t ansdermal syst m (twi e weekl) should not be us d during lacta ion Estrogen administration to nu s ing women has been shown to decrease the quant ty and qual ty of the brea t mi k Det ctable amounts of estrogens ha e been iden ified in the breast m lk of women receiving est ogens Caution shou d be exe cised when estradiol transde mal s stem (twice weekly) is administer d to a nu sing woman

8 4 Pediatric Use
E trogen the apy has b en used for the induction of puberty in adolescents with some fo ms of pube tal delay Safety and ffec iv ness in pediat ic pati nts ha e not o herwise been estab ished

Large and rep ated d ses of e trogen over an extended time period have been shown to accelerate epiphyseal clo sure which cou d r sult in sho t adu t stature f t eatm nt is in tiated before the completion of physiologic pube ty in norma ly dev loping ch ld en If estrogen is admini tered to patients whose bone g owth is not complete p riodic mon toring of bone maturation and effects on epiphy eal cente s is ecommended during est ogen administ ation

E trog n t eatment of prepubertal gi ls also induc s p ematu e b east development and vaginal co nifica ion and may induce vaginal bleeding

8 5 Geriatric Use
There have not be n suffi ient numbe s f g riatric wom n involved in clini al studi s u ilizing estradiol transd r mal system (twice weekl) to determine whe her those over 65 yea s of age differ from y unger subjects in their response to est adiol transde mal system (twice weekly)

The Women's Hea th Ini ia ive Studies In the WHI estrogen alone substudy daily CE 0 625 mg] alone ersus placebo) here was a higher relative isk of stroke in women gr ater than 65 ears of age *[see Warnings and P ecautions (5 1) and Clini al Studies (14 3)]*

In he WHI estr gen plus prog stin substudy (da ly CE 0 625 mg] plus MPA 2 5 mg] ver us pla ebo) the e was a higher r lative isk of nonfatal stroke and in asive breast cancer in women g eater than 65 yea s of age *[see Warnings and Precau ions (5 1) and C inical Studies 14 3]*

The Women's Heal h Initiative Memo y Study In he WHIMS an illary studies of postmenopausal women 65 to 79 years of age th re was an incr ased isk of developing probable demen ia in w men receiving estrogen alone or es trogen plus pr gestin when ompar d to placebo *[see Wa nings and P ecautions 5 3) and Clini a Studies (14 4)]* Since both anci la y tudi s were conducted in women 65 to 79 years of age t is unkn wn wh ther these findings apply to younger postmenopausal women *[see Warnings and Precau ions (5 3) and C inical Studies 14 4)]*

8 6 Renal Impairment
The e fect of renal impairm nt on the pha macokinetics f estradiol transde mal sy tem (twice weekly) has not been tudi d

8 7 Hepa ic Impairment
The e fect of hepatic impai ment on he pharmacokine ics of estradiol tran d rmal sy tem (twice weekly) has not been tudied

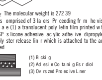
10 OVERDOSAGE
Overdosage of estrogen may cause nausea vom ting breast t nderness abdominal pain drowsin ss and fatigue and wi hd awal bleeding may ccur in women T eatm nt of ove d se consists of discontinuation of est adiol t ansdermal ystem twice w ekly) herapy with ins ituti n of approp iate s mptomatic ca e

11 DESCR PT ON
Est adiol t ansdermal ystem twice wee ly) contains stradiol in a mu tipolymeric adhesive The ystem is de signed to release est adiol con inuously up n application to intact skin

Fi e do age streng hs of e tradiol t ansdermal sy tem (twice we kl) a e a ailable to pro ide nominal *in vivo* d livery rates of 0 025 mg 0 0375 mg 0 05 mg 0 075 mg or 0 1 mg of estradiol per day via he s in Each cor esponding system has an ac ive su face area of 2 5 cm² 3 75 cm² 5 0 m² 7 5 m² r 10 0 cm² and contains 0 41 mg 0 62 mg 0 82 mg 1 23 mg or 1 64 mg of e tradiol USP re pectively The compo i ion of the systems per un t area is iden ical

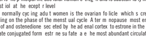
Est adiol USP is a white crystal ine powder chemica ly desc ibed as estra 1 3 5 (10) tri ne 3 17β diol

The structural f rmula is



The molecular f rmula of estradiol is $C_{18}H_{24}O_2$ The molecular weight is 272 39

Est adiol t ansdermal system (twi e weekl) is omprised of 3 la ers Pr ceeding fr m he vis ble surface toward the surfa e attached to the skin these laye s a e (1) a translucent poly lefin film printed w th b own ink 2) an adhesi e f rmulation containing est adiol USP s licone adhesive ac ylic adhe ive dipropylene glycol povidone and oleyl al ohol and 3) an ove sized sl t poly ster release lin r which is attached to the adhesive su face and must be removed b fore the system can be used



The a tive component of the s stem is estradiol The remaining components of the ystem a e pharmacologica ly inac ive

12 CLINICAL PHARMACO OGY
12 1 Mechanism of Ac ion
Endogenous strog ns are la gely respons ble for the development and maint nan e of the female eproduc ive system and secondary sexual chara teristics Alth ugh ci cula ing e trogens exist in a d namic equi ib ium of metabolic inte conve sions stradiol is he p incipal int ace lular human e trog n and is substan ia ly mo e p tent than its metabo it s est one and est iol at he ecept r level

The p ima y sou ce of est ogen in normally cyc ing adu t women is the ovarian fo licle which s cret s 70 to 500 mcg of est adiol da ly depending on the phase of the menst ual cycle A ter m nopause most endogenous est ogen is produced by c nversion of and ostenedione sec eted by he ad enal cortex to estrone in the periph ral tissues Thus estrone and the su fate conjugated form estr ne su fate a e he most abundant circulating estro gens in p stm nopausal women

Est ogens a t hrough binding to nuclear receptors in est ogen r sponsive tissues To date two estrogen rec ptors have b en dent fied These ary in propo tion f om tissue to issue

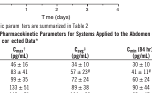
Ci culating e trogens m dulate the pituita y ecre ion of he gonadotropins luteinizing hormone LH) and fo licle stimulating ho mone (FSH) th ough a negative feedback mechanism Estrogens act to r du e he elevated l vels of these hormones seen in po tm nopausal women

12 2 Pha macodynamics
There are no pha macod namics data f r e tradiol t ansdermal ystem twice w ekl)

12 3 Pha macokinetics
Absorption In a mu tiple dose study onsis ing of thr e con ecutive ystem app ica ions of he o iginal formula ion of est adiol transde mal sy tem (twice weekly) which was conducted in 17 heal hy postmenopausal women blood le els of e tradiol and estrone we e compared following applicati n of these units to sites on the abd men and buttocks in a cro sover fashion Syst ms that deliver nominal est adiol do es of app oximately 0 0375 mg per day and 0 1 mg per day w re app i d to abdominal application s tes while he 0 1 mg per day doses we e also app ied to sites on the butto ks These ystems increas d estradiol levels above base ine w thin 4 hou s and maintained respe ti e mean l vels of 25 and 79 pg/mL above baseline following app ica ion to the abd men s ightly higher mean lev ls f 88 pg/mL above ba eline were obser ed fo l wing app ication to he buttocks At the ame time inc eases in str ne pla ma oncent ati ns ave aged about 12 and 50 pg/mL resp cti ely following app i a ion to the abd men and 61 pg/mL for he bu tocks While plasma concent ations of est adiol and estr ne r main d slightly ab ve base ine at 12 h u s following removal of the systems in this study r sults f om another study show these l vels to return to bas line values w thin 24 hou s following removal of the systems

Figu e 1 illustrates the mean plasma c ncent ati ns of estradiol at steady state du ing application f hese patches at four di fe ent dosages

Figure 1
S eady Sta e Es radiol Plasma Concen ra ions for Systems Applied o he Abdomen
Nonbaseline cor ected levels



The corr sponding pharmac kine ic param ters are summarized in Table 2

Table 2 Steady State Est adiol Pharmacokinetic Parameters for Systems Applied to the Abdomen (mean ± standard devia ion) Nonbaseline cor ected Data*

Dosage (mg/day)	C_{max}† (pg/mL)	C_{avg}‡ (pg/mL)	C_{min} (84 hr)§ (pg/mL)
0 0375	46 ± 16	34 ± 10	30 ± 10
0 05	83 ± 41	57 ± 23#	41 ± 11#
0 075	99 ± 35	72 ± 24	60 ± 24
0 1	133 ± 51	89 ± 38	90 ± 44
0 1¶	145 ± 71	104 ± 52	85 ± 47

*Mean baseline es radiol conc nt ation 11 7 pg/mL
†Peak pla ma conc nt ation
‡Ave age lasma oncen ra ion
§Minimum plasma oncen ra ion at 84 hr
#Measu ed o er 80 hr
¶App ied to he bu to ks

The revised formula ion of est adiol transde mal sy tem (twice weekly) w th sma ler s stem sizes was shown to be bio quivalent to he o iginal fo mulation of est adiol transde mal system (twice weekly) used in the clinical trials

Distribu ion No sp cific inves iga ion of he issue distr buti n of est adiol abso bed from est adiol transde mal system (twice weekly) in humans has be n conducted The dist ibu ion of exogenous estrogens is similar to that of endogenous estrogens Estrogens are widely distr buted in the body and are gene ally found in higher con entra ions in the sex h rm ne ta get organs Estrogens ci culate in the blo d la gely bound to ex ho mone binding gl bu in (SHBG) and albumin

Metabolism Exogenous est ogens are metabolized in the same manner as endogenous estr gens Circulating est ogens xist in a d namic equ l brium of metabo ic interconve sions hese transfo ma ions take place mainly in the li er by Cytochrome 450 isoforms CYP1A2 and CYP3A4 Est adiol unde goes further metabo ism to su fate and glucuron de c njugates Estradiol and ts metabol tes are glucu onidated by UGT1A1 and UGT2B7 E tradiol is conve ted reve sibly to estr ne and bo h can be onverted to e triol which is a major urinary metabol te Estrogens also undergo ente ohepatic eci culation ia u fate and glucuron de onjugation in he iver b liary sec eti n of conjugates into he intes ine and hydrolysis in he intes ine fo l wed by reabso pti n In postmenopausal women a significant po ti n of the circulating est ogens exist as su fate conjugates e p cia ly estrone sulfate which ser es as a circulating re ervoir for the fo mation of more active est ogens

Excre ion Estradiol est one and est iol a e ex reted in the urine al ng wi h glucu onide and su fate conjugates The half l fe values calculat d after dosing with the est adiol transdermal system (twice weekly) ranged from 5 9 to 7 7 hours A ter r moval of the t ansdermal syst ms se um concent ations of estradiol and estrone retu ned to base ine le els w thin 24 hours

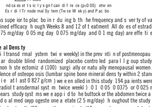
Use in Specific Populations No pharmac kine ic studies we e onducted with estradio transde mal s stem twice weekly) in specific populati ns including women w th enal or hepatic impairment

Adhesion Ba ed upon a de mal study for adhesion cha acte is ics in 228 subjects approximately 96% of est adiol t ansdermal syst m 0 025 mg/day (twice weekly) patches adhered ssentially c mpl te defined as greater han or equal to 90% adher d) to the skin over the 3 5 day wear pe iod Appr ximately 1% of the s stems detached during he 3 5 day w ar pe iod

13 NONCL NICAL OX CO OGY
13 1 Carcinogenesis Mutagenesis Impairment of Fer i ity
Long term continuous administ ati n of natural and synth tic est ogens in ertain animal species incr ases he f equency of carcinomas of the breast ute us cervix vagina testis and iv r

14 CLINICAL STUDIES
14 1 Effects on Vasomotor Symptoms
In a pharmacokine ic study the revised fo mula ion of estradiol tran dermal system (twi e weekly) was shown to be bioequivalent to the original fo mulation of estradi l transde mal sy tem (twice weekly) In two contro led clinical trials w th the original formula ion of estradi l tran dermal syst m (twice weekly) f 356 subjects the 0 075 mg day and 0 1 mg day do es we e supe ior to placebo in re ie ing vasomotor symptoms at Week 4 and maintained effica y h ough Weeks 8 and 12 of t eatment In this o iginal study he 0 0375 mg/day and 0 05 mg day do es however d d not d ff r from placebo unt l approximately Week 6 the efo e an add tional 12 week placebo contro led study in 255 pati nts was performed w th estradiol t ansdermal system (twice weekly) to establish he e ficacy of the lowest dose of 0 0375 mg day The bas line mean da ly number of hot flushes in these 255 pa ients was 11 5 Results at Weeks 4 8 and 12 of treatment a e sh wn in Figu e 2

Figu e 2
Mean SD) hange f om base i e n mean da ly number of lush s or Es rad ol T ansde mal S st m 0 03 5 mg/ ay Twic -W ekl) ver us P acebo n a 12 w ek r al

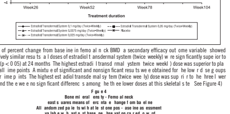


The 0 0375 mg/day dose was supe ior to plac bo in r du ing b th he frequency and s ver ty of vasomotor symp t ms at Week 4 and maintained efficacy h ough Weeks 8 and 12 of t eatment All do es of estradiol transde mal sy tem (twice weekly) (0 0375 mg/day 0 05 mg day 0 075 mg/day and 0 1 mg day) are effe ti e f r he control of vasomotor s mpt ms

14 2 Effects on Bone Mine al Dens ty
Effi acy and safety of estradi l transd rmal ystem twi e weekly) in the prev nti n of postmenopau al osteop rosis have been studied in a 2 y ar double blind randomized placebo contro led para l l g oup study A total of 261 hystere tomized (161) and non h ste ectomiz d (100) surgi ally or natu ally menopausal women (wi hin 5 yea s of menopause) wi h no ev dence of osteopo osis (lumbar spine bone mineral dens ty within 2 standa d deviations of ave age peak bone mass i e at l ast 0 827 g/cm) we e en olled in this study 194 pa ients were randomi ed to one of the four doses of estradiol t ansdermal syst m twice weekl) 0 1 0 05 0 0375 or 0 025 mg/da) and 67 patients to placebo Over 2 ears study syst ms we e app i d to he buttock or the abdomen twice a week Non hys t rectomized women eceived o al med oxyp ogeste one a etate (2 5 mg/day) h oughout the study

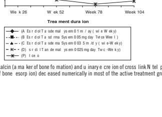
The study population compri ed natu ally (82 pe cent) or su gica ly (18 percen) menopausal hyst rectomized 61 pe cent) or non h ster ctomized (39 percen) w men w th a mean age of 52 ears (range 27 to 62 yea s) he mean dura ion of menopause was 31 7 m nths (range 2 to 72 months) Two hund ed hirty two (89 per ent) of rand mi ed subjects (173 on ac ive drug 59 on placeb) c ntr buted data to he analysis of perc nt change f om baseline in bone mineral den ity BMD) of the AP lumbar spine the prima y efficacy variable Pati nts we e given supplemental dietary calcium 1000 mg elem ntal cal ium/day) but no supplemental v tamin D here was an incr ase in BMD of the AP lumbar spine in all estradi l transde mal s stem twice wee ly) dose groups in contra t to his a decr ase in AP lumbar spine BMD was ob erved in placebo patients A l stradiol t ansdermal system twice w ekl) do es were sign ficantly supe ior to placebo (p < 0 05) at all ime points wi h the excep ion of e tradiol transde mal sy tem (twice weekly) 0 05 mg day at 6 months The highest dose of e tradiol tran dermal s stem twice we kly) was sup rior to the th ee lower doses There were no stati tica ly significant di fe ences in pairwise compari ons among the th ee lower doses (S e Figure 3)

Figure 3 Bone Mineral Dens ty AP Lumbar Spine
Least Squares Means of Pe centage Change from Base ine
A l Randomized Patients w th at Least One Po t base ine Assessment Ava lable wi h Last Post baseline Obse vation Carried Forward



Analysis of percent change from base ine in femo al n ck BMD a secondary efficacy out ome variable showed qua ita ively similar resu ts a l doses of estradiol t ansdermal system (twice weekly) w re sign ficantly supe ior to placebo (p < 0 05) at 24 months The highest estradi l transd rmal ystem twice weekl) dose was superior to pla cebo at all ime points A mixtu e of significant and nonsign ficant resu ts we e obtained for he low r d se g oups at ear i r ime p ints The highest est adiol transde mal sy tem (twice wee ly) dose was sup ri r to he hree l wer doses and the e we e no sign ficant differenc s among he th ee lower doses at this skeletal s te See Figure 4)

F gu e 4
Bone mi eral ens ty - Femo al neck
east s uares means of erc nta e hange f om ba el ne
All andom zed pa ie ts wi h at le st one pos - ase ine as essment va lab e w h ast p st base ne bse vat on ca r ed o w rd



The mean se um osteocalcin (a ma ker of bone fo mation) and u inary e cre ion of cross link N tel peptid s of T pe 1 collagen (a ma ker of bone esorp ion) dec eased numerically in most of the active treatment groups relative to

baseline However the decreases in both markers were consistent across treatment groups and the differences between active treatment groups and placebo were not statistically significant

14.5 Women's Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg) alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD [defined as nonfatal MI, silent MI and CHD death], with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other causes. These substudies did not evaluate the effects of CE alone or CE plus MPA on menopausal symptoms

WHI Estrogen-Alone Substudy The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints. Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 7.1 years are presented in Table 5

Table 5. Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI[a]

Event	Relative Risk CE vs Placebo (95% nCI[b])	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events[c]	0.95 (0.78 1.16)	54	57
Non-fatal MI[c]	*0.91 (0.73 1.14)*	*40*	*43*
CHD death[c]	*1.01 (0.71 1.43)*	*16*	*16*
All strokes[c]	1.33 (1.05 1.68)	45	33
Ischemic stroke[c]	*1.55 (1.19 2.01)*	*38*	*25*
Deep vein thrombosis[c,d]	1.47 (1.06 2.06)	23	15
Pulmonary embolism[c]	1.37 (0.90 2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62 1.04)	28	34
Colorectal cancer[e]	1.08 (0.75 1.55)	17	16
Hip fracture[c]	0.61 (0.41 0.91)	11	18
Vertebral fractures[c,d]	0.62 (0.42 0.93)	11	18
Lower arm/wrist fractures[c,d]	0.58 (0.47 0.72)	35	59
Total fractures[c,d]	0.71 (0.64 0.80)	144	197
Death due to other causes[e,f]	1.08 (0.88 1.32)	53	50
Overall mortality[c,d]	1.04 (0.88 1.22)	79	75
Global Index[g]	1.02 (0.92 1.13)	206	201

[a] [illegible]
[b] [illegible]
[c] [illegible]
[d] [illegible]
[e] [illegible]
[f] [illegible]
[g] [illegible]

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE alone was 12 more strokes while the absolute risk reduction per 10,000 women-years was seven fewer hip fractures. The absolute excess risk of events included in the "global index" was a nonsignificant five events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years (See Table 5)

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE alone compared to placebo. Estrogen alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined (See Table 5)

Timing of the initiation of estrogen therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy stratified by age showed in women 50 to 59 years of age a nonsignificant trend toward reduced risk for CHD [hazard ratio (HR) 0.63 (95 percent CI 0.36 to 1.09)] and overall mortality [HR 0.71 (95 percent CI 0.46 to 1.11)]

WHI Estrogen Plus Progestin Substudy The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were seven more CHD events, eight more strokes, ten more PEs, and eight more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were six fewer colorectal cancers and five fewer hip fractures

Results of the estrogen plus progestin substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 6. These results reflect centrally adjudicated data after an average follow-up of 5.6 years

Table 6. Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a]

Event	Relative Risk CE/MPA vs Placebo (95% nCI[b])	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99 1.53)	41	34
Non-fatal MI	*1.28 (1.00 1.63)*	*31*	*25*
CHD death	*1.10 (0.70 1.75)*	*8*	*8*
All strokes	1.31 (1.03 1.68)	33	25
Ischemic stroke	*1.44 (1.09 1.90)*	*26*	*18*
Deep vein thrombosis[c]	1.95 (1.43 2.67)	26	13
Pulmonary embolism	2.13 (1.45 3.11)	18	8
Invasive breast cancer[d]	1.24 (1.01 1.54)	41	33
Colorectal cancer	0.61 (0.42 0.87)	10	16
Endometrial cancer[c]	0.81 (0.48 1.36)	6	7
Cervical cancer[c]	1.44 (0.47 4.42)	2	1
Hip fracture	0.67 (0.47 0.96)	11	16
Vertebral fractures[c]	0.65 (0.46 0.92)	11	17
Lower arm/wrist fractures[c]	0.71 (0.59 0.85)	44	62
Total fractures[c]	0.76 (0.69 0.83)	152	199
Overall mortality[e]	1.00 (0.83 1.19)	52	52
Global Index[f]	1.13 (1.02 1.25)	184	165

[a] [illegible]
[b] [illegible]
[c] [illegible]
[d] [illegible]
[e] [illegible]
[f] [illegible]

Timing of the initiation of estrogen therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age a nonsignificant trend toward reduced risk for overall mortality [HR 0.69 (95 percent CI 0.44 to 1.07)]

14.6 Women's Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age and older (45 percent were 65 to 69 years of age, 36 percent were 70 to 74 years of age, and 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) alone on the incidence of probable dementia (primary outcome) compared to placebo

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE alone versus placebo was 1.49 (95 percent CI 0.83 to 2.66). The absolute risk of probable dementia for CE alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women (see *Warnings and Precautions (5.3) and Use in Specific Populations (8.5)*)

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were age 65 to 69 years, 35 percent were 70 to 74 years, and 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI 1.21 to 3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women (see *Warnings and Precautions (5.3) and Use in Specific Populations (8.5)*)

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI 1.19 to 2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women (see *Warnings and Precautions (5.3) and Use in Specific Populations (8.5)*)

15 REFERENCES

1 Rossouw JE, et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause. *JAMA* 2007;297:1465-1477
2 Hsia J, et al. Conjugated Equine Estrogens and Coronary Heart Disease. *Arch Int Med* 2006;166:357-365
3 Curb JD, et al. Venous Thrombosis and Conjugated Equine Estrogen in Women Without a Uterus. *Arch Int Med* 2006;166:772-780
4 Cushman M, et al. Estrogen Plus Progestin and Risk of Venous Thrombosis. *JAMA* 2004;292:1573-1580
5 Stefanick ML, et al. Effects of Conjugated Equine Estrogens on Breast Cancer and Mammography Screening in Postmenopausal Women With Hysterectomy. *JAMA* 2006;295:1647-1657
6 Chlebowski RT, et al. Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women. *JAMA* 2003;289:3234-3253
7 Anderson GL, et al. Effects of Estrogen Plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures. *JAMA* 2003;290:1739-1748
8 Shumaker SA, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. *JAMA* 2004;291:2947-2958
9 Jackson RD, et al. Effects of Conjugated Equine Estrogen on Risk of Fractures and BMD in Postmenopausal Women With Hysterectomy: Results From the Women's Health Initiative Randomized Trial. *J Bone Miner Res* 2006;21:817-828
10 Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. *Circulation* 2006;113:2425-2434

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Estradiol transdermal system (twice weekly) 0.025 mg per day: each 2.5 cm² system contains 0.41 mg of estradiol USP for nominal* delivery of 0.025 mg of estradiol per day
Patient Calendar Pack of 8 Systems NDC 0378-4644-26

Estradiol transdermal system (twice weekly) 0.0375 mg per day: each 3.75 cm² system contains 0.62 mg of estradiol USP for nominal* delivery of 0.0375 mg of estradiol per day
Patient Calendar Pack of 8 Systems NDC 0378-4643-26

Estradiol transdermal system (twice weekly) 0.05 mg per day: each 5.0 cm² system contains 0.82 mg of estradiol USP for nominal* delivery of 0.05 mg of estradiol per day
Patient Calendar Pack of 8 Systems NDC 0378-4642-26

Estradiol transdermal system (twice weekly) 0.075 mg per day: each 7.5 cm² system contains 1.23 mg of estradiol USP for nominal* delivery of 0.075 mg of estradiol per day
Patient Calendar Pack of 8 Systems NDC 0378-4641-26

Estradiol transdermal system (twice weekly) 0.1 mg per day: each 10.0 cm² system contains 1.64 mg of estradiol USP for nominal* delivery of 0.1 mg of estradiol per day
Patient Calendar Pack of 8 Systems NDC 0378-4640-26

**See DESCRIPTION (11)*

Storage and Handling

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature.]

Do not store unpouched. Apply immediately upon removal from the protective pouch

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

Advise patients to read the Patient Information and Instructions for Use. The complete text of the Patient Information and Instructions for Use is reprinted at the end of this document

Vaginal Bleeding Inform postmenopausal women of the importance of reporting unusual vaginal bleeding to their healthcare provider as soon as possible (see *Warnings and Precautions (5.2)*)

Possible Serious Adverse Reactions With Estrogen-Alone Therapy Inform postmenopausal women of possible serious adverse reactions of estrogen-alone therapy including Cardiovascular Disorders, Malignant Neoplasms and Probable Dementia (see *Warnings and Precautions (5.1, 5.2 and 5.3)*)

Possible Less Serious but Common Adverse Reactions With Estrogen-Alone Therapy Inform postmenopausal women of possible less serious but common adverse reactions of estrogen-alone therapy such as headache, breast pain and tenderness, nausea and vomiting

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PATIENT INFORMATION
ESTRADIOL TRANSDERMAL SYSTEM USP (TWICE WEEKLY)
(es" tra dye' ol)

Read this Patient Information before you start using estradiol transdermal system (twice weekly) and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment

What is the most important information I should know about estradiol transdermal system (twice weekly) (an estrogen hormone)?

- Using estrogen alone increases your chance of getting cancer of the uterus (womb)
  Report any unusual vaginal bleeding right away while you are using estradiol transdermal system (twice weekly). Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause
- Do not use estrogen alone to prevent heart disease, heart attacks, strokes, or dementia (decline in brain function)
- Using estrogen alone may increase your chances of getting strokes or blood clots
- Using estrogen alone may increase your chance of getting dementia, based on a study of women 65 years of age or older
- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes, or dementia
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years of age or older
- You and your healthcare provider should talk regularly about whether you still need treatment with estradiol transdermal system (twice weekly)

What is estradiol transdermal system (twice weekly)?

Estradiol transdermal system (twice weekly) is a prescription medicine patch (Transdermal System) that contains estradiol (an estrogen hormone). When applied to the skin as directed below, estradiol transdermal system (twice weekly) releases estrogen through the skin into the bloodstream

What is estradiol transdermal system (twice weekly) used for?

Estradiol transdermal system (twice weekly) is used after menopause to

- **Reduce moderate to severe hot flashes**

Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, 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 strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe

- **Treat moderate to severe menopausal changes in and around the vagina**

You and your healthcare provider should talk regularly about whether you still need treatment with estradiol transdermal system (twice weekly) to control these problems. If you use estradiol transdermal system (twice weekly) only to treat your menopausal changes in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you

- **Treat certain conditions in women before menopause if their ovaries do not produce enough estrogens naturally**
- **Help reduce your chances of getting osteoporosis (thin weak bones)**

Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use estradiol transdermal system (twice weekly) only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you

You and your healthcare provider should talk regularly about whether you should continue treatment with estradiol transdermal system (twice weekly)

Who should not use estradiol transdermal system (twice weekly)?

Do not start using estradiol transdermal system (twice weekly) if you

- **have unusual vaginal bleeding**

Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause

- **currently have or have had certain cancers**

Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use estradiol transdermal system (twice weekly)

- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **have been diagnosed with a bleeding disorder**
- **are allergic to estradiol transdermal system (twice weekly) or any of its ingredients**

See the list of ingredients in estradiol transdermal system (twice weekly) at the end of this leaflet

- **think you may be pregnant**

Estradiol transdermal system (twice weekly) is not for pregnant women. If you think you may be pregnant, you should have a pregnancy test and know the results. Do not use estradiol transdermal system (twice weekly) if the test is positive and talk to your healthcare provider

What should I tell my healthcare provider before I use estradiol transdermal system (twice weekly)?

Before you use estradiol transdermal system (twice weekly) tell your healthcare provider if you:

- **have any unusual vaginal bleeding**

Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause

- **have any other medical conditions**

Your healthcare provider may need to check you more carefully if you have certain conditions such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, angioedema (swelling of face and tongue), or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood

- **are going to have surgery or will be on bed rest**

Your healthcare provider will let you know if you need to stop using estradiol transdermal system (twice weekly)

- **are breastfeeding**

The hormone in estradiol transdermal system (twice weekly) can pass into your breast milk

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how estradiol transdermal system (twice weekly) works. Estradiol transdermal system (twice weekly) may also affect how other medicines work

How should I use estradiol transdermal system (twice weekly)?

For detailed instructions, see the step by step instructions for using estradiol transdermal system (twice weekly) at the end of this Patient Information

- Use estradiol transdermal system (twice weekly) exactly as your healthcare provider tells you to use it
- Estradiol transdermal system (twice weekly) is for skin use only
- Change your estradiol transdermal system (twice weekly) patch two times a week or every 3 to 4 days
- Apply your estradiol transdermal system (twice weekly) patch to a clean, dry area of your lower abdomen. This area must be clean, dry, and free of powder, oil or lotion for your patch to stick to your skin
- Apply your estradiol transdermal system (twice weekly) patch to a different area of your abdomen each time. Do not use the same application site two times in the same week
- Do not apply estradiol transdermal system (twice weekly) to your breasts
- If you forget to apply a new estradiol transdermal system (twice weekly) patch, you should apply a new patch as soon as possible
- You and your healthcare provider should talk regularly (every 3 to 6 months) about your dose and whether you still need treatment with estradiol transdermal system (twice weekly)

How to Change estradiol transdermal system (twice weekly)

- When changing the patch, peel off the used patch slowly from the skin
- After removal of estradiol transdermal system (twice weekly), patients usually have either no adhesive residue or light adhesive residue. If any adhesive residue remains on your skin after removing the patch, allow the area to dry for 15 minutes. Then, gently rub the area with oil or lotion to remove the adhesive from your skin
- Keep in mind, **the new patch must be applied to a different area of your lower abdomen**. This area must be clean, dry, cool and free of powder, oil, or lotion

What are the possible side effects of estradiol transdermal system (twice weekly)?

Side effects are grouped by how serious they are and how often they happen when you are treated

Serious but less common side effects include:

- heart attack
- stroke
- blood clots
- dementia
- breast cancer
- cancer of the lining of the uterus (womb)
- cancer of the ovary
- high blood pressure
- high blood sugar
- gallbladder disease
- liver problems
- changes in your thyroid hormone levels
- enlargement of benign tumors ("fibroids")

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- new breast lumps
- nipple discharge
- unusual vaginal bleeding
- changes in vision or speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness and fatigue
- swelling
- rash

Less serious but common side effects include:

- headache
- breast pain
- irregular vaginal bleeding or spotting
- painful periods
- stomach or abdominal cramps, bloating
- nausea and vomiting
- hair loss
- fluid retention
- vaginal yeast infection
- redness and/or irritation at patch placement site

These are not all the possible side effects of estradiol transdermal system (twice weekly). For more information, ask your healthcare provider or pharmacist for advice about side effects. Tell your healthcare provider if you have any side effect that bothers you or does not go away

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may report side effects to Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX)

What can I do to lower my chances of getting a serious side effect with estradiol transdermal system (twice weekly)?

- Talk with your healthcare provider regularly about whether you should continue using estradiol transdermal system (twice weekly)
- If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you

The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus (womb)

- See your healthcare provider right away if you get vaginal bleeding while using estradiol transdermal system (twice weekly)
- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else

If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often

- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease

Ask your healthcare provider for ways to lower your chances for getting heart disease

How should I store and throw away used estradiol transdermal system (twice weekly) patches?

- Store at 20° to 25°C (68° to 77°F)
- Do not store estradiol transdermal system (twice weekly) patches outside of their pouches. Apply immediately upon removal from the protective pouch
- Used patches still contain estrogen. To throw away the patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Used patches should not be flushed in the toilet

Keep estradiol transdermal system (twice weekly) and all medicines out of the reach of children

General information about safe and effective use of estradiol transdermal system (twice weekly)

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use estradiol transdermal system (twice weekly) for conditions for which it was not prescribed. Do not give estradiol transdermal system (twice weekly) to other people, even if they have the same symptoms you have. It may harm them

This leaflet provides a summary of the most important information about estradiol transdermal system (twice weekly). If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about estradiol transdermal system (twice weekly) that is written for health professionals. For more information, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX)

What are the ingredients in estradiol transdermal system (twice weekly)?

Active ingredient: estradiol

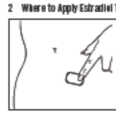
Inactive ingredients: a translucent polyolefin backing film, brown ink, silicone and acrylic adhesives, dipropylene glycol, povidone, oleyl alcohol, and a polyester release liner

INSTRUCTIONS FOR USE
ESTRADIOL TRANSDERMAL SYSTEM USP (TWICE WEEKLY)
(es" tra dye' ol)

1 Determine Your Schedule for Your Twice a Week Application

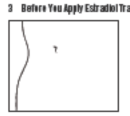
- Decide upon which 2 days you will change your patch
- Your estradiol transdermal system (twice weekly) individual carton contains a calendar card printed on its inner flap. Mark the 2 day schedule you plan to follow on your carton's inner flap
- Be consistent
- If you forget to change your patch on the correct date, apply a new one as soon as you remember
- No matter what day this happens, stick to the schedule you have marked on the inner flap of your carton (your calendar card)

2 Where to Apply Estradiol Transdermal System (Twice Weekly)



- Apply patch to a dry area of the skin of the trunk of the body, including the lower abdomen, or buttocks. Avoid the waistline, since clothing may cause the patch to rub off
- Do not apply patch to breasts
- When changing your patch, based on your twice a week schedule, apply your new patch to a different site. Do not apply a new patch to that same area for at least 1 week

3 Before You Apply Estradiol Transdermal System (Twice Weekly)

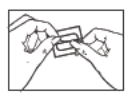


Make sure your skin is:

- Clean (freshly washed), dry and cool
- Free of any powder, oil, moisturizer or lotion
- Free of cuts or irritations (rashes or other skin problems)

4 How to Apply Estradiol Transdermal System (Twice Weekly)

- Each patch is individually sealed in a protective pouch
- Tear open the pouch at the tear notch (do not use scissors)
- Remove the patch

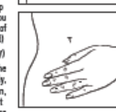


- **Apply the patch immediately after removing from the pouch**
- Holding the patch with the rigid oversized protective liner facing you, remove half of the protective liner, which covers the sticky surface of the patch

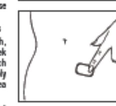
- **Avoid touching the sticky side of the patch with your fingers**
- Using the other half of the rigid protective liner as a handle, apply the sticky side of the patch to the selected area of the abdomen or buttocks

- Press the sticky side of the patch firmly into place
- Smooth it down
- While still holding the sticky side down, fold back the other half of the patch

- Grasp an edge of the remaining protective liner and gently pull it off
- **Avoid touching the sticky side of the patch with your fingers**



- Press the entire patch firmly into place with the palm of your hand
- Continue to apply pressure, with the palm of your hand over the patch, for approximately 10 seconds



- Make sure that the patch is properly adhered to your skin
- Go over the edges with your finger to ensure good contact around the patch

Note:

- Showering will not cause your patch to fall off
- If your patch falls off reapply it. If you cannot reapply the patch, apply a new patch to another area and continue to follow your original placement schedule
- If you stop using your estradiol transdermal system (twice weekly) patch or forget to apply a new patch as scheduled, you may have spotting, or bleeding, and recurrence of symptoms

5 Throwing Away Your Used Patch

- When it is time to change your patch, remove the old patch before you apply a new patch
- To throw away the patch, fold the sticky side of the patch together, place it in a sturdy child proof container, and place the container in the trash. Used patches should not be flushed in the toilet

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration

Mylan®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

REVISED AUGUST 2014
ETSTW:R5

PL:ETSTW:R4

060204

PATIENT INFORMATION
ESTRADIOL TRANSDERMAL SYSTEM, USP (TWICE-WEEKLY)
(es″ tra dye′ ol)

Read this Patient Information before you start using estradiol transdermal system (twice-weekly) and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about estradiol transdermal system (twice-weekly) (an estrogen hormone)?

- Using estrogen-alone increases your chance of getting cancer of the uterus (womb).

  Report any unusual vaginal bleeding right away while you are using estradiol transdermal system (twice-weekly). Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes, or dementia (decline in brain function).
- Using estrogen-alone may increase your chances of getting strokes or blood clots.
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women 65 years of age or older.
- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes, or dementia.
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years of age or older.
- You and your healthcare provider should talk regularly about whether you still need treatment with estradiol transdermal system (twice-weekly).

What is estradiol transdermal system (twice-weekly)?

Estradiol transdermal system (twice-weekly) is a prescription medicine patch (Transdermal System) that contains estradiol (an estrogen hormone). When applied to the skin as directed below, estradiol transdermal system (twice-weekly) releases estrogen through the skin into the bloodstream.

What is estradiol transdermal system (twice-weekly) used for?

Estradiol transdermal system (twice-weekly) is used after menopause to:

- **Reduce moderate to severe hot flashes**

Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, 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 strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe.

- **Treat moderate to severe menopausal changes in and around the vagina**

You and your healthcare provider should talk regularly about whether you still need treatment with estradiol transdermal system (twice-weekly) to control these problems. If you use estradiol transdermal system (twice-weekly) only to treat your menopausal changes in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

- **Treat certain conditions in women before menopause if their ovaries do not produce enough estrogens naturally**
- **Help reduce your chances of getting osteoporosis (thin weak bones)**

Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use estradiol transdermal system (twice-weekly) only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you.

You and your healthcare provider should talk regularly about whether you should continue treatment with estradiol transdermal system (twice-weekly).

Who should not use estradiol transdermal system (twice-weekly)?

Do not start using estradiol transdermal system (twice-weekly) if you:

- **have unusual vaginal bleeding**

Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- **currently have or have had certain cancers**

Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use estradiol transdermal system (twice-weekly).

- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **have been diagnosed with a bleeding disorder**
- **are allergic to estradiol transdermal system (twice-weekly) or any of its ingredients**

See the list of ingredients in estradiol transdermal system (twice-weekly) at the end of this leaflet.

- **think you may be pregnant**

Estradiol transdermal system (twice-weekly) is not for pregnant women. If you think you may be pregnant, you should have a pregnancy test and know the results. Do not use estradiol transdermal system (twice-weekly) if the test is positive and talk to your healthcare provider.

What should I tell my healthcare provider before I use estradiol transdermal system (twice-weekly)?

Before you use estradiol transdermal system (twice-weekly), tell your healthcare provider if you:

- **have any unusual vaginal bleeding**

Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- **have any other medical conditions**

Your healthcare provider may need to check you more carefully if you have certain conditions such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, angioedema (swelling of face and tongue), or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **are going to have surgery or will be on bed rest**

Your healthcare provider will let you know if you need to stop using estradiol transdermal system (twice-weekly).

- **are breastfeeding**

The hormone in estradiol transdermal system (twice-weekly) can pass into your breast milk.

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how estradiol transdermal system (twice-weekly) works. Estradiol transdermal system (twice-weekly) may also affect how other medicines work.

How should I use estradiol transdermal system (twice-weekly)? For detailed instructions, see the step-by-step instructions for using estradiol transdermal system (twice-weekly) at the end of this Patient Information.

- Use estradiol transdermal system (twice-weekly) exactly as your healthcare provider tells you to use it.
- Estradiol transdermal system (twice-weekly) is for skin use only.
- Change your estradiol transdermal system (twice-weekly) patch two times a week or every 3 to 4 days.
- Apply your estradiol transdermal system (twice-weekly) patch to a clean, dry area of your lower abdomen. This area must be clean, dry, and free of powder, oil or lotion for your patch to stick to your skin.
- Apply your estradiol transdermal system (twice-weekly) patch to a different area of your abdomen each time. Do not use the same application site two times in the same week.
- Do not apply estradiol transdermal system (twice-weekly) to your breasts.
- If you forget to apply a new estradiol transdermal system (twice-weekly) patch, you should apply a new patch as soon as possible.
- You and your healthcare provider should talk regularly (every 3 to 6 months) about your dose and whether you still need treatment with estradiol transdermal system (twice-weekly).

How to Change estradiol transdermal system (twice-weekly)

- When changing the patch, peel off the used patch slowly from the skin.
- After removal of estradiol transdermal system (twice-weekly), patients usually have either no adhesive residue or light adhesive residue. If any adhesive residue remains on your skin after removing the patch, allow the area to dry for 15 minutes. Then, gently rub the area with oil or lotion to remove the adhesive from your skin.
- Keep in mind, **the new patch must be applied to a different area of your lower abdomen.** This area must be clean, dry, cool and free of powder, oil, or lotion.

What are the possible side effects of estradiol transdermal system (twice-weekly)?

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:

- heart attack
- stroke
- blood clots
- dementia
- breast cancer
- cancer of the lining of the uterus (womb)
- cancer of the ovary
- high blood pressure
- high blood sugar
- gallbladder disease
- liver problems
- changes in your thyroid hormone levels
- enlargement of benign tumors ("fibroids")

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- new breast lumps
- nipple discharge
- unusual vaginal bleeding
- changes in vision or speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness and fatigue
- swelling
- rash

Less serious, but common side effects include:

- headache
- breast pain
- irregular vaginal bleeding or spotting
- painful periods
- stomach or abdominal cramps, bloating
- nausea and vomiting

- hair loss
- fluid retention
- vaginal yeast infection
- redness and/or irritation at patch placement site

These are not all the possible side effects of estradiol transdermal system (twice-weekly). For more information, ask your healthcare provider or pharmacist for advice about side effects. Tell your healthcare provider if you have any side effect that bothers you or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may report side effects to Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX).

What can I do to lower my chances of getting a serious side effect with estradiol transdermal system (twice-weekly)?

- Talk with your healthcare provider regularly about whether you should continue using estradiol transdermal system (twice-weekly).
- If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you.

The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus (womb).

- See your healthcare provider right away if you get vaginal bleeding while using estradiol transdermal system (twice-weekly).
- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else.

If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.

- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease.

Ask your healthcare provider for ways to lower your chances for getting heart disease.

How should I store and throw away used estradiol transdermal system (twice-weekly) patches?

- Store at 20° to 25°C (68° to 77°F)
- Do not store estradiol transdermal system (twice-weekly) patches outside of their pouches. Apply immediately upon removal from the protective pouch.
- Used patches still contain estrogen. To throw away the patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Used patches should not be flushed in the toilet.

Keep estradiol transdermal system (twice-weekly) and all medicines out of the reach of children.

General information about safe and effective use of estradiol transdermal system (twice-weekly)

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use estradiol transdermal system (twice-weekly) for conditions for which it was not prescribed. Do not give estradiol transdermal system (twice-weekly) to other people, even if they have the same symptoms you have. It may harm them.

This leaflet provides a summary of the most important information about estradiol transdermal system (twice-weekly). If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about estradiol transdermal system (twice-weekly) that is written for health professionals. For more information, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX).

What are the ingredients in estradiol transdermal system (twice-weekly)?

Active ingredient: estradiol

Inactive ingredients: a translucent polyolefin backing film, brown ink, silicone and acrylic adhesives, dipropylene glycol, povidone, oleyl alcohol, and a polyester release liner.

INSTRUCTIONS FOR USE
ESTRADIOL TRANSDERMAL SYSTEM, USP (TWICE-WEEKLY)
(es″ tra dye′ ol)

1. Determine Your Schedule for Your Twice-a-Week Application

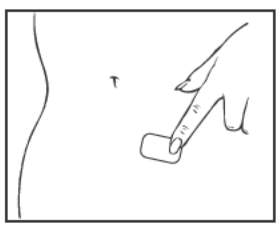
Estradiol
Transdermal System, USP
(Twice-Weekly)

Change patch only on these two days

❑ Sun/Wed	❑ Thu/Sun
❑ Mon/Thu	❑ Fri/Mon
❑ Tue/Fri	❑ Sat/Tue
❑ Wed/Sat	

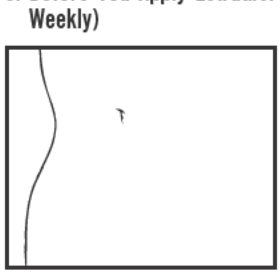
- Decide upon which 2 days you will change your patch.
- Your estradiol transdermal system (twice-weekly) individual carton contains a calendar card printed on its inner flap. Mark the 2 day schedule you plan to follow on your carton's inner flap.
- Be consistent.
- If you forget to change your patch on the correct date, apply a new one as soon as you remember.
- No matter what day this happens, stick to the schedule you have marked on the inner flap of your carton (your calendar card).

2. Where to Apply Estradiol Transdermal System (Twice-Weekly)



- Apply patch to a dry area of the skin of the trunk of the body, including the lower abdomen, or buttocks. Avoid the waistline, since clothing may cause the patch to rub off.
- Do not apply patch to breasts.
- When changing your patch, based on your twice-a-week schedule, apply your new patch to a different site. Do not apply a new patch to that same area for at least 1 week.

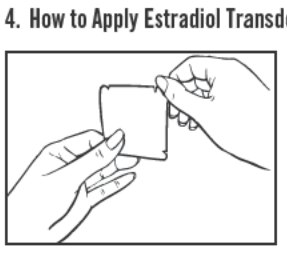
3. Before You Apply Estradiol Transdermal System (Twice-Weekly)



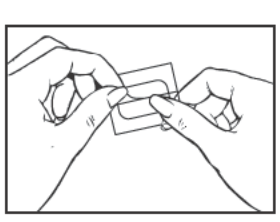
Make sure your skin is:

- Clean (freshly washed), dry and cool.
- Free of any powder, oil, moisturizer or lotion.
- Free of cuts or irritations (rashes or other skin problems).

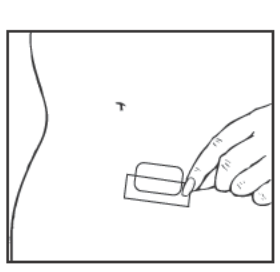
4. How to Apply Estradiol Transdermal System (Twice-Weekly)



- Each patch is individually sealed in a protective pouch.
- Tear open the pouch at the tear notch (do not use scissors).
- Remove the patch.



- **Apply the patch immediately after removing from the pouch.**
- Holding the patch with the rigid oversized protective liner facing you, remove **half** of the protective liner, which covers the sticky surface of the patch.



- **Avoid touching the sticky side of the patch with your fingers.**
- Using the other half of the rigid protective liner as a handle, apply the sticky side of the patch to the selected area of the abdomen or buttocks.

- Press the sticky side of the patch firmly into place.
- Smooth it down.
- While still holding the sticky side down, fold back the other half of the patch.

- Grasp an edge of the remaining protective liner and gently pull it off.
- **Avoid touching the sticky side of the patch with your fingers.**

- Press the entire patch firmly into place with the palm of your hand.
- Continue to apply pressure, with the palm of your hand over the patch, for approximately 10 seconds.

- Make sure that the patch is properly adhered to your skin.
- Go over the edges with your finger to ensure good contact around the patch.

Note:

- Showering will not cause your patch to fall off.
- If your patch falls off reapply it. If you cannot reapply the patch, apply a new patch to another area and continue to follow your original placement schedule.
- If you stop using your estradiol transdermal system (twice-weekly) patch or forget to apply a new patch as scheduled, you may have spotting, or bleeding, and recurrence of symptoms.

5. Throwing Away Your Used Patch

- When it is time to change your patch, remove the old patch before you apply a new patch.
- To throw away the patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place the container in the trash. Used patches should not be flushed in the toilet.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Mylan®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

REVISED AUGUST 2014
PL:ETSTW:R4

Estradiol 0.025 mg/day
Transdermal System, USP
(Twice-Weekly)

Patient Instruction:

1. Start at notched corner, tear pouch open. Remove patch from pouch.
2. Hold patch with protective liner facing you.
3. Peel off one side of protective liner and discard.
4. Apply sticky side of patch to clean and dry area of the abdomen.
5. Carefully remove the other piece of protective liner and discard. Press patch firmly in place.

To open

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Morgantown, WV 26505 U.S.A.

M4644-26-BC:R3

426

Delivers 0.025 mg/day

Each 2.5 cm² system contains 0.41 mg of estradiol, USP.

Inactive components: silicone adhesive, acrylic adhesive, dipropylene glycol, povidone, oleyl alcohol, polyolefin backing film, polyester release liner.

Apply immediately upon removal from pouch. Do not store unpouched.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Usual Dosage: See prescribing information.

Estradiol 0.025 mg/day
Transdermal System, USP
(Twice-Weekly)

Includes 8 Systems

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Includes 8 Systems

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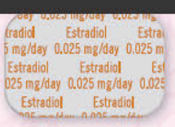
NDC 0378-4644-26 Rx only



Estradiol
Transdermal System, USP
(Twice-Weekly)

0.025 mg/day

Important: Package not child-resistant.

Keep out of the reach of children.

FOR TRANSDERMAL USE ONLY

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Estradiol 0.025 mg/day
Transdermal System, USP
(Twice-Weekly)

Includes 8 Systems

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Estradiol 0.025 mg/day
Transdermal System, USP
(Twice-Weekly)

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Estradiol
Transdermal System, USP (Twice-Weekly)

Change patch only on these two days

- ❑ Sun/Wed
- ❑ Mon/Thu
- ❑ Tue/Fri
- ❑ Wed/Sat
- ❑ Thu/Sun
- ❑ Fri/Mon
- ❑ Sat/Tue

M4644-26-8C:R3-Back

Estradiol
Transdermal System, USP (Twice-Weekly)

- Read patient information before use
- Apply as directed
- Rotate application site
- Mark your twice-weekly schedule

Estradiol 0.0375 mg/day
Transdermal System, USP
(Twice-Weekly)

Patient Instruction:

1. Start at notched corner, tear pouch open. Remove patch from pouch.
2. Hold patch with protective liner facing you.
3. Peel off one side of protective liner and discard.
4. Apply sticky side of patch to clean and dry area of the abdomen.
5. Carefully remove the other piece of protective liner and discard. Press patch firmly in place.

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M4643-26-8C-R3

Delivers 0.0375 mg/day

Each 3.75 cm^2 system contains 0.62 mg of estradiol, USP.

Inactive components: silicone adhesive, acrylic adhesive, dipropylene glycol, povidone, oleyl alcohol, polyolefin backing film, polyester release liner.

Apply immediately upon removal from pouch. Do not store unpouched.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Usual Dosage: See prescribing information.

Estradiol 0.0375 mg/day
Transdermal System, USP
(Twice-Weekly)

Includes 8 Systems

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Includes 8 Systems

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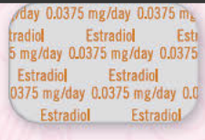
NDC 0378-4643-26 Rx only



Estradiol
Transdermal System, USP (Twice-Weekly)

0.0375 mg/day

Important: Package not child-resistant.

Keep out of the reach of children.

FOR TRANSDERMAL USE ONLY

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Estradiol 0.0375 mg/day
Transdermal System, USP
(Twice-Weekly)

Includes 8 Systems

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Estradiol 0.0375 mg/day
Transdermal System, USP
(Twice-Weekly)

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428

Estradiol
Transdermal System, USP (Twice-Weekly)

Change patch only on these two days

- ❑ Sun/Wed
- ❑ Mon/Thu
- ❑ Tue/Fri
- ❑ Wed/Sat
- ❑ Thu/Sun
- ❑ Fri/Mon
- ❑ Sat/Tue

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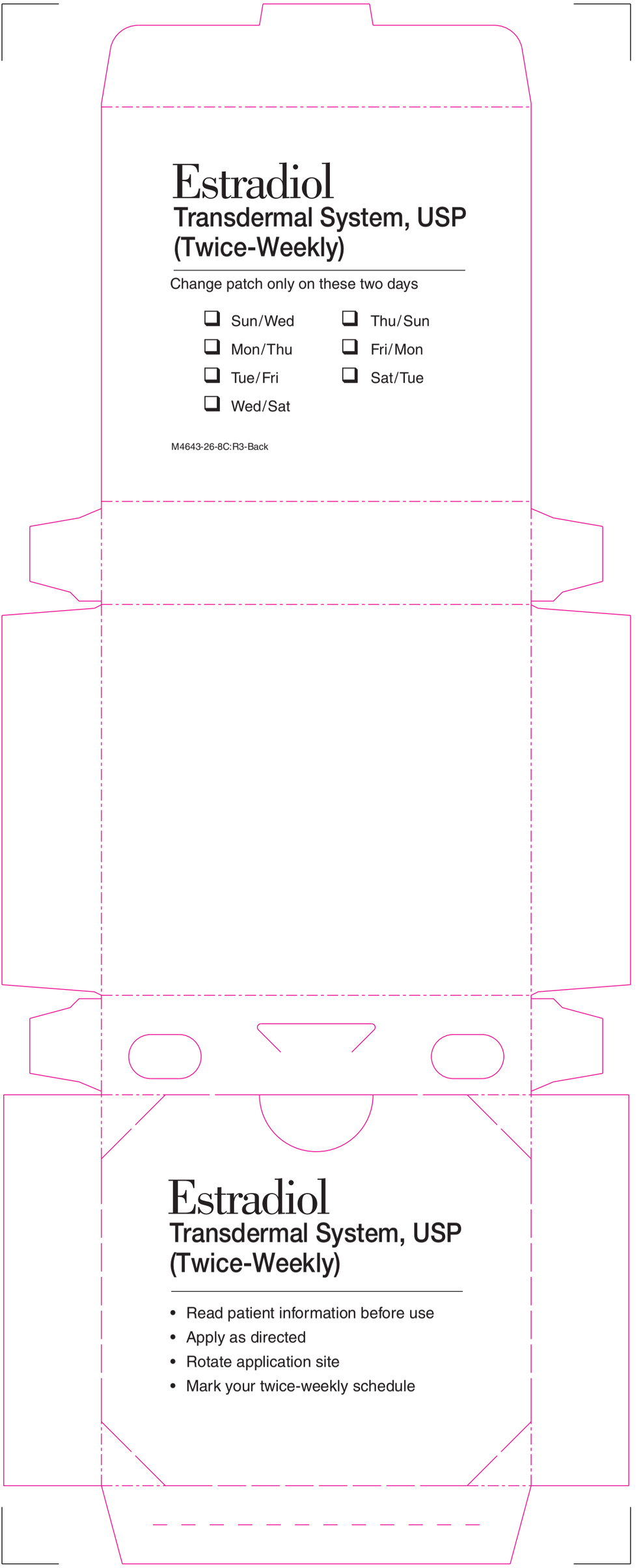

Estradiol
Transdermal System, USP (Twice-Weekly)

- Read patient information before use
- Apply as directed
- Rotate application site
- Mark your twice-weekly schedule

Estradiol 0.05 mg/day
Transdermal System, USP
(Twice-Weekly)

Patient Instruction:

1. Start at notched corner, tear pouch open. Remove patch from pouch.
2. Hold patch with protective liner facing you.
3. Peel off one side of protective liner and discard.
4. Apply sticky side of patch to clean and dry area of the abdomen.
5. Carefully remove the other piece of protective liner and discard. Press patch firmly in place.

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M4642-26-8C:R3

429

Usual Dosage: See prescribing information.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Apply immediately upon removal from pouch. Do not store unpouched.

Inactive components: silicone adhesive, acrylic adhesive, dipropylene glycol, povidone, oleyl alcohol, polyolefin backing film, polyester release liner.

Delivers 0.05 mg/day

Each 5.0 cm² system contains 0.82 mg of estradiol, USP.

Estradiol 0.05 mg/day
Transdermal System, USP
(Twice-Weekly)

Includes 8 Systems

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Includes 8 Systems

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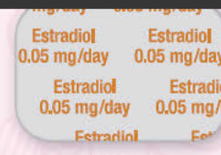

Estradiol
Transdermal System, USP
(Twice-Weekly)

0.05 mg/day

Important: Package not child-resistant.

Keep out of the reach of children.

FOR TRANSDERMAL USE ONLY

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Estradiol 0.05 mg/day
Transdermal System, USP
(Twice-Weekly)

Includes 8 Systems

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Estradiol 0.05 mg/day
Transdermal System, USP
(Twice-Weekly)

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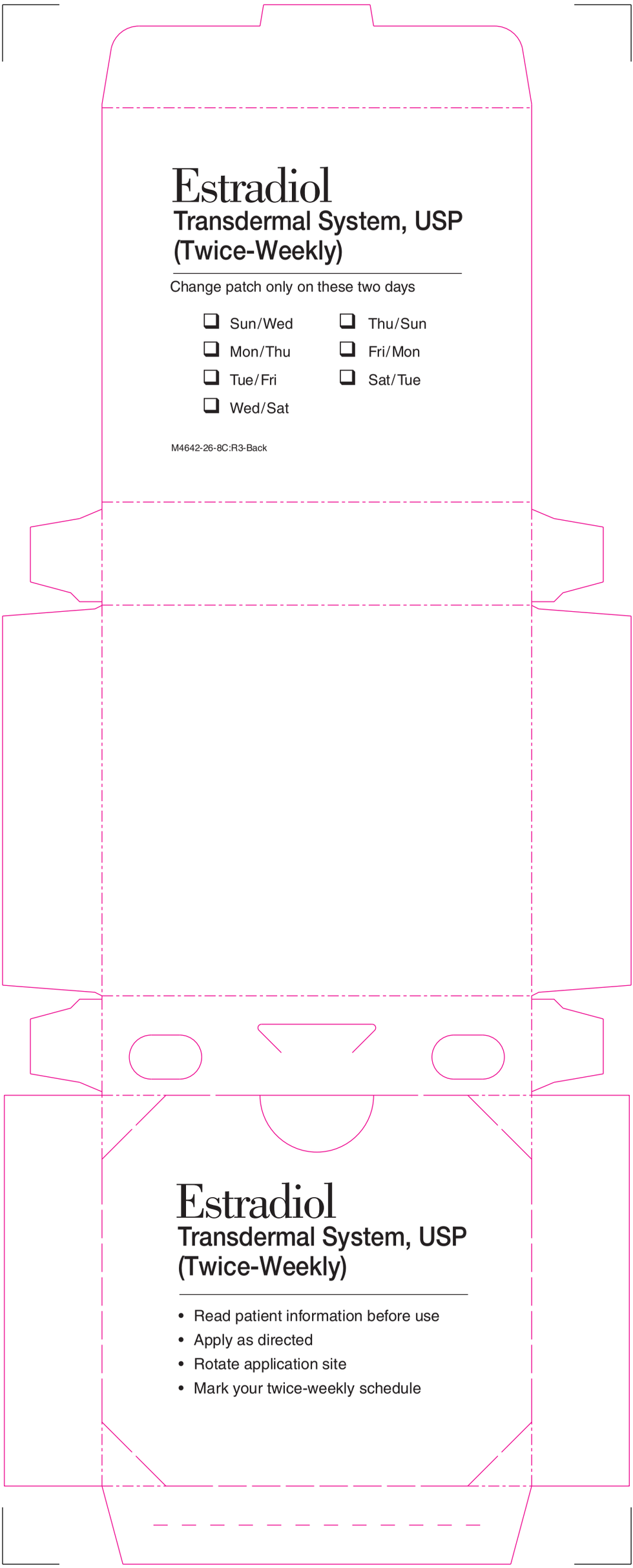
Estradiol
Transdermal System, USP (Twice-Weekly)

Change patch only on these two days

- ❑ Sun/Wed
- ❑ Mon/Thu
- ❑ Tue/Fri
- ❑ Wed/Sat
- ❑ Thu/Sun
- ❑ Fri/Mon
- ❑ Sat/Tue

M4642-26-8C:R3-Back



Estradiol
Transdermal System, USP (Twice-Weekly)

- Read patient information before use
- Apply as directed
- Rotate application site
- Mark your twice-weekly schedule

Estradiol 0.075 mg/day
Transdermal System, USP
(Twice-Weekly)

Patient Instruction:

1. Start at notched corner, tear pouch open. Remove patch from pouch.
2. Hold patch with protective liner facing you.
3. Peel off one side of protective liner and discard.
4. Apply sticky side of patch to clean and dry area of the abdomen.
5. Carefully remove the other piece of protective liner and discard. Press patch firmly in place.

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M4641-26-8C-R3

430

Delivers 0.075 mg/day

Each 7.5 cm² system contains 1.23 mg of estradiol, USP.

Inactive components: silicone adhesive, acrylic adhesive, dipropylene glycol, povidone, oleyl alcohol, polyolefin backing film, polyester release liner.

Apply immediately upon removal from pouch. Do not store unpouched.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Usual Dosage: See prescribing information.

Estradiol 0.075 mg/day
Transdermal System, USP
(Twice-Weekly)

Includes 8 Systems

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Estradiol 0.075 mg/day

Estradiol 0.075 mg/day

Estradiol
Transdermal System, USP
(Twice-Weekly)

0.075 mg/day

Important: Package not child-resistant.

Keep out of the reach of children.

FOR TRANSDERMAL USE ONLY

OPEN HERE

Estradiol 0.075 mg/day
Transdermal System, USP
(Twice-Weekly)

Includes 8 Systems

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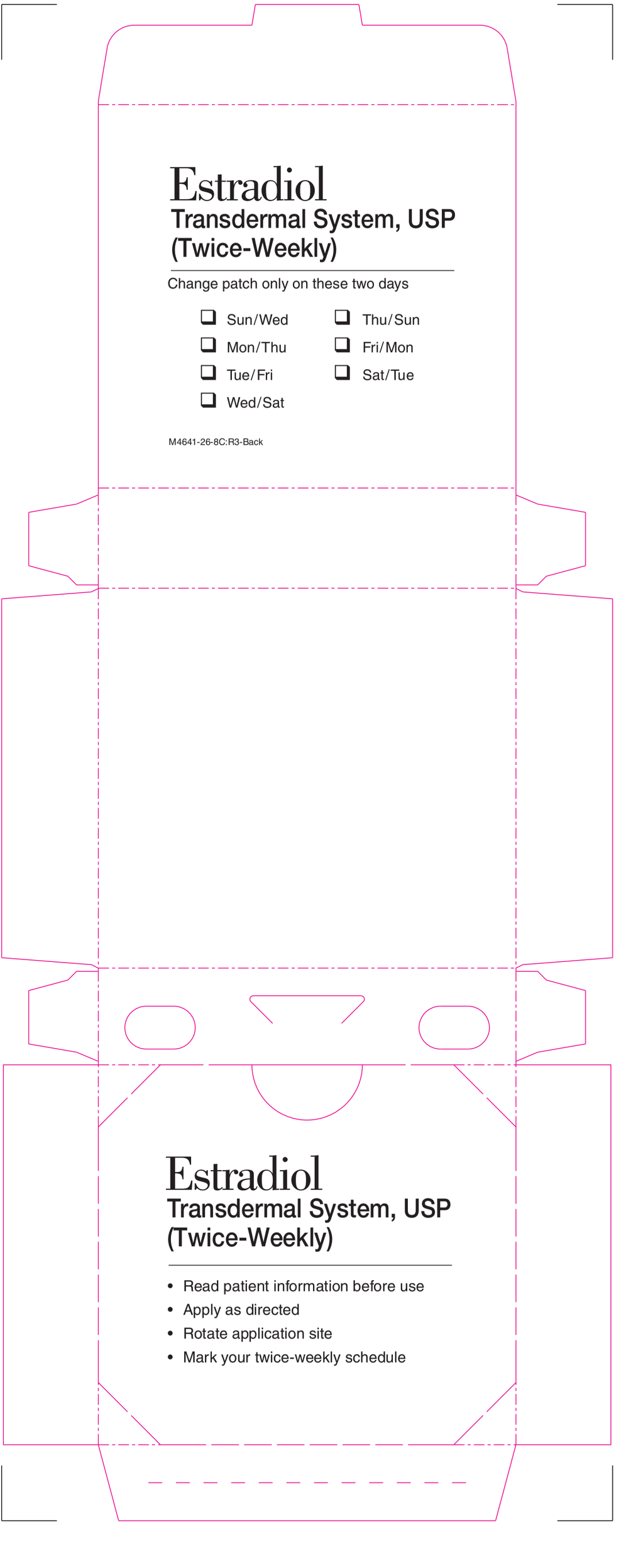
Estradiol
Transdermal System, USP (Twice-Weekly)

Change patch only on these two days

- ❑ Sun/Wed
- ❑ Mon/Thu
- ❑ Tue/Fri
- ❑ Wed/Sat
- ❑ Thu/Sun
- ❑ Fri/Mon
- ❑ Sat/Tue

M4641-26-8C:R3-Back



Estradiol
Transdermal System, USP (Twice-Weekly)

- Read patient information before use
- Apply as directed
- Rotate application site
- Mark your twice-weekly schedule

Estradiol 0.1 mg/day
Transdermal System, USP
(Twice-Weekly)

Patient Instruction:

1. Start at notched corner, tear pouch open. Remove patch from pouch.
2. Hold patch with protective liner facing you.
3. Peel off one side of protective liner and discard.
4. Apply sticky side of patch to clean and dry area of the abdomen.
5. Carefully remove the other piece of protective liner and discard. Press patch firmly in place.

To open

pull here

OPEN HERE

Estradiol 0.1 mg/day
Transdermal System, USP
(Twice-Weekly)

N 3 0378-4640-26 5

Estradiol 0.1 mg/day
Transdermal System, USP
(Twice-Weekly)

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Mylan® www.mylan.com

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

M4640-26-8C:R3

Usual Dosage: See prescribing information.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Apply immediately upon removal from pouch. Do not store unpouched.

Inactive components: silicone adhesive, acrylic adhesive, dipropylene glycol, povidone, oleyl alcohol, polyolefin backing film, polyester release liner.

Delivers 0.1 mg/day

Each 10.0 cm^2 system contains 1.64 mg of estradiol, USP.

Estradiol 0.1 mg/day
Transdermal System, USP
(Twice-Weekly)

Includes 8 Systems

Mylan®

Mylan®

Includes 8 Systems

www.mylan.com

NDC 0378-4640-26 Rx only

Estradiol
Transdermal System, USP
(Twice-Weekly)

0.1 mg/day

Important: Package not child-resistant.

Keep out of the reach of children.

FOR TRANSDERMAL USE ONLY

OPEN HERE

Estradiol 0.1 mg/day
Transdermal System, USP
(Twice-Weekly)

Includes 8 Systems

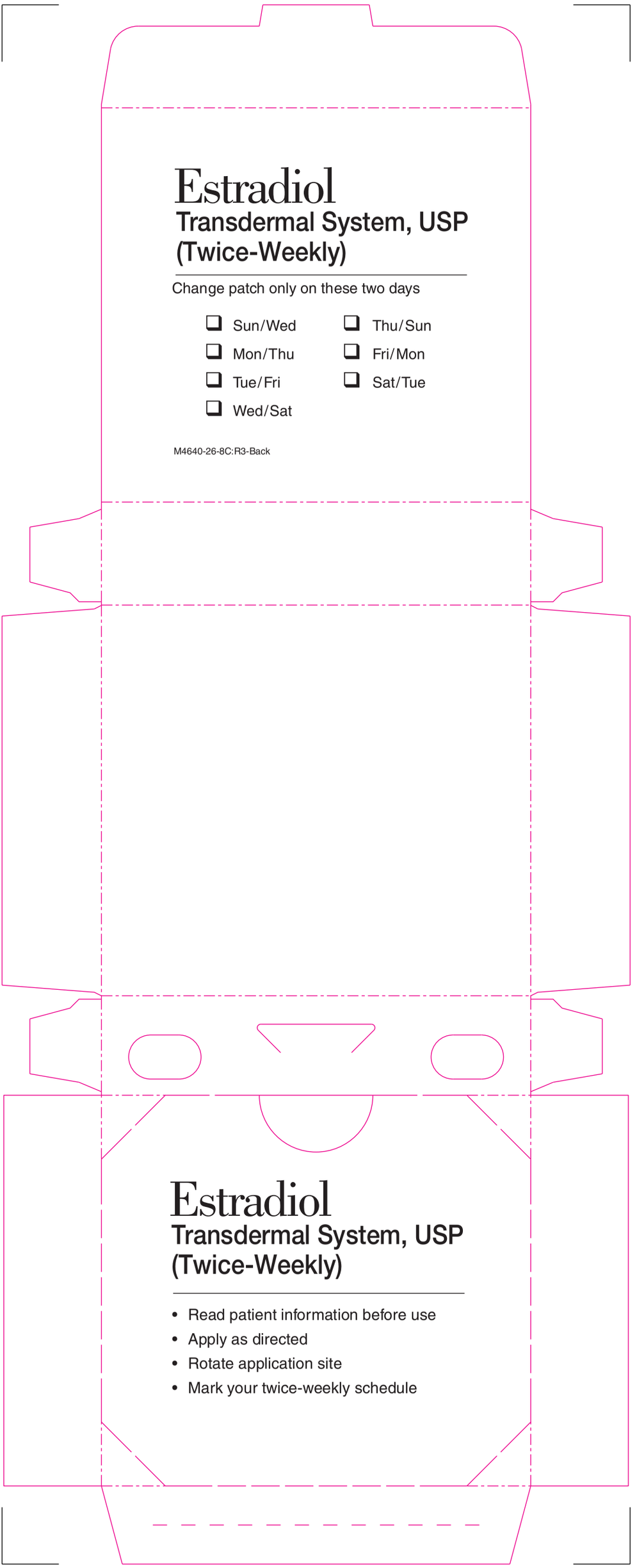
Mylan®

Estradiol
Transdermal System, USP (Twice-Weekly)

Change patch only on these two days

- ❑ Sun/Wed
- ❑ Mon/Thu
- ❑ Tue/Fri
- ❑ Wed/Sat
- ❑ Thu/Sun
- ❑ Fri/Mon
- ❑ Sat/Tue

M4640-26-8C:R3-Back



Estradiol
Transdermal System, USP (Twice-Weekly)

- Read patient information before use
- Apply as directed
- Rotate application site
- Mark your twice-weekly schedule

413

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4644:2

NDC 0378-4644-16 Rx only

Estradiol 0.025 mg/day

Transdermal System, USP (Twice-Weekly)

Delivers 0.025 mg/day

Contents: One 2.5 cm² System

Each 2.5 cm² system contains 0.41 mg of estradiol, USP.

Inactive components: silicone adhesive, acrylic adhesive, dipropylene glycol, povidone, oleyl alcohol, polyolefin backing film, polyester release liner.

Important: Package not child-resistant.

Keep out of the reach of children.

Apply immediately upon removal from pouch. Do not store unpouched. **Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]**

4644:2

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www.mylan.com

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Morgantown, WV 26505 U.S.A.

N 3 0378-4644-16 4

Mylan®

www.mylan.com

4643:2

NDC 0378-4643-16 Rx only

Estradiol 0.0375 mg/day

Transmdermal System, USP (Twice-Weekly)

Delivers 0.0375 mg/day

Contents: One 3.75 cm² System

Each 3.75 cm² system contains 0.62 mg of estradiol, USP.

Inactive components: silicone adhesive, acrylic adhesive, dipropylene glycol, povidone, oleyl alcohol, polyolefin backing film, polyester release liner.

Important: Package not child-resistant.

Keep out of the reach of children.

Apply immediately upon removal from pouch. Do not store unpouched. **Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]**

4643:2

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www.mylan.com

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Morgantown, WV 26505 U.S.A.

N 3 0378-4643-16 7

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www.mylan.com

4642:2

NDC 0378-4642-16

Rx only

Estradiol 0.05 mg/day

Transdermal System, USP (Twice-Weekly)

Delivers 0.05 mg/day

Contents: One 5.0 cm² System

Each 5.0 cm² system contains 0.82 mg of estradiol, USP.

Inactive components: silicone adhesive, acrylic adhesive, dipropylene glycol, povidone, oleyl alcohol, polyolefin backing film, polyester release liner.

Important: Package not child-resistant.

Keep out of the reach of children.

Apply immediately upon removal from pouch. Do not store unpouched. **Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]**

4642:2

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4641:2

NDC 0378-4641-16

Rx only

Estradiol 0.075 mg/day

Transdermal System, USP (Twice-Weekly)

Delivers 0.075 mg/day

Contents: One 7.5 cm² System

Each 7.5 cm² system contains 1.23 mg of estradiol, USP.

Inactive components: silicone adhesive, acrylic adhesive, dipropylene glycol, povidone, oleyl alcohol, polyolefin backing film, polyester release liner.

Important: Package not child-resistant.

Keep out of the reach of children.

Apply immediately upon removal from pouch. Do not store unpouched. **Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]**

4641:2

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N 3 0378-4641-16 3

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4640:2

NDC 0378-4640-16

Rx only

Estradiol 0.1 mg/day

Transdermal System, USP (Twice-Weekly)

Delivers 0.1 mg/day

Contents: One 10.0 cm² System

Each 10.0 cm² system contains 1.64 mg of estradiol, USP.

Inactive components: silicone adhesive, acrylic adhesive, dipropylene glycol, povidone, oleyl alcohol, polyolefin backing film, polyester release liner.

Important: Package not child-resistant.

Keep out of the reach of children.

Apply immediately upon removal from pouch. Do not store unpouched. **Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]**

4640:2

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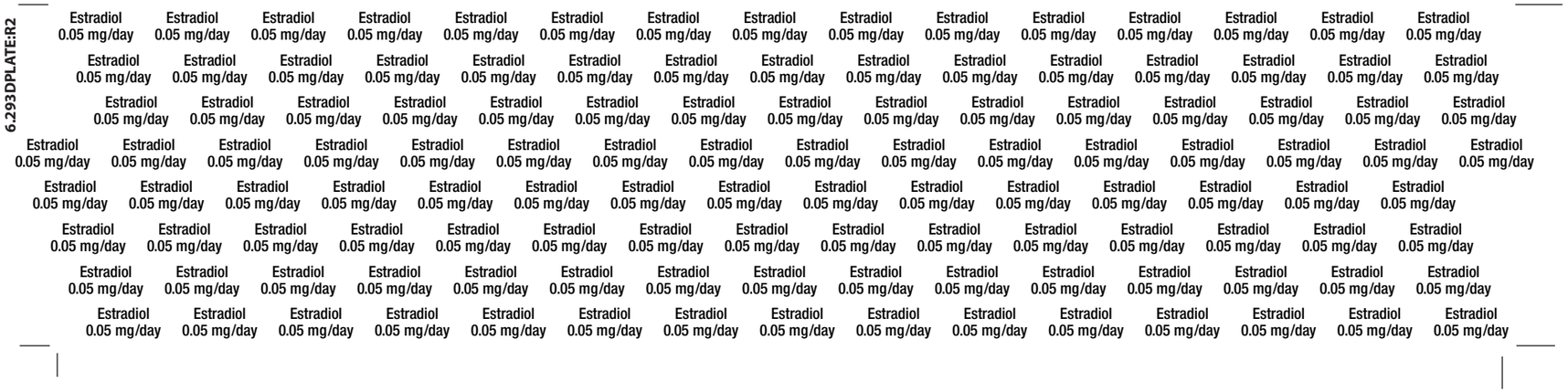
N 3 0378-4640-16 6

6.290DPLATE:R2

Estradiol 0.025 mg/day

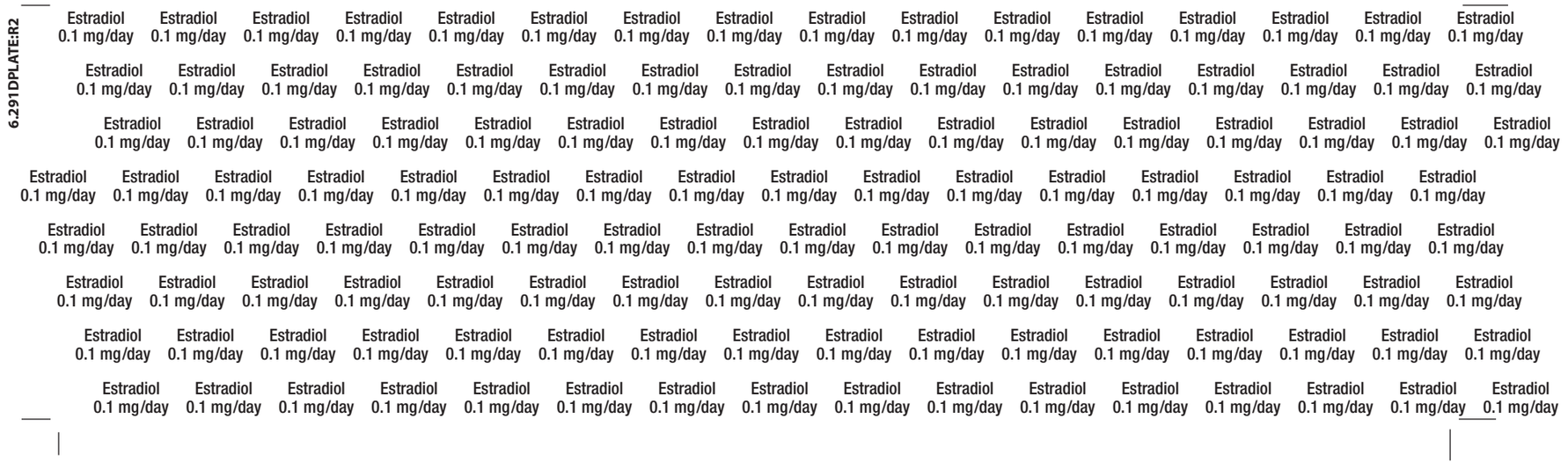
6.292DPLATE:R2

Estradiol 0.0375 mg/day


6.293DPLATE:R2
Estradiol 0.05 mg/day

6.294DPLATE:R2

Estradiol 0.075 mg/day


6.291DPLATE:R2
Estradiol 0.1 mg/day

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201675Orig1s000

LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING #3

APPROVAL SUMMARY (Supersedes Approval Summary Dated 01/23/2013)

DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	201675
Date of Submission	08/15/2013
Applicant's Name	Mylan Technologies Inc.
Established Name	Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice Weekly)
Proprietary Name	None

Labeling Comments below are considered:
☐ **Minor Deficiency ***
*** Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.**

☒ **No Comments (Labeling Approval Summary or Tentative Approval Summary)**

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated August 15, 2013.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

REMS required?

MedGuides and/or PPIs (505-1(e))	☐ Yes	☒ No	
Communication plan (505-1(e))	☐ Yes	☒ No	
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No	
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No	
Timetable for assessment (505-1(d))	☐ Yes	☒ No	
ANDA REMS acceptable?	☐ Yes	☐ No	☒ n/a

	Date submitted	Final or Draft	Recommendation
CARTON Each carton contains 8 systems (patch).	04/25/12	FPL	No Further Comments
POUCH One system (patch) per pouch	04/25/12	FPL	No Further Comments
PATCH Each system (patch) delivers: 0.025 mg/day of estradiol, 0.0375 mg/day of estradiol, 0.05 mg/day of estradiol, 0.075 mg/day of estradiol, or 0.1 mg/day of estradiol.	04/25/12	FPL	No Further Comments
PRESCRIBING INFORMATION	08/15/13	FPL	No Further Comments
PATIENT INFORMATION	08/15/13	FPL	No Further Comments
SPL	08/15/13		No Further Comments

REVISIONS NEEDED POST APPROVAL?
-None

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:
-None

FOR THE RECORD:

1. **MODEL LABELING**:
   The RLD is Vivelle-Dot® (estradiol transdermal system) (NDA 020538). The model RLD labeling used for this review is NDA 020538/S-030, 029, and 028 approved May 16, 2013.

   Regulatory History:
   Vivelle and Vivelle-DOT, FDA-approved in 1994 and 1996 respectively, are transdermal systems containing estradiol with continuous delivery for twice-weekly application. Vivelle-DOT is a revised formulation with smaller system sizes shown to be bioequivalent to the original Vivelle product. (per review by Mark Miller signed off 9/29/2010).

   The sponsor of this ANDA refers to Vivelle as the original formulation estradiol transdermal system (twice weekly), and Vivelle-DOT as the revised formulation estradiol transdermal system (twice weekly) in Prescribing Information.

2. **USP & PF**

Packaging and Storage:	Preserve in hermetic, light-resistant, unit-dose pouches.
Labeling:	The label states the total amount of estradiol in the Transdermal System and the release rate, in mg/day, for the duration of application of one system.

3. **MEDWATCH:**

The posting is in regards to labeling updates found in the last approved supplement.

4. **PATENT AND EXCLUSIVITY**

Patent Data – NDA

No	Expiration	Use Code	Use	**How filed**	**Labeling Impact**
5474783	Aug 12, 2014			PIV	None
6024976	Jan 7, 2014			PIV	None

There is no unexpired exclusivity for this product.

5. INACTIVE INGREDIENTS

Components	Pharmaceutical Function	% w/w	mg per system				
			0.025 mg/ day	0.0375 mg/ day	0.05 mg/ day	0.075 mg/ day	0.1 mg/ day
Active Ingredient							
Estradiol (b) (4) (b) (4) USP,	Active Ingredient	(b) (4)	0.41	0.62	0.82	1.23	1.64
Inactive Ingredients							
(b) (4) Oleyl Alcohol (b) (4)	(b) (4)	(b) (4)					
Dipropylene Glycol (b) (4)							
Povidone (b) (4) (b) (4)							
Silicone Adhesive (b) (4)	Adhesive						
Acrylic Adhesive (b) (4)	Adhesive						
(b) (4)	(b) (4)						
Theoretical Total Matrix3							
Components of the Delivery and Packaging System							
Polyolefin Film (b) (4)	Backing	(b) (4)					
Brown Ink (b) (4)	Imprinting Ink						
Polyester Film (b) (4)	Oversized Release Liner						

6. MANUFACTURING FACILITY

Mylan Technologies
110 Lake Street, St. Albans, Vermont

7. **FINISHED PRODUCT DESCRIPTION**

RLD: Patient Calendar Pack of 8 Systems and Carton of 3 Patient Calendar Packs of 8 Systems. Delivery rates of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5, 3.75, 5.0, 7.5, or 10.0 cm2 and contains 0.39, 0.585, 0.78, 1.17, or 1.56 mg of estradiol USP, respectively.

ANDA: Five dosage strengths of estradiol transdermal system (twice-weekly) are available to provide nominal *in vivo* delivery rates of 0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5 cm^2, 3.75 cm^2, 5.0 cm^2, 7.5 cm^2, or 10.0 cm^2 and contains 0.41 mg, 0.62 mg, 0.82 mg, 1.23 mg, or 1.64 mg of estradiol, USP, respectively. The composition of the systems per unit area is identical.

8. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Store at controlled room temperature at 25°C (77°F).

ANDA: Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

9. **PRODUCT LINE**

RLD:

HOW SUPPLIED

Vivelle-Dot® (estradiol transdermal system), 0.025 mg/day - each 2.5 cm^2 system contains 0.39 mg of estradiol USP for nominal* delivery of 0.025 mg of estradiol per day.

Patient Calendar Pack of 8 Systems..... NDC 0078-0365-42
Carton of 3 Patient Calendar Packs of 8 Systems..... NDC 0078-0365-45

Vivelle-Dot® (estradiol transdermal system), 0.0375 mg/day - each 3.75 cm^2 system contains 0.585 mg of estradiol USP for nominal* delivery of 0.0375 mg of estradiol per day. Patient Calendar Pack of 8 Systems..... NDC 0078-0343-42
Carton of 3 Patient Calendar Packs of 8 Systems..... NDC 0078-0343-45

Vivelle-Dot® (estradiol transdermal system), 0.05 mg/day - each 5.0 cm^2 system contains 0.78 mg of estradiol USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 Systems..... NDC 0078-0344-42
Carton of 3 Patient Calendar Packs of 8 Systems..... NDC 0078-0344-45

Vivelle-Dot® (estradiol transdermal system), 0.075 mg/day - each 7.5 cm^2 system contains 1.17 mg of estradiol USP for nominal* delivery of 0.075 mg of estradiol per day.

Patient Calendar Pack of 8 Systems..... NDC 0078-0345-42
Carton of 3 Patient Calendar Packs of 8 Systems..... NDC 0078-0345-45

Vivelle-Dot® (estradiol transdermal system), 0.1 mg/day - each 10.0 cm^2 system contains 1.56 mg of estradiol USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 Systems..... NDC 0078-0346-42
Carton of 3 Patient Calendar Packs of 8 Systems..... NDC 0078-0346-45

*See DESCRIPTION.

ANDA:

10. **CONTAINER/CLOSURE**

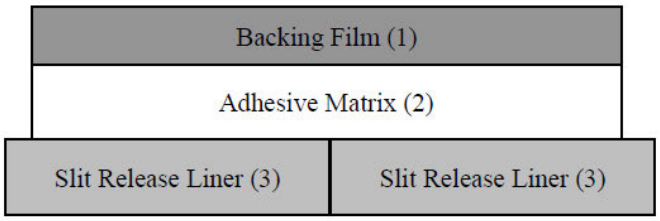
Container Closure System:

Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice-Weekly) – Each Mylan Estradiol Transdermal System (Twice-Weekly) is packaged in a square, flat pouch that is notched near the corners and imprinted with the lot number and expiration date. The multilayer pouching material is pre-printed with the approved labeling and consists of a laminate of (b) (4) (b) (4) A pouch is formed by placing a patch between two layers of pouching material, with the (b) (4) forming the inner surface of the pouch, and heat sealing along the four edges. Eight (8) sealed pouches of Estradiol Transdermal System (Twice- Weekly) are placed in a carton along with labeling.

A complete description of the container/closure system is provided in 3.2.P.7.

Mylan's Estradiol Transdermal Systems USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice-Weekly) are transdermal drug delivery systems of identical composition and the product strength is determined by the patch size. They are matrix "solution" transdermal systems in which the estradiol active ingredient is dissolved in a solid adhesive matrix. The figure below is a schematic representation of Mylan's Estradiol Transdermal System USP (Twice-Weekly), which is designed to be therapeutically equivalent to Novartis' Vivelle-Dot® transdermal system. Proceeding from the visible surface towards the surface attached to the skin, these layers are (1) a translucent polyolefin backing film printed with brown ink, (2) an adhesive formulation containing estradiol USP, silicone adhesive, acrylate adhesive, dipropylene glycol, povidone, oleyl alcohol, and (3) an oversized slit polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.

Figure 1: Schematic Diagram of Mylan's Estradiol Transdermal System (Twice-Weekly)



Note: Relative dimensions for 0.1 mg/day; vertical scale exaggerated 50×

(b) (4)

11. **RELATED APPLICATIONS**

- ANDA 075182 for Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.06 mg/day, 0.075 mg/day and 0.1 mg/day (Once-Weekly) (RLD Climara®; NDA 020375)

12. **SPL DATA ELEMENTS**

13. **ESTRADIOL**
estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0378-4644
Route of Administration	TRANSDERMAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (ESTRADIOL)	ESTRADIOL	0.025 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL	
POVIDONE	
OLEYL ALCOHOL	

Packaging

#	Item Code	Package Description
1	NDC:0378-4644-26	8 in 1 CARTON
1	NDC:0378-4644-16	1 in 1 POUCH
1		3.5 d in 1 PATCH

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201675	03/27/2015	

ESTRADIOL
estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:0378-4643

Route of Administration	TRANSDERMAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (ESTRADIOL)	ESTRADIOL	0.0375 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL	
POVIDONE	
OLEYL ALCOHOL	

Packaging

#	Item Code	Package Description	

1	NDC:0378-4643-26	8 in 1 CARTON
1	NDC:0378-4643-16	1 in 1 POUCH
1		3.5 d in 1 PATCH

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201675	03/27/2015	

ESTRADIOL
estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0378-4642
Route of Administration	TRANSDERMAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (ESTRADIOL)	ESTRADIOL	0.05 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL	
POVIDONE	
OLEYL ALCOHOL	

Packaging

#	Item Code	Package Description
1	NDC:0378-4642-26	8 in 1 CARTON

1	NDC:0378-4642-16	1 in 1 POUCH
1		3.5 d in 1 PATCH

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201675	03/27/2015	

ESTRADIOL
estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0378-4641
Route of Administration	TRANSDERMAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (ESTRADIOL)	ESTRADIOL	0.075 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL	
POVIDONE	
OLEYL ALCOHOL	

Packaging

#	Item Code	Package Description
1	NDC:0378-4641-26	8 in 1 CARTON
1	NDC:0378-4641-16	1 in 1 POUCH

1		3.5 d in 1 PATCH

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201675	03/27/2015	

ESTRADIOL
estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0378-4640
Route of Administration	TRANSDERMAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength

ESTRADIOL (ESTRADIOL)	ESTRADIOL	0.1 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL	
POVIDONE	
OLEYL ALCOHOL	

Packaging

#	Item Code	Package Description
1	NDC:0378-4640-26	8 in 1 CARTON
1	NDC:0378-4640-16	1 in 1 POUCH
1		3.5 d in 1 PATCH

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201675	03/27/2015	

Labeler - Mylan Pharmaceuticals Inc. (059295980)

Registrant - Mylan Pharmaceuticals Inc. (059295980)

Establishment

Name	Address	ID/FEI	Business Operations
Mylan Technologies Inc.		063790265	ANALYSIS(0378-4644, 0378-4643, 0378-4642, 0378-4641, 0378-4640), MANUFACTURE(0378-4644, 0378-4643, 0378-4642, 0378-4641, 0378-4640), LABEL(0378-4644, 0378-4643, 0378-4642, 0378-4641, 0378-4640), PACK(0378-4644, 0378-4643, 0378-4642, 0378-4641, 0378-4640)

Revised: 02/2012

Mylan Pharmaceuticals Inc.

14. **LABELING FORMAT:**

Style: TradeGothic-CondEighteen Size: 8 Sample of Patient Information:	Style: TradeGothic-CondEighteen Size: 6 Sample of Prescribing Information:
Read this PATIENT INFORMATION before you start using estradiol transdermal system, (b) (4) (twice-weekly) and (b) (4) (b) (4) each time (b) (4) There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.	**INDICATIONS AND USAGE** Estradiol transdermal system, (b) (4) twice-weekly) is indicated in: 1. Treatment of moderate to severe vasomotor symptoms (b) (4) menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (b) (4) menopause. When prescribing solely for the treatment of (b) (4) vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

15. **CITIZENS PETITION/PROPRIETARY NAME/CONSULTS**

Consult regarding adhesion issues:

Adhesion:
In the CLINICAL PHARMACOLOGY, Adhesion section, innovator adhesion information has been replaced with adhesion information specific to the Mylan product.

> "Adhesion: Based upon a dermal study for adhesion characteristics in 228 subjects, approximately 96% of estradiol transdermal system 0.025 mg/day (twice-weekly) patches adhered essentially complete (defined as greater than or equal to 90% adhered) to the skin over the 3.5-day wear period. Approximately 1% of the systems detached during the 3.5-day wear period."

Statement is accurate based on statistical review.

From: Lee, Nicole
Sent: Tuesday, October 30, 2012 11:26 AM
To: Hoppes, Charles V
Subject: RE: ANDA 201675 Mylan's Estradiol Patch

Hi Charlie,
Just an FYI that the stats report is finalized and in DARRTS.
Thanks,
Nicole

From: Hoppes, Charles V
Sent: Thursday, February 02, 2012 2:10 PM
To: Lee, Nicole
Subject: RE: ANDA 201675 Mylan's Estradiol Patch

Great,
Thanks Nicole,

Charlie.

From: Lee, Nicole
Sent: Thursday, February 02, 2012 2:05 PM
To: Hoppes, Charles V
Subject: RE: ANDA 201675 Mylan's Estradiol Patch

Charlie,
The statistical reviewer does not normally look at the labeling statement when doing their review. After the statistical review is done, I can forward you the review, if that helps. I will also put a note in the comments section of the RFS to double check the labeling statement.

Nicole

From: Hoppes, Charles V
Sent: Thursday, February 02, 2012 2:01 PM
To: Lee, Nicole
Subject: RE: ANDA 201675 Mylan's Estradiol Patch

Thanks Nicole,

Sounds good.

Will the reviewer look at Mylan's specific labeling statement for accuracy when they review?
Thanks,

Charlie

From: Lee, Nicole
Sent: Thursday, February 02, 2012 1:17 PM
To: Patel, Nitin K. (CDER/OGD)
Cc: Hoppes, Charles V
Subject: RE: ANDA 201675 Mylan's Estradiol Patch

Hi Charlie,
This information is correct based on the data provided by the firm. However, this has not been analyzed by the FDA statistician yet, so a final conclusion has not been made.

Hope this helps.

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From: Patel, Nitin K. (CDER/OGD)
Sent: Thursday, February 02, 2012 12:57 PM
To: Lee, Nicole
Cc: Hoppes, Charles V; Patel, Nitin K. (CDER/OGD)
Subject: FW: ANDA 201675 Mylan's Estradiol Patch

Hi Nicole,

Could you please assist Charlie with the question below.
Thanks,

Nitin

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Sent: Thursday, February 02, 2012 12:18 PM

To: Patel, Nitin K. (CDER/OGD)
Subject: ANDA 201675 Mylan's Estradiol Patch

Nitin,

I have picked up the labeling review of this application and found the following product specific passage in the insert labeling.

To clinical review team reviewer, Nitin Patel:

Greetings,

I have picked up the labeling review of this application and found the following product specific passage in the insert labeling.

Adhesion: Based upon a dermal study for adhesion characteristics in 228 subjects, approximately 96% of estradiol transdermal system 0.025 mg/day (twice-weekly) patches adhered essentially complete (defined as greater than or equal to 90% adhered) to the skin over the 3.5-day wear period. Approximately 1% of the systems detached during the 3.5-day wear period.

Could you verify this information is accurate and consistent with Mylan's application?

Thanks,

Charlie.

Could you verify this information is accurate and consistent with Mylan's application?

Thanks,

Charlie.

4.2 Conclusions

For adhesion and irritation, the test product was found to be, in general, inferior to the reference product based on mixed model analysis. However, the upper confidence bounds for the difference in proportions of test *versus* reference, based on binary analysis, were low, with the test exceeding the reference by no more than 6 percentage points in all cases. None of the subjects were considered to be potentially sensitized to either product. The test might exceed the reference by at most 1.9 percentage points based on the 95% upper confidence bound for the difference in sensitization rates.

Given the results, the clinical decision should be made using medical judgment as well as statistics.

Taken from Statistical Review and Evaluation dated 10/22/2012

Date of Review	10/30/2013
Primary Reviewer	Malik Imam
Team Leader	Lillie Golson

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MALIK M IMAM
10/31/2013

LILLIE D GOLSON
10/31/2013

REVIEW OF PROFESSIONAL LABELING #2

APPROVAL SUMMARY

DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	201675
Date of Submission	04/25/2012
Applicant's Name	Mylan Technologies Inc.
Established Name	Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice Weekly)
Proprietary Name	None

Labeling Comments below are considered:

☐ NOT easily correctable (applicant cannot respond within 10 business days)

☐ Easily correctable (respond within 10 business days)

☒ No Comments **(**Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

For AP SUMMARY:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated April 25, 2012

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

REMS required?

MedGuides and/or PPIs (505-1(e)) ☐ Yes ☒ No

Communication plan (505-1(e))	☐ Yes	☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No
Timetable for assessment (505-1(d))	☐ Yes	☒ No
ANDA REMS acceptable?	☐ Yes	☐ No ☒ n/a

	Date submitted	Final or Draft	Recommendation
CARTON Each carton contains 8 systems (patch).	04/25/12	FPL	No Further Comments
POUCH One system (patch) per pouch	04/25/12	FPL	No Further Comments
PATCH Each system (patch) delivers: 0.025 mg/day of estradiol, 0.0375 mg/day of estradiol, 0.05 mg/day of estradiol, 0.075 mg/day of estradiol, or 0.1 mg/day of estradiol.	04/25/12	FPL	No Further Comments
PRESCRIBING INFORMATION	04/25/12	FPL	No Further Comments
PATIENT INFORMATION	04/25/12	FPL	No Further Comments
SPL	04/25/12		No Further Comments

REVISIONS NEEDED POST APPROVAL?
-None

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:
-None

FOR THE RECORD:

1. **MODEL LABELING**:
   The RLD is Vivelle-Dot® (estradiol transdermal system) (NDA 020538). The model RLD labeling used for this review is NDA 020538/S-024 approved August 6, 2004. This supplemental new drug application provides for labeling revisions to update the labeling regarding the Women's Health Initiative Memory Study (WHIMS), a substudy of the Women's Health Initiative (WHI) trial.

   Regulatory History:

Vivelle and Vivelle-DOT, FDA-approved in 1994 and 1996 respectively, are transdermal systems containing estradiol with continuous delivery for twice-weekly application. Vivelle-DOT is a revised formulation with smaller system sizes shown to be bioequivalent to the original Vivelle product. (per review by Mark Miller signed off 9/29/2010)

2. **USP & PF**

Packaging and Storage: Preserve in hermetic, light-resistant, unit-dose pouches.
Labeling: The label states the total amount of estradiol in the Transdermal System and the release rate, in mg/day, for the duration of application of one system.

3. **MEDWATCH:**

There are no postings regarding this product, however a search under the active ingredient had the following result:

Safety

Evamist (estradiol transdermal spray): Drug Safety Communication - Unintended Exposure of Children and Pets to Topical Estrogen

[Posted 07/29/2010]

AUDIENCE: OB/GYN, Patient

ISSUE: FDA notified healthcare professionals and patients that it is reviewing reports of adverse effects from Evamist, an estrogen hormone used to reduce hot flashes during menopause. Children unintentionally exposed to the drug through skin contact with women may experience premature puberty. Female children may experience nipple swelling and breast development. Male children may experience breast enlargement.

BACKGROUND: Evamist is a topical product, sprayed on the skin on the inside of the forearm between the elbow and the wrist. FDA is currently reviewing reported adverse events and is working with the company to identify any factors that may contribute to unintended exposure. The Agency will update the public when this review is complete. FDA and the company are also evaluating ways to minimize the risk.

RECOMMENDATION: Patients should make sure that children are not exposed to Evamist and that children do not come into contact with any skin area where the drug was applied. Women who cannot avoid contact with children should wear a garment with long sleeves to cover the application site. Additional information for Healthcare Professionals, Information for Patients, and a Data Summary are provided in the Drug Safety Communication at the link below.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

4. **PATENT AND EXCLUSIVITY**

Patent Data – NDA

No	Expiration	Use Code	Use	**How filed**	**Labeling Impact**
5474783	Aug 12, 2014			PIV	None
6024976	Jan 7, 2014			PIV	None

There is no unexpired exclusivity for this product.

5. **INACTIVE INGREDIENTS**

Components	Pharmaceutical Function	% w/w	mg per system				
			0.025 mg/ day	0.0375 mg/ day	0.05 mg/ day	0.075 mg/ day	0.1 mg/ day
Active Ingredient							
Estradiol (b) (4) USP, (b) (4)	Active Ingredient	(b) (4)	0.41	0.62	0.82	1.23	1.64
Inactive Ingredients							
Oleyl Alcohol (b) (4) (b) (4)	(b) (4)	(b) (4)					(b) (4)
Dipropylene Glycol (b) (4)							
Povidone (b) (4) (b) (4)							
Silicone Adhesive (b) (4)	Adhesive						
Acrylic Adhesive (b) (4)	Adhesive						
		(b) (4)					
Theoretical Total Matrix3							
Components of the Delivery and Packaging System							
Polyolefin Film (b) (4)	Backing						(b) (4)
Brown Ink (b) (4)	Imprinting Ink						
Polyester Film (b) (4)	Oversized Release Liner						

6. **MANUFACTURING FACILITY**
Mylan Technologies
110 Lake Street, St. Albans, Vermont

7. **FINISHED PRODUCT DESCRIPTION**

RLD: Patient Calendar Pack of 8 Systems and Carton of 3 Patient Calendar Packs of 8 Systems. Delivery rates of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5, 3.75, 5.0, 7.5, or 10.0 cm2 and contains 0.39, 0.585, 0.78, 1.17, or 1.56 mg of estradiol USP, respectively.

ANDA: Five dosage strengths of estradiol transdermal system (twice-weekly) are available to provide nominal *in vivo* delivery rates of 0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5 cm^2, 3.75 cm^2, 5.0 cm^2, 7.5 cm^2, or 10.0 cm^2 and contains 0.41 mg, 0.62 mg, 0.82 mg, 1.23 mg, or 1.64 mg of estradiol, USP, respectively. The composition of the systems per unit area is identical.

Although the sponsor's total amount of estradiol in each patch is higher than the RLD's the delivery rate is the same. This concept has been reviewed in other transdermal patch systems (e.g., ANDA 200910 G.E Ortho Evra).

8. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Store at controlled room temperature at 25°C (77°F).

ANDA: Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

9. **PRODUCT LINE**

RLD:

HOW SUPPLIED

Vivelle-Dot® (estradiol transdermal system), 0.025 mg/day - each 2.5 cm^2 system contains 0.39 mg of estradiol USP for nominal* delivery of 0.025 mg of estradiol per day.

Patient Calendar Pack of 8 Systems..... NDC 0078-0365-42
Carton of 3 Patient Calendar Packs of 8 Systems..... NDC 0078-0365-45

Vivelle-Dot® (estradiol transdermal system), 0.0375 mg/day - each 3.75 cm^2 system contains 0.585 mg of estradiol USP for nominal* delivery of 0.0375 mg of estradiol per day. Patient Calendar Pack of 8 Systems..... NDC 0078-0343-42
Carton of 3 Patient Calendar Packs of 8 Systems..... NDC 0078-0343-45

Vivelle-Dot® (estradiol transdermal system), 0.05 mg/day - each 5.0 cm^2 system contains 0.78 mg of estradiol USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 Systems..... NDC 0078-0344-42
Carton of 3 Patient Calendar Packs of 8 Systems..... NDC 0078-0344-45

Vivelle-Dot® (estradiol transdermal system), 0.075 mg/day - each 7.5 cm^2 system contains 1.17 mg of estradiol USP for nominal* delivery of 0.075 mg of estradiol per day.

Patient Calendar Pack of 8 Systems..... NDC 0078-0345-42
Carton of 3 Patient Calendar Packs of 8 Systems..... NDC 0078-0345-45

Vivelle-Dot® (estradiol transdermal system), 0.1 mg/day - each 10.0 cm^2 system contains 1.56 mg of estradiol USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 Systems..... NDC 0078-0346-42
Carton of 3 Patient Calendar Packs of 8 Systems..... NDC 0078-0346-45

---

*See DESCRIPTION.

Please note:
Your Vivelle-Dot® (estradiol transdermal system) individual carton contains a calendar card printed on its inner flap. Mark the two-day schedule you plan to follow on your carton's inner flap.

ANDA:

Please note:
Your estradiol transdermal system (twice-weekly) individual carton contains a calendar card printed on its inner flap. Mark the 2 day schedule you plan to follow on your carton's inner flap.

10. **CONTAINER/CLOSURE**

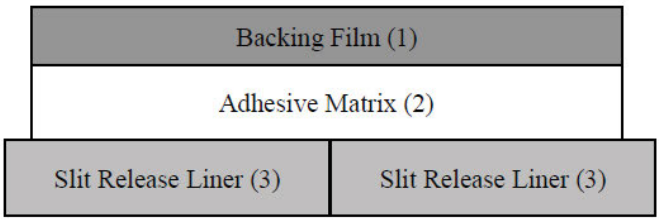
Container Closure System:

Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice-Weekly) – Each Mylan Estradiol Transdermal System (Twice-Weekly) is packaged in a square, flat pouch that is notched near the corners and imprinted with the lot number and expiration date. The multilayer pouching material is pre-printed with the approved labeling and consists of a laminate of (b) (4) (b) (4). A pouch is formed by placing a patch between two layers of pouching material, with the (b) (4) forming the inner surface of the pouch, and heat sealing along the four edges. Eight (8) sealed pouches of Estradiol Transdermal System (Twice- Weekly) are placed in a carton along with labeling.

A complete description of the container/closure system is provided in 3.2.P.7.

Mylan's Estradiol Transdermal Systems USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice-Weekly) are transdermal drug delivery systems of identical composition and the product strength is determined by the patch size. They are matrix "solution" transdermal systems in which the estradiol active ingredient is dissolved in a solid adhesive matrix. The figure below is a schematic representation of Mylan's Estradiol Transdermal System USP (Twice-Weekly), which is designed to be therapeutically equivalent to Novartis' Vivelle-Dot® transdermal system. Proceeding from the visible surface towards the surface attached to the skin, these layers are (1) a translucent polyolefin backing film printed with brown ink, (2) an adhesive formulation containing estradiol USP, silicone adhesive, acrylate adhesive, dipropylene glycol, povidone, oleyl alcohol, and (3) an oversized slit polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.

Figure 1: Schematic Diagram of Mylan's Estradiol Transdermal System (Twice-Weekly)



Note: Relative dimensions for 0.1 mg/day; vertical scale exaggerated 50×

(b) (4)

11. **RELATED APPLICATIONS**

- ANDA 075182 for Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.06 mg/day, 0.075 mg/day and 0.1 mg/day (Once-Weekly) (RLD Climara®; NDA 020375)

12. **SPL DATA ELEMENTS**

13. **ESTRADIOL**
estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0378-4644
Route of Administration	TRANSDERMAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (ESTRADIOL)	ESTRADIOL	0.025 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL	
POVIDONE	
OLEYL ALCOHOL	

Packaging

#	Item Code	Package Description
1	NDC:0378-4644-26	8 in 1 CARTON
1	NDC:0378-4644-16	1 in 1 POUCH
1		3.5 d in 1 PATCH

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201675	03/27/2015	

ESTRADIOL
estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:0378-4643

Route of Administration	TRANSDERMAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (ESTRADIOL)	ESTRADIOL	0.0375 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL	
POVIDONE	
OLEYL ALCOHOL	

Packaging

#	Item Code	Package Description	

1	NDC:0378-4643-26	8 in 1 CARTON
1	NDC:0378-4643-16	1 in 1 POUCH
1		3.5 d in 1 PATCH

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201675	03/27/2015	

ESTRADIOL
estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0378-4642
Route of Administration	TRANSDERMAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (ESTRADIOL)	ESTRADIOL	0.05 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL	
POVIDONE	
OLEYL ALCOHOL	

Packaging

#	Item Code	Package Description
1	NDC:0378-4642-26	8 in 1 CARTON

1	NDC:0378-4642-16	1 in 1 POUCH
1		3.5 d in 1 PATCH

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201675	03/27/2015	

ESTRADIOL
estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0378-4641
Route of Administration	TRANSDERMAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (ESTRADIOL)	ESTRADIOL	0.075 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL	
POVIDONE	
OLEYL ALCOHOL	

Packaging

#	Item Code	Package Description
1	NDC:0378-4641-26	8 in 1 CARTON
1	NDC:0378-4641-16	1 in 1 POUCH

1		3.5 d in 1 PATCH

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201675	03/27/2015	

ESTRADIOL
estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0378-4640
Route of Administration	TRANSDERMAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength

ESTRADIOL (ESTRADIOL)	ESTRADIOL	0.1 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
DIPROPYLENE GLYCOL	
POVIDONE	
OLEYL ALCOHOL	

Packaging

#	Item Code	Package Description
1	NDC:0378-4640-26	8 in 1 CARTON
1	NDC:0378-4640-16	1 in 1 POUCH
1		3.5 d in 1 PATCH

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201675	03/27/2015	

Labeler - Mylan Pharmaceuticals Inc. (059295980)

Registrant - Mylan Pharmaceuticals Inc. (059295980)

Establishment

Name	Address	ID/FEI	Business Operations
Mylan Technologies Inc.		063790265	ANALYSIS(0378-4644, 0378-4643, 0378-4642, 0378-4641, 0378-4640), MANUFACTURE(0378-4644, 0378-4643, 0378-4642, 0378-4641, 0378-4640), LABEL(0378-4644, 0378-4643, 0378-4642, 0378-4641, 0378-4640), PACK(0378-4644, 0378-4643, 0378-4642, 0378-4641, 0378-4640)

Revised: 02/2012

Mylan Pharmaceuticals Inc.

14. **LABELING FORMAT:**

Style: TradeGothic-CondEighteen Size: 8 Sample of Patient Information:	Style: TradeGothic-CondEighteen Size: 6 Sample of Prescribing Information:

Read this PATIENT INFORMATION before you start using estradiol transdermal system (b) (4) (twice-weekly) and (b) (4) each time (b) (4) here may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.	**INDICATIONS AND USAGE** Estradiol transdermal system (b) (4) twice-weekly) is indicated in: 1. Treatment of moderate to severe vasomotor symptoms (b) (4) menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (b) (4) menopause. When prescribing solely for the treatment of (b) (4) vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

15. **CITIZENS PETITION/PROPRIETARY NAME/CONSULTS**
Consult regarding adhesion issues:

Adhesion:
In the CLINICAL PHARMACOLOGY, Adhesion section, innovator adhesion information has been replaced with adhesion information specific to the Mylan product.

> "Adhesion: Based upon a dermal study for adhesion characteristics in 228 subjects, approximately 96% of estradiol transdermal system 0.025 mg/day (twice-weekly) patches adhered essentially complete (defined as greater than or equal to 90% adhered) to the skin over the 3.5-day wear period. Approximately 1% of the systems detached during the 3.5-day wear period."

Statement is accurate based on statistical review.

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For adhesion and irritation, the test product was found to be, in general, inferior to the reference product based on mixed model analysis. However, the upper confidence bounds for the difference in proportions of test *versus* reference, based on binary analysis, were low, with the test exceeding the reference by no more than 6 percentage points in all cases. None of the subjects were considered to be potentially sensitized to either product. The test might exceed the reference by at most 1.9 percentage points based on the 95% upper confidence bound for the difference in sensitization rates.

Given the results, the clinical decision should be made using medical judgment as well as statistics.

Taken from Statistical Review and Evaluation dated 10/22/2012

Date of Review	01/02/2013
Primary Reviewer	Malik Imam
Team Leader	Lillie Golson

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MALIK M IMAM
01/22/2013

LILLIE D GOLSON
01/23/2013

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 201675 Date of Submission: 4/26/2010

Applicant's Name: Mylan Technologies

Established Name: Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice Weekly)

Labeling Deficiencies:

A. GENERAL COMMENTS:

We note that you have provided product specific information regarding the adhesion properties of your transdermal system. We have asked the Office of Generic Drugs Clinical Review Team to verify the accuracy of this information and defer comment on that part of the labeling until the time that their review has been completed.

B. PACKAGE INSERT:

1. See GENERAL COMMENTS above.

2. Improve the resolution of figures appearing in the insert labeling when submitting final print labeling.

C. PATIENT LABELING:

Revise to delete [redacted] (b) (4). Alternatively explain how you believe patients will understand the meaning of [redacted] (b) (4)

Submit final printed labeling (or draft if you prefer) electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the last approved labeling of the RLD with all differences annotated and explained.

BASIS OF APPROVAL:
APPROVAL SUMMARY

POUCH LABEL:
Satisfactory in draft.

PATCH LABEL:
Satisfactory in draft.

CARTON LABELING:
Satisfactory in draft.

PACKAGE INSERT (draft labeling):
See comments above.

PATIENT LABELING (draft labeling):
See comments above.

FUTURE REVISIONS:

BASIS OF APPROVAL:
Was this approval based upon a petition?
What is the RLD on the 356(h) form:
NDA Number: 020538
NDA Drug Name: Vivelle Dot®
NDA Firm: Novartis
Date of Approval of NDA Insert and supplement #:020538/S-024, approved August 6, 2004
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Other Comments

FOR THE RECORD:

1. The RLD is Vivelle-Dot® (estradiol transdermal system) (NDA 020538). The model RLD labeling used for this review is NDA 020538/S-024 approved August 6, 2004. This supplemental new drug application provides for labeling revisions to update the labeling regarding the Women's Health Initiative Memory Study (WHIMS), a substudy of the Women's Health Initiative (WHI) trial.

   Regulatory History:

   Vivelle and Vivelle-DOT, FDA-approved in 1994 and 1996 respectively, are transdermal systems containing estradiol with continuous delivery for twice-weekly application. Vivelle-DOT is a revised formulation with smaller system sizes shown to be bioequivalent to the original Vivelle product. (per review by Mark Miller signed off 9/29/2010)

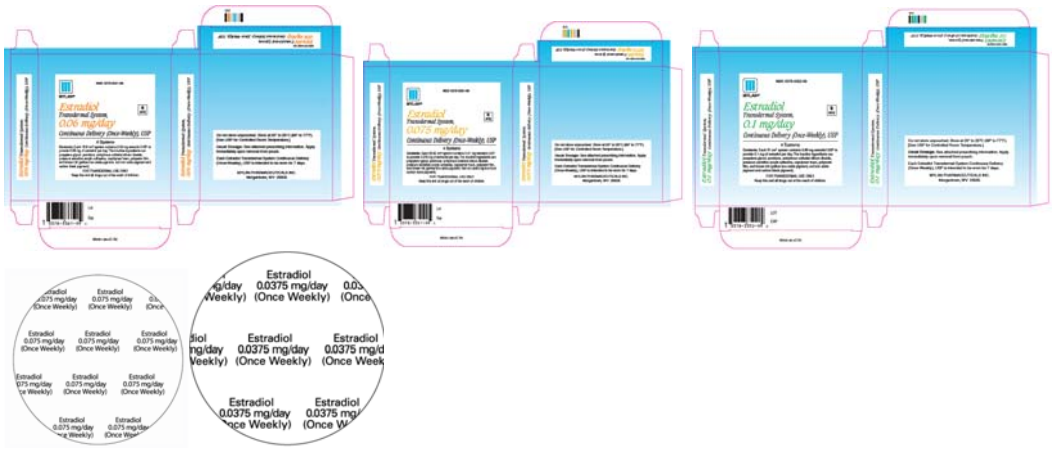
   Patent Data For NDA 020538

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5474783	Dec 12, 2012			PIII	None
5656286	Aug 12, 2014			PIV	None
5958446	Dec 12, 2012			PIII	None
6024976	Jan 7, 2014			PIV	None

   Exclusivity Data For NDA 020538

   There is no unexpired exclusivity for this product.

2. RELATED APPLICATION(S)
   - (b) (4)
   - ANDA 075182 for Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.06 mg/day, 0.075 mg/day and 0.1 mg/day (Once-Weekly) (RLD Climara®; NDA 020375)



3. MANUFACTURING FACILITY
Mylan Technologies
110 Lake Street, St. Albans, Vermont

4. STORAGE CONDITIONS/DISPENSING RECOMMENDATIONS/COMPATIBILITY:

RLD
Store at controlled room temperature at 25°C (77°F). Do not store unpouched. Apply immediately upon removal from the protective pouch.
ANDA
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Do not store unpouched. Apply immediately upon removal from the protective pouch.
USP:

Estradiol Transdermal System
Packaging and storage— Preserve in hermetic, light-resistant, unit-dose pouches.
Labeling— The label states the total amount of estradiol in the Transdermal System and the release rate, in mg per day, for the duration of application of one system.

PF:

PF 31(4): Labeling— When more than one Drug Release Test is given, the labeling states the Drug Release Test used only if Test 1 is not used.

5. INACTIVE INGREDIENTS:

The description of inactive ingredients in the insert labeling is consistent with the components and composition statement.

6. PACKAGING CONFIGURATIONS/ SYSTEM DESCRIPTION:

RLD:

Patient Calendar Pack of 8 Systems and Carton of 3 Patient Calendar Packs of 8 Systems. Delivery rates of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via the skin. Each

Components	Pharmaceutical Function	% w/w	mg per system				
			0.025 mg/ day	0.0375 mg/ day	0.05 mg/ day	0.075 mg/ day	0.1 mg/ day
Active Ingredient							
Estradiol (b) (4), USP, (b) (4)	Active Ingredient	(b) (4)	0.41	0.62	0.82	1.23	1.64
Inactive Ingredients							
Oleyl Alcohol (b) (4) (b) (4)	(b) (4)						
Dipropylene Glycol (b) (4)							
Povidone (b) (4) (b) (4)							
Silicone Adhesive (b) (4)	Adhesive						
Acrylic Adhesive (b) (4)	Adhesive						
(b) (4) (b) (4)	(b) (4)						
Theoretical Total Matrix3							
Components of the Delivery and Packaging System							
Polyolefin Film (b) (4)	Backing						
Brown Ink (b) (4)	Imprinting Ink						
(b) (4) Polyester Film (b) (4)	Oversized Release Liner						

corresponding system has an active surface area of 2.5, 3.75, 5.0, 7.5, or 10.0 cm2 and contains 0.39, 0.585, 0.78, 1.17, or 1.56 mg of estradiol USP, respectively.

ANDA:

Eight (8) sealed pouches in a single carton. Mylan's Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice-Weekly) are single disk, self-adhering systems for transdermal administration of estradiol. The 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day systems contain 0.41 mg, 0.62 mg, 0.82 mg, 1.23 mg, and 1.64 mg estradiol, respectively, in a multipolymeric adhesive matrix.

- Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day (Twice-Weekly): Square pouch 66 mm x 66 mm; heat sealed on four sides.
- Estradiol Transdermal System USP, 0.075 mg/day, 0.1 mg/day (Twice-Weekly): Square pouch 76 mm x 76 mm; heat sealed on four sides.

USP: Packaging and storage— Preserve in hermetic, light-resistant, unit-dose pouches.

(b) (4) (b) (4) Material provides adequate protection from light, exposure to reactive gases and contamination. The paper and foil layers form a barrier to light transmission.

1

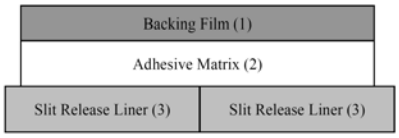
Moisture vapor transmission is limited to (b) (4) by the pouching material specifications. The ability to heat seal the pouching material is controlled within the material specifications to a limit of (b) (4) (b) (4). Seal integrity is further ensured with pouch integrity leak testing of finished pouched systems. Collectively, these product and process controls ensure the patch is protected from light, moisture, and microbial contamination for the duration of patch shelf-life.

(b) (4)

September 10, 2010 gratuitous amendment:

Mylan's Estradiol Transdermal System USP is comprised of three layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are (1) a translucent polyolefin backing film printed with brown ink, (2) an adhesive formulation containing estradiol USP, silicone adhesive, acrylate adhesive, dipropylene glycol, povidone, oleyl alcohol, and (3) an oversized slit polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.

Figure 1: Schematic Diagram of Mylan's Estradiol Transdermal System USP



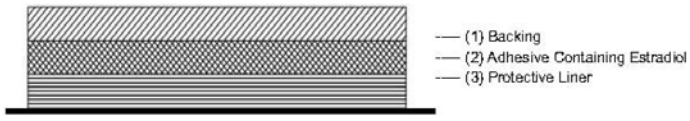
Note: Relative dimensions for 0.1 mg/day; vertical scale exaggerated 50×

Vivelle-Dot® is also constructed of three consecutive layers, as described in the following excerpt from the product labeling:

Vivelle-Dot is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin film (2) an adhesive formulation containing estradiol, acrylic adhesive, silicone adhesive, oleyl alcohol, NF, povidone, USP and dipropylene glycol, and (3) a polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.

A schematic of the Reference product is shown in Figure 2.

Figure 2: Schematic of Vivelle-Dot® (estradiol transdermal system)



Note: Relative dimensions not to scale

A comparison of the composition of the two products is shown in Table 2. The Mylan Estradiol Transdermal System USP is effectively a direct copy of Vivelle-Dot® and does not vary in any appreciable way from that patch.

7. Adhesion Issues

Adhesion:

In the CLINICAL PHARMACOLOGY, Adhesion section, innovator adhesion information has been replaced with adhesion information specific to the Mylan product.

"Adhesion: Based upon a dermal study for adhesion characteristics in 228 subjects, approximately 96% of estradiol transdermal system 0.025 mg/day (twice-weekly) patches adhered essentially complete (defined as greater than or equal to 90% adhered) to the skin over the 3.5-day wear period. Approximately 1% of the systems detached during the 3.5-day wear period."

Need to verify the accuracy of the information with the clinical review team.

To clinical review team reviewer, Nitin Patel:

Greetings,

I have picked up the labeling review of this application and found the following product specific passage in the insert labeling.

> ***Adhesion:*** Based upon a dermal study for adhesion characteristics in 228 subjects, approximately 96% of estradiol transdermal system 0.025 mg/day (twice-weekly) patches adhered essentially complete (defined as greater than or equal to 90% adhered) to the skin over the 3.5-day wear period. Approximately 1% of the systems detached during the 3.5-day wear period.

Could you verify this information is accurate and consistent with Mylan's application?

Thanks,

Charlie.

Charlie,
The statistical reviewer does not normally look at the labeling statement when doing their review. After the statistical review is done, I can forward you the review, if that helps. I will also put a note in the comments section of the RFS to double check the labeling statement.

Nicole

From: Hoppes, Charles V
Sent: Thursday, February 02, 2012 2:01 PM
To: Lee, Nicole
Subject: RE: ANDA 201675 Mylan's Estradiol Patch

Thanks Nicole,

Sounds good.

Will the reviewer look at Mylan's specific labeling statement for accuracy when they review?

Thanks,

Charlie

From: Lee, Nicole
Sent: Thursday, February 02, 2012 1:17 PM
To: Patel, Nitin K. (CDER/OGD)
Cc: Hoppes, Charles V
Subject: RE: ANDA 201675 Mylan's Estradiol Patch

Hi Charlie,
This information is correct based on the data provided by the firm. However, this has not been analyzed by the FDA statistician yet, so a final conclusion has not been made.

Hope this helps.

Nicole

RLD labels and labeling available at \\Cdsesub1\evsprod\NDA020538\0010\m1\us

Placebo Pouch: According to the RLD website, women may "Try a non-medicated sample patch to help you determine if this tiny estrogen patch might be right for you." http://www.vivelledot.com/consumer/about-vivelle-dot/request-a-non-medicated-sample/default.aspx

8. Proprietary Name Review

The sponsor has not submitted a proprietary name.

9. Bio – PN review:

Sponsor has submitted irritability and adhesion studies per filing checklist.

10. SPL - See Addendum

11. FINISHED PRODUCT DESCRIPTION:

0.025 mg/day: A rectangular patch with rounded corners. Opaque, white to cream adhesive layer, matte film backing randomly printed with "Estradiol 0.025 mg/day (Twice-Weekly)" in brown ink, and a clear release liner. Each patch is contained in a square, flat, notched pouch. The pouch is imprinted with the lot number and expiration date. Substantial cold flow is not observed.

0.0375 mg/day: A rectangular patch with rounded corners. Opaque, white to cream adhesive layer, matte film backing randomly printed with "Estradiol 0.0375 mg/day (Twice-Weekly)" in brown ink, and a clear release liner. Each patch is contained in a square, flat, notched pouch. The pouch is imprinted with the lot number and expiration date. Substantial cold flow is not observed.

0.05 mg/day: A rectangular patch with rounded corners. Opaque, white to cream adhesive layer, matte film backing randomly printed with "Estradiol 0.05 mg/day (Twice-Weekly)" in brown ink, and a clear release liner. Each patch is contained in a square, flat, notched pouch. The pouch is imprinted with the lot number and expiration date. Substantial cold flow is not observed.

0.075 mg/day: A rectangular patch with rounded corners. Opaque, white to cream adhesive layer, matte film backing randomly printed with "Estradiol 0.075 mg/day (Twice-Weekly)" in brown ink, and a clear release liner. Each patch is contained in a square, flat, notched pouch. The pouch is imprinted with the lot number and expiration date. Substantial cold flow is not observed.

0.1 mg/day: A rectangular patch with rounded corners. Opaque, white to cream adhesive layer, matte film backing randomly printed with "Estradiol 0.1 mg/day (Twice-Weekly)" in brown ink, and a clear release liner. Each patch is contained in a square, flat, notched pouch. The pouch is imprinted with the lot number and expiration date. Substantial cold flow is not observed.

Date of Review:	February 2, 2012	Date of Submission:	4/26/2010
Primary Reviewer:	Charlie Hoppes	Team Leader:	John Grace

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHARLES V HOPPES
02/03/2012

JOHN F GRACE
02/06/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201675Orig1s000

MEDICAL REVIEW(S)

Addendum Review of Skin Irritation, Sensitization and Adhesion Studies

ANDA:	201675
Drug Product:	Estradiol Transdermal System, USP 0.025 mg/day; 0.0375 mg/day; 0.05 mg/day; 0.075 mg/day and 0.1 mg/day
Sponsor:	Mylan Pharmaceuticals Inc.
Reference Listed Drug (RLD):	Vivelle-Dot® Transdermal System (NDA 020538), Novartis Pharmaceutical Corporation
Original Submission Date:	4/26/2010
Amendment Submission Dates:	12/30/2013
Original Primary Reviewer:	Nicol Lee, Pharm.D.

On 04/26/2010, Mylan Pharmaceuticals Inc. (Mylan) submitted an abbreviated new drug application (ANDA) for Estradiol Transdermal System, USP 0.025 mg/day; 0.0375 mg/day; 0.05 mg/day; 0.075 mg/day and 0.1 mg/day. In support for the ANDA, Mylan conducted a skin adhesion, irritation and sensitization study (#EDOT-0908).

Study #EDOT-0908 was an open-label, multiple dose, randomized application site, two-treatment, three-phase, one-period study investigating the adhesion, cumulative induction of dermal irritation and contact sensitization by repetitive applications of the transdermal delivery system to the same skin sites. This study was initiated with two hundred twenty-eight (228) subjects, and 221 subjects completed the study. Using the adhesion analysis as outlined in the Draft Guidance on Estradiol Film, Extended Release/Transdermal, (Nov 2010), the FDA statistician concluded that Mylan's Estradiol Transdermal System failed to demonstrate that its adhesion performance is no worse than that of the RLD. In addition, FDA statisticians concluded that Mylan's Estradiol Transdermal System is, in fact, statistically more irritating than the RLD system. As a result, the application was not recommended for approval.

However, based on the Memorandum "Waiver of Statistical Non-Inferiority Analysis for Highly Adhering Patch Drug Products" dated 2/10/2014 by Bryan Newman, Ph.D. of the Science Team (Appendix 1), the adhesion data in Mylan's skin adhesion, irritation and sensitization study (#EDOT-0908) was reconsidered. In re-evaluation, this study meets the new 90/90 analysis criteria (See FDA Statistical Review finalized on 3/12/14 by Huaixiang Li, Ph.D. in Appendix 2). Therefore, the statistical adhesion non-inferiority analysis with the RLD is considered satisfactory based on this new memorandum by the Science Team. However, the FDA Statistician reviewed the information submitted in the 12/30/2013 amendment and did not agree with Mylan's proposed alternate irritation statistical analysis method (Appendix 2). Therefore, our conclusion that Mylan's Estradiol Transdermal System is more irritating than the RLD system has not changed. As such, we do **not** recommend this application for approval.

{See appended electronic signature page}

Sarah H. Seung, Pharm.D.
Clinical Reviewer, Division of Clinical Review
Office of Generic Drugs

Date

{See appended electronic signature page}

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs

Date

{See appended electronic signature page}

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

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows ___ YES __X__NO

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 201675 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Estradiol Transdermal System, USP 0.025 mg/day; 0.0375 mg/day; 0.05 mg/day; 0.075 mg/day and 0.1 mg/day

The Division of Clinical Review has completed its review and the following deficiency has been identified:

You have not provided adequate data to ensure that the irritation potential of your product is non-inferior to the RLD.

The information you provided in your amendment dated 12/30/2013 is not adequate.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. These comments are subject to revision if additional concerns are raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

{See appended electronic signature page}

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

Appendix 1

MEMORANDUM

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

DATE: February 10, 2014

FROM: Bryan Newman, Ph.D.
ORISE Fellow, Science Staff
Office of Generic Drugs
Center for Drug Evaluation and Research

THROUGH: Robert Lionberger, Ph.D.
Acting Deputy Director for Science
Office of Generic Drugs
Center for Drug Evaluation and Research

TO: John Peters, M.D.
Director for the Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECT: Waiver of Statistical Non-Inferiority Analysis for Highly Adhering Patch Drug Products

Executive Summary

The FDA's recommended approach to establish non-inferiority (NI) of a generic patch's adhesive properties to that of the RLD uses linear mixed models, which carry the assumption that both the random effects model parameters and the residuals of the data follow a normal distribution. However, this approach is no longer appropriate for products that are highly adhering since the concentration of zero scores (≥ 90% attached) results in a highly right-skewed distribution. Performing a mixed model analysis to establish NI between a highly adhering generic and its highly adhering RLD often results in an inability to establish NI. Generics in this situation have little room to improve, since their adhesion profiles have reached the upper limits for adhesiveness, and so reach an inappropriate block to their approval.

To resolve this situation, products that meet or exceed ≥ 90% of patches having ≥ 90% adhesion throughout the entire study (defined as 90/90) can be said to have demonstrated a sufficiently adhesive product and can waive the current NI requirement. To support this waiver criterion, adhesion data from 15 ANDAs and their respective RLDs were analyzed to determine which product could meet this condition. Of the 5 ANDAs that met the 90/90 criterion, 3 were at the upper limits of adhesiveness (98-100% of adhesion scores were zero, indicating ≥ 90% adhesion) and all failed to establish NI using the recommended statistical method. Thus, waiving the statistical requirement of NI for these

products is appropriate given that, in terms of product quality, the generic patches demonstrated sufficient adhesive performance to permit approval.

Lastly, adhesion studies used to establish NI should contain a minimum of 60 subjects to qualify for the adhesion waiver. To determine the minimum sample size, adhesion data for each ANDA was bootstrapped (with replacement) to generate 5 sets of 10,000 studies, with each set using one of the sample sizes listed: 20, 36, 40, 60, 80 subjects. Results from the analysis showed that decreasing the number of subjects in the study increased the percentage of studies meeting the waiver criterion (i.e. increased the false positive rate). A sample size of 60 subjects maintained the false positive rate below 10%. Lastly, for products whose adhesion data is on the borderline of meeting the waiver criterion (89.0 to 89.9% average adhesion throughout the study duration), the product could be viewed as having met the waiver criterion if the study sample size is $\geq$ 60, and no instances of poor product adhesion (i.e. no full detachments / adhesion scores = 4) are reported. This decision would be left for the clinical reviewer. Lastly, it is important to note that the minimum sample size is solely for the qualification of the adhesion waiver, and not for studies using the FDA recommended method for establishing NI.

FDA's Guidance for Conducting Adhesion Studies for Patch Drug Products

During the ANDA review process for topical and transdermal patch dosage forms, ANDA sponsors must ensure that the submitted generic meets both the standards for demonstrating bioequivalence and those that ensure product quality. For patch dosage forms, the tolerability and reliability of the adhesives used to retain the drug product on the skin are vital parameters in which the Agency gauges product quality. In terms of tolerability, patch irritation and sensitization are determined via trained observers that following inspection of the skin, record dermal (irritation) and other (sensitization) responses using the established FDA scoring system. In a similar fashion, patch reliability is assessed in terms of the adhesiveness of the patch throughout the labeled period of administration.

To compare the amount of detachment between the generic and RLD patches, each patch is first given an adhesion score that describes the amount of attachment to the skin at the time of observation, as assessed by a trained observer. The scoring system currently approved by the FDA is shown below.

Percent Attachment from Skin	Adhesion Score
$\geq$ 90% Attached	0
< 90% to $\geq$ 75% Attached	1
< 75% to $\geq$ 50% Attached	2
< 50% to $\geq$ 25% Attached	3
Complete Detachment	4

These scores are used to derive a mean adhesion score for a single patch for each subject. The number of adhesion measurements taken per patch is a function of the duration of wear; patches worn for 12 and 24 hours have one adhesion measurement whereas patches worn for 168 hours have seven adhesion measurements. A summary of all the

recommended measurement schedules contained in the bioequivalence guidance documents that measure adhesion is provided in Table 1.

Table 1. Summary of Patch Adhesion Sampling Regimes for Bioequivalence Guidance Documents with a Transdermal/Topical Route of Administration

Active Ingredient	RLD	Study	Total No. of TEST Patches	Length of Wear/Patch	Sampling Regime/Patch
Clonidine	18891	21-Day Induction Phase	3	168 hours (7 days)	Only take measurements on the *first* patch (See Item 3); daily measurements for 84 hours for a total of *4 measurements* (24, 48, 72, and 84 hours).
Estradiol	19081	21-Day Induction Phase	6	84 hours	Only take measurements on the *first* patch (See Item 19); daily measurements for 84 hours for a total of *4 measurements* (24, 48, 72, and 84 hours).
Estradiol	20375	21-Day Induction Phase	3	168 hours (7 days)	Only take measurements on the *first* patch (See Item 19); daily measurements for 7 days for a total of *7 measurements* (24, 48, 72, 96, 120, 144, and 168 hours).
Estradiol	21674	21-Day Induction Phase	6	84 hours	Only take measurements on the *first* patch (See Item 19); daily measurements for 84 hours for a total of *4 measurements* (24, 48, 72, and 84 hours).
Estradiol	20538	21-Day Induction Phase	6	84 hours	Only take measurements on the *first* patch (See Item 19); daily measurements for 84 hours for a total of *4 measurements* (24, 48, 72, and 84 hours).
Ethinyl Estradiol; Norelgestromin	21180	7-Day PK Bioequivalence	1	168 hours (7 days)	Daily measurements for 7 days (See Item 4) for a total of *7 measurements* (24, 48, 72, 96, 120, 144, and 168 hours).
Fentanyl	19813	3-Day PK Bioequivalence	1	72 hours	Daily measurements for 3 days (See Item 1) for a total of *3 measurements* (24, 48, and 72).
Granisetron	22198	7-Day PK Bioequivalence	1	168 hours (7 days)	Daily measurements for 7 days (See Item 4) for a total of *7 measurements* (24, 48, 72, 96, 120, 144, and 168 hours).
Lidocaine	20612	Guidance unclear			
Methylphenidate	21514	21-Day Induction Phase	9	48-72 hours	Only take measurements on the *first* patch (See Item 18). There does not seem to be any recommendation regarding the number of measurements other than 9 hours after application.
Nitroglycerin	74559	21-Day	21	24 hours	Only take measurements on the *first*

Table 1. Summary of Patch Adhesion Sampling Regimes for Bioequivalence Guidance Documents with a Transdermal/Topical Route of Administration

Active Ingredient	RLD	Study	Total No. of TEST Patches	Length of Wear/Patch	Sampling Regime/Patch
		Induction Phase			patch (See Item 2); *1 measurement* 24 hours after application.
Nitroglycerin	20145	1/2-Day PK Bioequivalence	1	12 hours	*One measurement* 12 hours after application (see Item 3).
Oxybutynin	21351	4-Day PK Bioequivalence	1	96 hours	Daily measurements for 4 days (See Item 2) for a total of *4 measurements* (24, 48, 72, and 96).
Rivastigmine	22083	1-Day PK Bioequivalence	1	24 hours	*One measurement* 24 hours after application (See Item 1).
Scopolamine	17874	3-Day PK Bioequivalence	1	72 hours	Daily measurements for 3 days (See Item 1) for a total of *3 measurements* (24, 48, and 72).
Selegilin	21336	21-Day Induction Phase	21	24 hours	Only take measurements on the *first* patch (See Item 2); *1 measurement* 24 hours after application.

In contrast to clinical trials which seek to show that a new drug product performs better than a comparator, non-inferiority (NI) trials are designed to determine whether the differences in treatment effect or product quality between a new drug product or generic equivalent and the comparator (RLD) are small and statistically non-significant, as discussed in the Agency's draft guidance on NI clinical trials.[1] For patch adhesion, ensuring that the generic is non-inferior to the RLD requires that the instances of detachment in the generic fall below the adjusted level of detachments observed in the RLD during the length of wear. The design structure for an NI adhesion trial is a randomized complete block or a two-period crossover; in both types of studies the treatment structure is a one-way with two levels, test and RLD. Each subject wears both the test and RLD patch simultaneously or in sequence. The response variable is the mean adhesion score except in those cases where the duration of wear allows for only one adhesion measurement. Therefore the response variable can be a single measurement or the mean of three, four, or seven measurements. The mean can range from zero to four, but the number of possible outcomes increases with the number of measurements. For example, there are five possible outcomes for a single adhesion measurement and 35 possible outcomes when adhesion is measured 3 times.

Current Methodology for Establishing NI

The NI evaluation of the test product versus the RLD must demonstrate that the upper bound of a one-sided 95% confidence limit of the mean adhesion score for the test

[1] FDA Guidance for Industry – Draft Guidance on Non-Inferiority Clinical Trials. Last accessed on November 20, 2013 via http://www.fda.gov/downloads/Drugs/.../Guidances/UCM202140.pdf

product minus 1.25 times the mean adhesion score for the RLD product is less than or equal to 0. The hypotheses are:

$$H_0: \mu_{Test} - 1.25\mu_{RLD} > 0 \quad \text{vs.} \quad H_a: \mu_{Test} - 1.25\mu_{RLD} \leq 0$$

where μ_{Test} is the least squares mean for the test product and μ_{RLD} is the least squares mean for the reference. If the 95% upper limit is less than or equal to zero, the null hypothesis is rejected and the test is considered NI to the RLD.

The null hypothesis is evaluated using a linear mixed model with "Treatment" as a fixed effect and "Subject" as a random effect. It is recommended the analysis be conducted in SAS® using the following code.

```
Proc Mixed Data = <dataset name>;
Class Subject Treatment;
Model MCA = Treatment / DDFM = Satterth;
Repeated Treatment / sub = Subject type = fa0(2) r;
Estimate 'Test – 1.25*Reference' int – 0.25 Treatment 1-1.25 / cl alpha = 0.1;
LSMeans Treatment;
Run;
```

Issues with the Approach

Past use of linear mixed model analysis has been appropriate for assessing NI with these types of products. However, as generic and RLD patch drug products have improved their adhesive performance, the appropriateness of the FDA recommended method for establishing NI has come under question. One of the key assumptions when using linear mixed models is that both the model parameters for the random effects portion and the residuals from the data follow a normal distribution (see Appendix I for details). With highly adhering products, adhesion scoring becomes dominated by zeros (≥ 90% attached), and in extreme cases, is entirely comprised of zeros. This results in data that are highly right skewed and thus non-normal. When using data from highly skewed distributions in a mixed model analysis where inferences are based on the *t*-distribution, it is not clear if the true coverage probability approximates the nominal coverage probability.

To get a better sense of the types of adhesion score distributions submitted to the FDA, adhesion scoring data from 15 ANDAs were used to determine the frequency of each score level (i.e. 0, 1, 2, 3, 4) in each adhesion study (see Appendix II and III for more details). The results are shown below in Table 2.

Table 2: Adhesion Score Frequency of Patch Drug Products and Their Ability to Pass FDA's Recommended Non-Inferiority Analysis

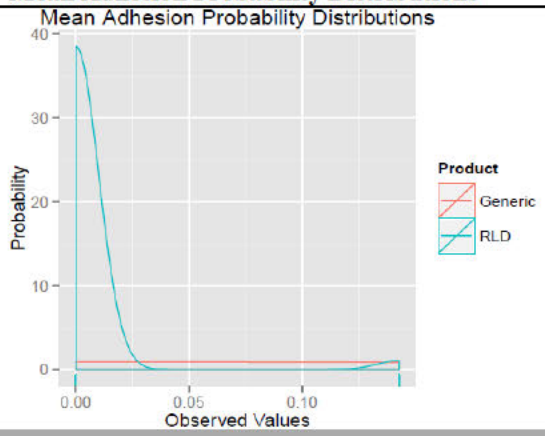
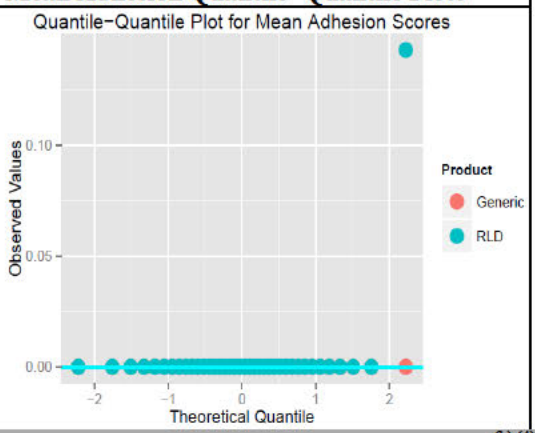
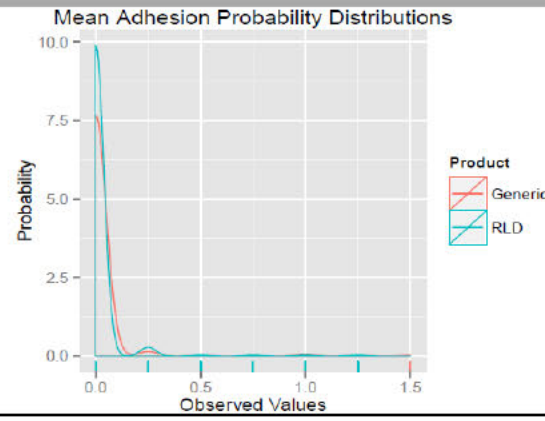
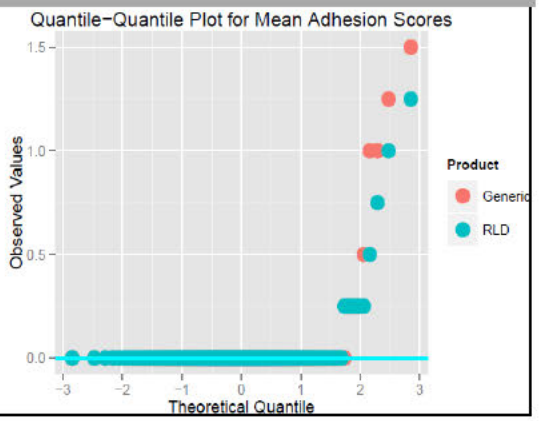
Drug Products	ANDA	RLD	Number of Time Points	TEST %Score = 0	TEST %Score = 1	TEST %Score = 2	TEST %Score = 3	TEST %Score = 4	REFERENCE %Score = 0	REFERENCE %Score = 1	REFERENCE %Score = 2	REFERENCE %Score = 3	REFERENCE %Score = 4	Passed NI (Ran by Statistician)	Passed NI (Ran by Bryan Newman)
Norelgestromin/ Estradiol TDS	200910	21180	7	100.0%	0.0%	0.0%	0.0%	0.0%	99.6%	0.4%	0.0%	0.0%	0.0%	no	CNR*
(b) (4)															
Estradiol TDS	201675	20538	4	98.5%	1.1%	0.0%	0.1%	0.3%	98.8%	0.8%	0.1%	0.1%	0.2%	no	no
(b) (4)															
Lidocaine	200675	20612	7	91.4%	6.0%	2.0%	0.6%	0.0%	91.4%	6.0%	2.0%	0.6%	0.0%	yes	yes
Clonidine	76157	18891	7	86.1%	7.3%	1.4%	0.7%	4.5%	72.5%	18.6%	3.0%	1.8%	4.1%	yes	yes
(b) (4)															
(b) (4)															
Clonidine TDS	79090	18891	8	82.8%	13.6%	0.0%	0.8%	2.8%	92.0%	3.4%	0.8%	0.6%	3.2%	yes	yes
Fentanyl	202097	19813	7	77.0%	21.1%	1.9%	0.0%	0.0%	74.5%	25.5%	0.0%	0.0%	0.0%	no	no
Scopolamine	78830	17874	6	61.5%	31.6%	5.2%	1.7%	0.0%	59.2%	35.6%	2.9%	0.0%	2.3%	no	no
(b) (4)															
Lidocaine	202346	20612	6	34.7%	52.8%	11.8%	0.7%	0.0%	47.2%	29.9%	11.8%	3.5%	7.6%	yes	yes

*** Convergence Not Reached**

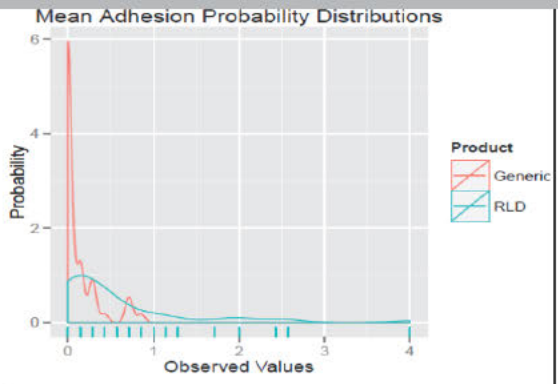
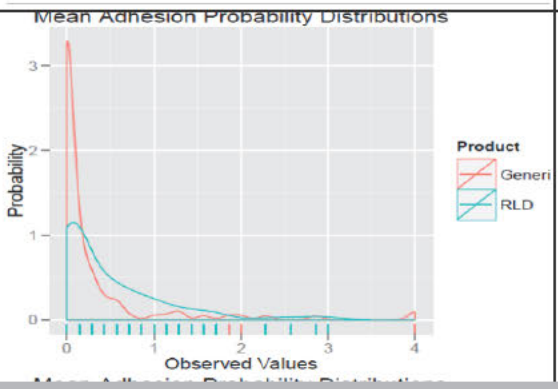
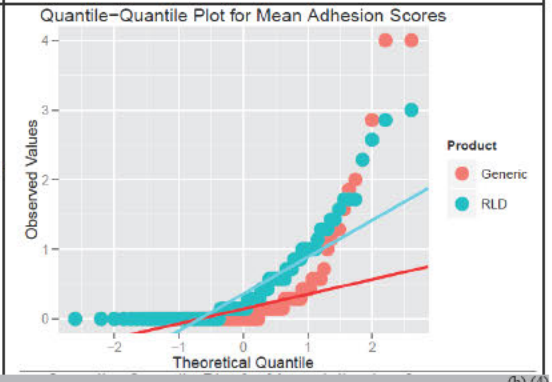
As shown in Table 2, adhesion scoring frequency varies considerably, with the highest adhering products Norelgestromin/Ethinyl Estradiol (ANDA 200910), [redacted] (b) (4) Estradiol (ANDA 201675), [redacted] (b) (4), and Lidocaine (ANDA 200675) having greater than 90% of the reported adhesion scores being zero. Importantly, when the adhesion scoring frequency for zero scores approached 100%, the mixed model analysis either failed to establish NI, or the SAS procedure failed to converge.

In addition to the adhesion score frequency, probability distributions and quantile-quantile plots were created for the mean adhesion score values from each of the 15 ANDAs (Table 3). While the normality of the mean adhesion values from many of the drug products is questionable [redacted] (b) (4) being the likeliest product to meet the normality assumption), the top 3 highly adhering products (98-100% zero scores) clearly deviate from what would be expected if the mean adhesion values were normally distributed.

Table 3: Comparison of the Mean Adhesion Probability Distributions and Quantile-Quantile Plots for the Top 5 Generic and Brand Patch Drug Products

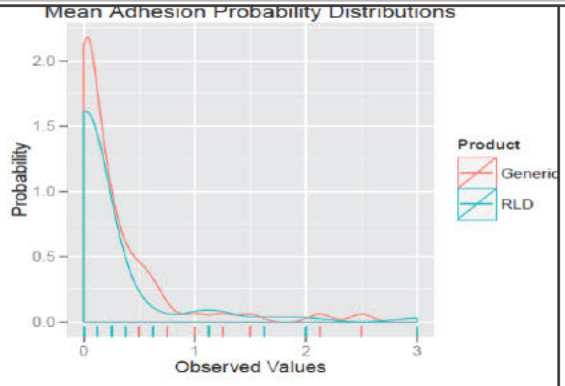
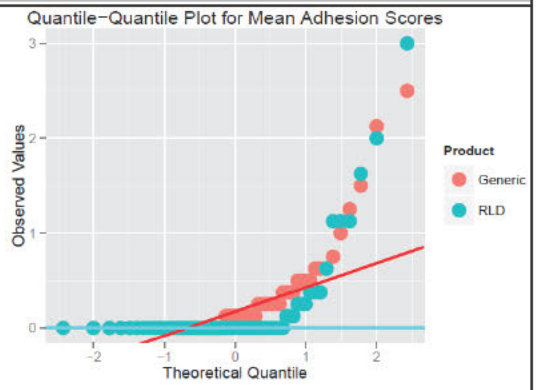
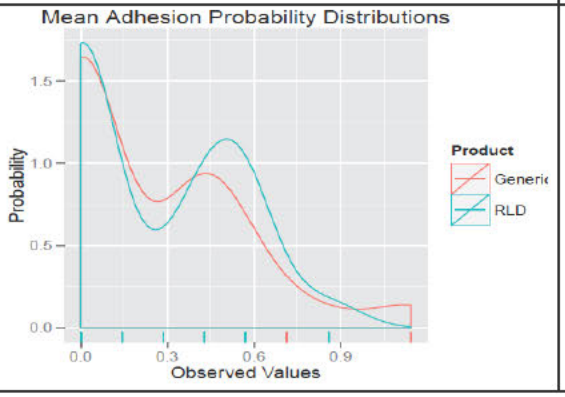
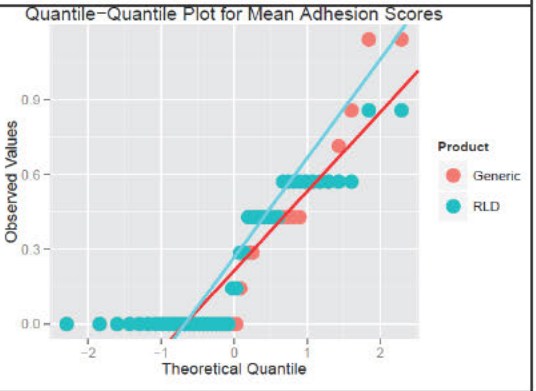
Drug Product	ANDA	RLD	Mean Adhesion Probability Distributions	Mean Adhesion Quantile- Quantile Plots
Norelgestromin/ Estradiol TDS	200910	21180		
[redacted] (b) (4)				
Estradiol TDS	201675	20538		

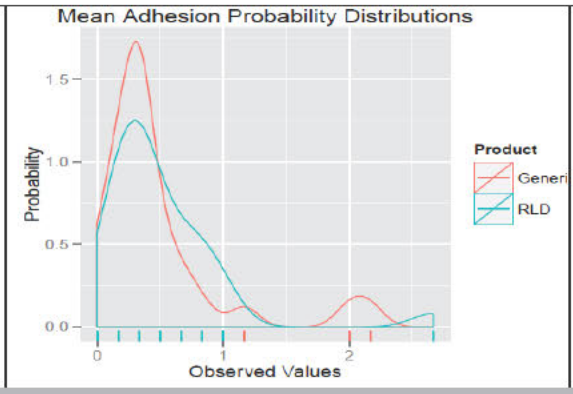
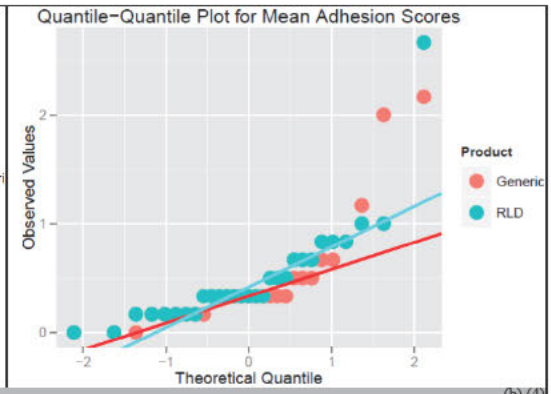
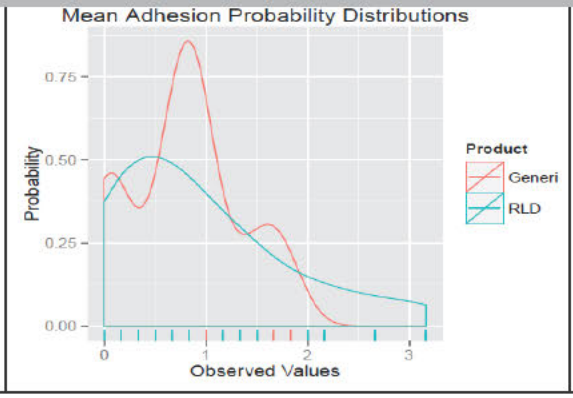
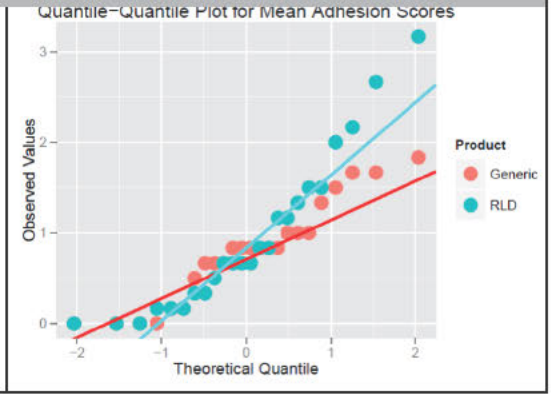
(b) (4)

Lidocaine	**200675**	**20612**		
Clonidine	**76157**	**18891**		

(b) (4)

(b) (4)

Clonidine TDS	**79090**	**18891**		
Fentanyl	**202097**	**19813**		

Scopolamine	**78830**	**17874**		
[redacted] (b) (4)				
Lidocaine	**202346**	**20612**		

It can be argued that, while using mixed model analysis is inappropriate when the distribution of mean adhesion values is non-normal, it is still possible for a generic product to pass NI testing if its level of adhesion is sufficiently better than the RLD being compared. As previously mentioned above, past innovator products often had worse adhesive properties compared to their generic counterparts, since generics would have access to current, more favorable adhesives that were not available to the innovator during product development. However, today's patch drug products often show highly adhering properties, leaving little room for generics to improve upon. Thus, a new methodology is required to handle highly adhering products where the extreme non-normal distribution of the mean adhesion values clearly invalidates using mixed model analysis to establish NI.

Identification of Criterion for Demonstrating High Adherence and Waiver for the Non-inferiority Statistical Test

Given that the current approval process for evaluating adhesion is not acceptable, a simple remedy for this problem would be to identify a criterion that the Agency would consider a measure of high adherence. Generic products that were found to either meet or exceed this criterion would be viewed as having a sufficiently high adhesion rate that the current FDA NI requirement could be waived.

In 2012, the EMA published their *Draft Guidance on Quality of Transdermal Patches*[2], which, in terms of adhesive product quality, states

> In general, a mean adherence of greater than 90% should be expected and no instances of detachment should be seen. Poor adherence events should be investigated and possible causes and risk factors determined.

In order to determine whether "≥ 90% adhesion" for a generic product is a sufficient condition to serve as the waiver criterion for high adherence, this condition must be interpreted under the current FDA scoring paradigm. Given that the FDA adhesion score of zero implies ≥ 90% adhesion, verifying "≥ 90% adhesion" for a given study could be accomplished by determining the percentage of patches having ≥ 90% adhesion at each measurement event throughout the study and taking the average of these percentages. If the average percentage was ≥ 90%, the Agency would view this product as having displayed sufficiently high adherence and the NI statistical analysis could be waived.

To illustrate the procedure, this analysis was performed with ANDA 201675, an estradiol containing transdermal patch sponsored by Mylan. The RLD for this drug product is Novartis's Vivelle-Dot®, approved on January 8, 1999 for the treatment of menopause-related symptoms and prevention of post-menopausal osteoporosis.[3] As seen previously

[2] EMA. Draft Guideline on Quality of Transdermal Patches. August 23, 2012. Last accessed December 16, 2013 via http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/09/WC500132404.pdf

[3] Drugs@FDA Drug Label for Vivelle-Dot (Estradiol) Transdermal System. Last accessed December 16, 2013 via http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020538s028s029s030lbl.pdf

in Table 2, both Mylan's product and the RLD are highly adhering, with zero score frequency close to 100%. When this approach is used to assess ANDA 201675, both the generic and RLD meet the claim of ≥ 90% adhesion (Table 4).

Table 4. Waiver Analysis for Mylan's Estradiol Patch (ANDA 201675) and the RLD

TEST (ANDA 201675)				REFERENCE (Vivelle-Dot ®)			
	Percentage of Patches with Score = 0		Average Adhesion Across Time Points		Percentage of Patches with Score = 0		Average Adhesion Across Time Points
T1	228 / 228	100.00%	98.46%	T1	228 / 228	100.00%	98.79%
T2	227 / 228	99.56%		T2	228 / 228	100.00%	
T3	224 / 228	98.25%		T3	227 / 228	99.56%	
T4	219 / 228	96.05%		T4	218 / 228	95.61%	

This approach was applied to the remaining 14 ANDAs to further gauge how this method would assess a range of adhesion data. Of the 15 ANDAs, 5 were found to meet the criterion (see Figure 1 and Table 5). In addition to a criterion of ≥ 90% of patches having ≥ 90% adhesion (referred to as 90/90), lower percentages for the average percentage were included in the analysis (80/90 and 75/90).

Figure 1. Waiver Analysis for All 15 ANDAs and Their Respective RLD

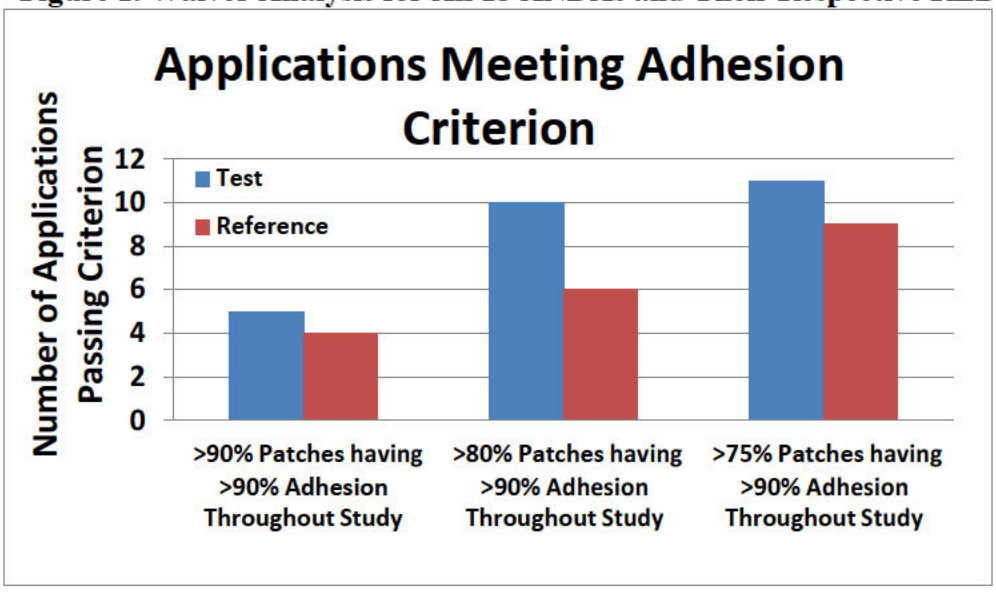


Table 5. Waiver Analysis for All 15 ANDAs and Their Respective RLD

ANDAs Passing 90/90 Criterion		Passed Non-Inferiority Testing: Ran by Statistician	Ran by B. Newman	RLD	RLD Passed 90/90
Norelgestromin/Estradiol TDS	200910	no	CNR*	21180	yes
(b) (4)					
Estradiol TDS	201675	no	no	20538	yes
(b) (4)					
Lidocaine	200675	yes	yes	20612	no
ANDAs Failing 90/90 Criterion		**Ran by Statistician**	**Ran by B. Newman**	**RLD**	**RLD Passed 90/90**
Clonidine	76157	yes	yes	18891	no
(b) (4)					
Clonidine TDS	79090	yes	yes	18891	no
Fentanyl	202097	no	no	19813	no
Scopolamine	78830	no	no	17874	no
(b) (4)					
Lidocaine	202346	yes	yes	20612	no

*CNR – Convergence Not Reached

ANDA 200910 (Norelgestromin/Ethinyl Estradiol TDS) was one of the 5 applications found to meet the 90/90 criterion. In the adhesion study that assessed NI between ANDA 200910 and the RLD, only a single adhesion score was nonzero (at one measurement event, the RLD had an adhesion score of 1). This is an extreme case where the adhesion profiles from both the generic and RLD display near perfect adhesion and mixed model analysis by the statistical reviewer found the generic inferior to the RLD. (b) (4) In this case the linear mixed model method failed to converge and no conclusion could be reached. In contrast, the 90/90 criterion can handle both these extreme cases.

It is also important to note that of the products failing to meet the 90/90 criterion, the majority passed the current FDA NI analysis.[5] Given that many of the quantile-quantile plots for these products were questionable in their degree of normality, additional work is

(b) (4)

[5] In cases where the statistical review was not available for the ANDA, Bryan Newman performed the non-inferiority test using mixed model analysis with standard SAS code provided in most statistical reviews. Non-inferiority analysis was also done for ANDAs where the statistical review was complete to ensure accuracy of the method.

needed to understand these differences and develop a statistical method that is appropriate for all types of adhesion data.

Effect of Sample Size on Meeting Adhesion Criterion

In addition to identifying an acceptable adhesion criterion, it is also necessary to determine the minimum number of subjects that, will provide the agency with the confidence that the study size is adequate to determine whether the product meets the Agency's measure of high adhesion.

In order to determine an acceptable minimum sample size, adhesion data from each of the 15 ANDA applications were bootstrapped using random sampling of subjects with replacement to generate 5 sets of 10,000 bootstrap samples. In each set, a sample size was selected from the following list: 20, 36, 40, 60, and 80 subjects. Using these five bootstrapped sets, the number of studies meeting the adhesion criterion was tabulated to observe the effects of sample size on passing the criterion. If the adhesion study data submitted with the original product application failed the waiver criterion, than any study from the bootstrap data that passed the criterion can be viewed as a false positive. Therefore, the minimum sample size should be the number that keeps the false positive rate below a defined limit (i.e. 10%). Results for products originally found to fail the 90/90 waiver criterion are shown in Figure 4 and Figure 5 below.

Figure 4. Effect of Sample Size on Percentage of Studies Passing for ANDAs that Originally Failed the 90/90 Adhesion Criterion Waiver

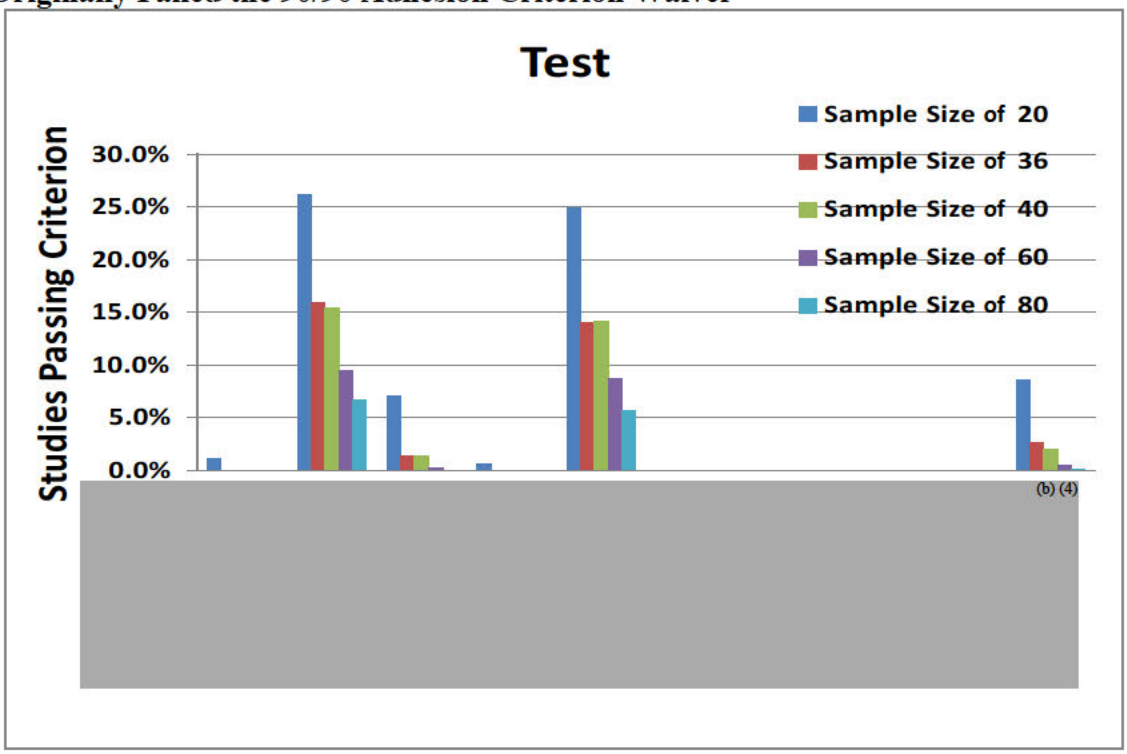
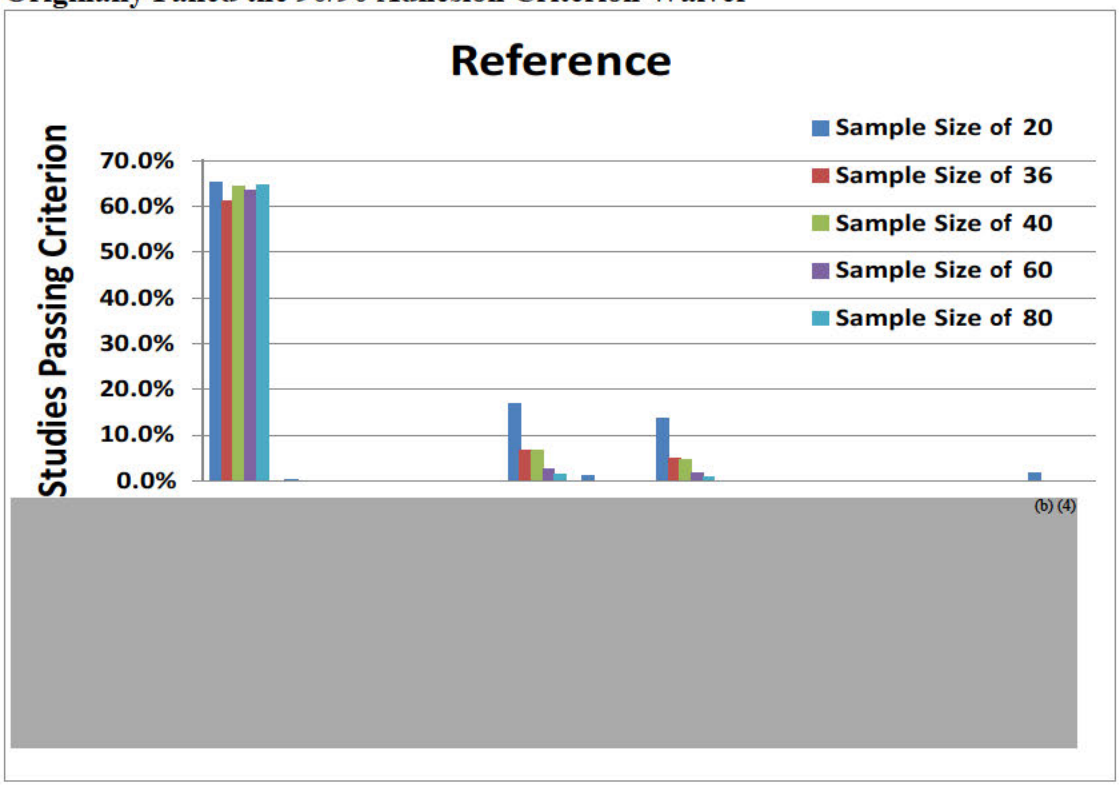


Figure 5. Effect of Sample Size on Percentage of Studies Passing for RLDs that Originally Failed the 90/90 Adhesion Criterion Waiver



Results for several of the applications showed that, regardless of the bootstrap sample size the adhesion scores were too high (indicating poor adhesion) to produce a passing study. The effect of sample size was more apparent for products whose original analyses were close to the waiver criterion. For Clonidine 076157, the test product showed 86% of patches had ≥ 90% adhesion for 90% of the study duration. As seen in the bootstrap analysis, decreasing the number of subjects in the study increased the percentage of passing studies (i.e. increasing the false positive rate). Studies consisting of 20 subjects showed a passing rate of slightly more than 25%. However, when 60 subjects were used the false positive rate fell below 10%. This trend was also seen with (b) (4) where a small sample size for the test product generated an unacceptable false positive rate (25%), while 60 subjects reduced the false positive rate to below 10%. Only the reference product used in (b) (4) had a false positive rate greater than 10%, regardless of sample size. The original adhesion study data for this product showed that 89% of the reference patches had ≥ 90% adhesion for 90% of the study duration. For cases such as these (where the product falls slightly below the waiver criterion, i.e., 89.0 to 89.9% average adhesion throughout the study duration), the product could be viewed as having met the waiver criterion if the study sample size is ≥ 60, and no instances of poor product adhesion (i.e. no full detachments / adhesion scores = 4) are reported. This decision would be left for the clinical reviewer. In conclusion, these results demonstrate that adhesion studies consisting of at least 60 subjects provide sufficient data

to determine whether high adhesion has been demonstrated and the statistical NI analysis can be waived.

Summary

Highly adhering patch drug products that meet or exceed the adhesion criterion of 90/90 (≥ 90% of patches having ≥ 90% adhesion throughout the entire study) should be permitted to waive the requirement of passing the NI statistical test, since meeting or exceeding these conditions is sufficient evidence for demonstrating high adhesion.

Additionally, for products to qualify for the adhesion statistical waiver, it is recommended that the adhesion studies contain a minimum of 60 subjects. This minimum subject number should provide the Agency with the confidence that the adhesion study is large enough to adequately determine whether a product meets the measure of high product quality. Lastly, it is important to note that the minimum sample size is solely for the qualification of the adhesion waiver, and not for studies using the FDA recommended method for establishing NI.

Reviewed By:

Bryan Newman, Ph.D. Date
Office of Generic Drugs, Science Staff
Center of Drug Research and Evaluation

Concurrence:

Robert Lionberger, Ph.D. Date
Acting Deputy Director for Science
Office of Generic Drugs
Center of Drug Research and Evaluation

APPENDIX

Appendix I: Details Regarding Linear Mixed Model Analysis and Assumptions

Application of a test and reference patch in an adhesion NI trial occurs simultaneously for each subject, with each subject's adhesion scores likely correlated. To handle these potential correlations, linear mixed model analysis is performed. An example of a linear mixed model is shown below in matrix notation:

$$\mathbf{Y} = \mathbf{X}\beta + \mathbf{Z}\gamma + \varepsilon$$

where Y is the vector of observations, X and Z are the design matrices for the fixed and random variables respectively, β is the vector of fixed effects parameters, γ is the vector of random effects parameters, and ε is the vector of the residuals. [6,7,8] The random effects portion of the mixed model is assumed to both assess and reflect the subject related correlations, while effects from the different treatments are handled in the fixed effects portion.

One of the key assumptions when using linear mixed models is that the random effects parameters γ and residuals ε from the data follow a normal (Gaussian) distribution with

$$\mathrm{E}\begin{bmatrix}\gamma\\ \epsilon\end{bmatrix} = \begin{bmatrix}0\\ 0\end{bmatrix}$$

$$\mathrm{Var}\begin{bmatrix}\gamma\\ \epsilon\end{bmatrix} = \begin{bmatrix}\mathbf{G} & 0\\ 0 & \mathbf{R}\end{bmatrix}$$

where G and R are the covariance matrices for the random effects parameters and residuals, respectively. [9] In order for the model to provide estimates for the fixed and random parameters, G and / or R must be estimated. Given a normally distributed γ and ε, a likelihood-based approach, such as the restricted maximum likelihood (REML) method, can be used to estimate G and R. [10,11,12,13,14]

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[6] Henderson, CR. Statistical Method in Animal Improvement:Historical Overview. *Advances in Statistical Methods for Genetic Improvement Livestock*.1990; 1-14, New York: Springer-Verlag.
[7] Searle, SR, Casella, G, McCulloch, CE. Variance Components. 1992: Wiley, New York.
[8] SAS 9.2 User's Guide – Second Edition. Mixed Model Theory. Last accessed December 16, 2013 via http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer htm#statug_mixed_sect022.htm
[9] SAS 9.2 User's Guide – Second Edition. Mixed Model Theory. Last accessed December 16, 2013 via http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer htm#statug_mixed_sect022.htm
[10] Harley, HO., Rao, JNK. Maximum likelihood estimation for the mixed analysis of variance model. *Biometrika*. 1967; 54: 93-108
[11] Patterson, HD., Thompson, R. Recovery of inter-block information when block sizes are unequal. *Biometrika*. 1971; 58:545-554
[12] Harville, DA. Maximum-likelihood approaches to variance component estimation and to related problems. *J Amer Statist Assoc*. 1977; 72:320-340
[13] Laird, NM., Ware, JH. Random-effects models of longitudinal data. *Biometrics*. 1982; 38(4):963-74
[14] Jennrich, RI., Schluchter, MD. Unbalanced repeated-measures models with structured covariance matrices. *Biometrics*. 1986; 42(4):805-820

Appendix II: ANDA Data Set

ANDA		RLD Reference	Source of Adhesion Data	File Name
Clonidine	076157	18891	Study 160-0609-01	Ad2.xpt
Clonidine	079090	18891	Study 10616246	Crosstab.xpt
(b) (4)				
Estradiol	201675	20538	Study EDOT-0908	0908adhes.xpt
Fentanyl	202097	19813	Study S09-0330	Adh.xpt
(b) (4)				
Lidocaine	200675	20612	Study R09-0723	A73.xpt
Lidocaine	202346	20612	Study Lido-1044	1044rawadhes.xpt
(b) (4)				
Norelgestromin/Estradiol	200910	21180	Study ORTH-09198	09198adadhes.xpt
(b) (4)				
Scopolamine	078830	17874	Study PRG-604	Adh31201.xpt

***Adhesion score frequency tabulated in Table 2 (pg. 6) used data from files listed above**

Appendix III: Frequency Data for each ANDA

*** Frequency data used in calculation of average percent adhesion used for 90/90 determination was taken from charts found in study reports or statistics reviews (if available)**

Clonidine	076157	18891	Study 160-0609-01	Ad2.xpt

Appendix B. Frequency table of Daily Adhesion Scores per Patch:

Adhesion Score / Evaluation Day		Score 0	1	2	3	4	Total Subjects with Score: Greater Or Equal 3	Equal 4
Day 2	Test	98	8	0	0	2	2	2
	Reference	93	14	1	0	0	0	0
Day 3	Test	98	6	1	1	2	3	2
	Reference	80	24	4	0	0	0	0
Day 4	Test	98	7	0	0	3	3	3
	Reference	73	31	3	0	1	1	1
Day 5	Test	93	9	2	0	4	4	4
	Reference	79	20	3	3	3	6	3
Day 6	Test	93	9	0	0	6	6	6
	Reference	75	23	3	2	5	7	5
Day 7	Test	85	11	2	2	8	10	8
	Reference	74	16	4	8	6	14	6
Day 8	Test	90	4	5	1	8	9	8
	Reference	76	11	5	1	15	16	15

A= Test Clonidine Patch B = Test Overlay
C =Reference Clonidine Patch D = Reference Overlay

TRT dylADH

Frequency Ro"" Pet	100	Total
A	68 100.00	68
B	68 100.00	68
C	68 100.00	68
D	68 100.00	68
Total	272	272

TRT dy2ADH

Frequency Row Pet	75	85	95	100	Total
A	0 0.00	0 0.00	4 5.97	63 94.03	67
B	1 1.49	0 0.00	2 2.99	64 95.52	67
C	0 0.00	1 1.49	4 5.97	62 92.54	67
D	0 0.00	1 1.49	2 2.99	64 95.52	67
Total	1	2	12	253	268

Frequency Missing = 4

TRT dy3ADH

Frequency Row Pet	0	85	95	100	Total
A	0 0.00	0 0.00	9 13.B	58 86.57	67
B	1 1.49	1 1.49	1 1. 9	64 95.52	67
C	2 2.99	2 2.99	9 13.B	54 80.60	67
D	1 1.49	1 1.49	0 0.00	65 97.01	67
Total	4	4	19	241	268

Frequency Missing = 4

TRT dy4ADH

Frequency Row Pct	0	75	85	95	100	Total
A	1 1.49	1 1.49	6 8.96	31 46.27	28 41.79	67
B	0 0.00	0 0.00	0 0.00	1 1.52	65 98.48	66
C	1 1.54	2 3.08	5 7.69	31 47.69	26 40.00	65
D	0 0.00	0 0.00	1 1.52	0 0.00	65 98.48	66
Total	2	3	12	63	184	264

Frequency Missing = 8

TRT dy5ADH

Frequency Row Pct	0	65	75	85	95	100	Total
A	1 1.54	0 0.00	2 3.08	9 13.85	38 58.46	15 23.08	65
B	1 1.54	2 3.08	0 0.00	1 1.54	0 0.00	61 93.85	65
C	1 1.59	0 0.00	2 3.17	12 19.05	39 61.90	9 14.29	63
D	2 3.08	0 0.00	0 0.00	1 1.54	1 1.54	61 93.85	65
Total	5	2	4	23	78	146	258

Frequency Missing = 14

TRT dy6ADH

Frequency Row Pet	0	35	45	55	75	85	95	100	Total
A	1 1.56	0 0.00	1 1.56	0 0.00	1 1.56	B 12.50	28 43.75	25 39.06	64
B	1 1.56	0 0.00	0 0.00	1 1.56	1 1.56	4 6.25	10 15.63	47 73.44	64
C	0 0.00	0 0.00	0 0.00	1 1.61	4 6.45	11 17.74	30 48.39	16 25.81	62
D	2 3.13	1 1.56	0 0.00	0 0.00	0 0.00	0 0.00	7 10.94	54 84.38	64
Total	4	1	1	2	6	23	75	142	254

Frequency Missing 18

TRT dy7ADH

Frequency Row Pet	0	15	25	35	45	75	85	95	D0	':eta:.
A	- 3.27	0 n.on	0 n nn	0 o.nn	1 1.h1	1 3.61	1G ?.C\ ■;	12 1 .1	31 o.o:1	
B	- 1.G:	1 1.61	0 0.00	1 1.61	0 0.00	1 1.61	4 G.!:;	12 13.3!:;	42 G7.74	52
C	3 4.92	0 0.00	1 1.64	0 0.00	1 1.64	4 6.56	16 26.23	10 15.39	25 42.62	51
D	- 1.6:	0 0.00	0 0.00	0 0.00	0 0.00	2 3.2;	3 4.84	10 15.13	45 74.B	52
Totnl	6	1	1	1	2	0	3)		HS	247

Frequencyissing 25

TRT dy8ADH

Frequency Row Pct	0	5	25	45	55	75	85	95	100	Total
A	1 1.61	0 0.00	0 0.00	2 3.23	0 0.00	5 8.06	23 37.10	21 33.87	10 16.13	62
B	3 4.76	0 0.00	1 1.59	0 0.00	1 1.59	2 3.17	5 7.94	16 25.40	35 55.56	63
C	2 3.39	1 1.69	0 0.00	1 1.69	2 3.39	6 10.17	27 45.76	18 30.51	2 3.39	59
D	1 1.59	0 0.00	0 0.00	0 0.00	0 0.00	1 1.59	6 9.52	17 26.98	38 60.32	63
Total	7	1	1	3	3	14	61	72	85	247

Frequency Missing = 25

(b) (4)

[redacted]

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Estradiol	201675	20538	Study EDOT-0908	0908adhes.xpt

Table 2: Frequency of adhesion scores (ADHPP)

Visit	Treatment	Adhesion score				
		0	1	2	3	4
2	Test	228	0	0	0	0
	Reference	228	0	0	0	0
3	Test	227	1	0	0	0
	Reference	228	0	0	0	0
4	Test	224	4	0	0	0
	Reference	227	1	0	0	0
5	Test	219	5	0	1	3
	Reference	218	6	1	1	2

Fentanyl	202097	19813	Study S09-0330	Adh.xpt

Table 12: Frequency of adhesion scores

Evaluation hours	Treatment	Adhesion score		
		0	1	2
0	Test	46		
	Reference	46		
12	Test	45	1	
	Reference	44	2	
24	Test	42	4	
	Reference	44	2	
36	Test	38	8	
	Reference	33	13	
48	Test	28	16	2
	Reference	27	19	
60	Test	25	19	2
	Reference	23	23	
72	Test	24	20	2
	Reference	23	23	

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Lidocaine	200675	20612	Study R09-0723	A73.xpt

Number (Percent) of Subjects for Evaluated Adhesion Score at Each Time Point (per sponsor)

Treatment	Score	Hour 0	Hour 2	Hour 4	Hour 6	Hour 8	Hour 10	Hour 12
A	0	50(100%)	50(100%)	50(100%)	50(100%)	47(94%)	38(76%)	35(70%)
A	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (6%)	8 (16%)	10 (20%)
A	2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (8%)	3 (6%)
A	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (4%)
A	4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
B	0	49 (98%)	49 (98%)	46 (92%)	39 (78%)	27(54%)	18(36%)	19(38%)
B	1	0 (0%)	0 (0%)	2 (4%)	6 (12%)	14(28%)	18(36%)	18(36%)
B	2	0 (0%)	0 (0%)	1 (2%)	2 (4%)	2 (4%)	6 (12%)	3 (6%)
B	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (6%)	2 (4%)	3 (6%)
B	4	1 (2%)	1 (2%)	1 (2%)	3 (6%)	4 (8%)	6 (12%)	7 (14%)

Treatment A: test
Treatment B: reference

Lidocaine	202346	20612	Study Lido-1044	1044rawadhes.xpt

Table 11: Frequency of adhesion scores (ADHFPP)

Evaluation hours	Treatment	Adhesion score				
		0	1	2	3	4
2	Test	16	8			
	Reference	23	1			
4	Test	11	12	1		
	Reference	19	4		1	
6	Test	9	12	3		
	Reference	9	11	2		2
8	Test	15	7	2		
	Reference	10	6	4	2	2
10	Test	14	7	3		
	Reference	7	8	5	1	3
12	Test	12	10	1	1	
	Reference	4	9	6	1	4

(b) (4)

Norelgestromin/Estradiol	200910	21180	Study ORTH-09198	09198adadhes.xpt

Adhesion Scores

Hours	Adhesion Score Evaluation Day		Score 0	1	2	3	4
24	Day 2	Test	38				
		Reference	38				
48	Day 3	Test	38				
		Reference	38				
72	Day 4	Test	38				
		Reference	38				
96	Day 5	Test	38	0			
		Reference *	37	1			
120	Day 6	Test	38				
		Reference	38				
144	Day 7	Test	38				
		Reference	38				
168	Day 8	Test	38				
		Reference	38				

*: Subject No 18 in the Reference product at visit 96 Hours

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Scopolamine	078830	17874	Study PRG-604	Adh31201.xpt

Table 11: Frequency of adhesion scores

Evaluation hours	Treatment	Adhesion score				
		0	1	2	3	4
12	Test	22	6		1	
	Reference	25	5			
24	Test	12	15	2		
	Reference	14	16			
36	Test	24	2	3		
	Reference	24	5			1
48	Test	18	9	2		
	Reference	12	15	2		1
60	Test	24	4		1	
	Reference	24	4	1		1*
72	Test	7	19	2	1	
	Reference	9	18	2		1*

*: Subjects, #3 reference patch fell off after Hour 48. A score 4 at Hour 48 was carried forward to Hour 60 and 72.

Clinical Consultation

Estradiol Transdermal System

Drug Product:	Estradiol Transdermal System (extended release film), USP 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice-Weekly)
Drug Class:	Estrogen derivative
Chemical Name:	Estra-1,3,5(10)-triene-3,17β-diol (b) (4) Estra-1,3,5(10)-triene-3,17-diol, (17β) (b) (4)
ANDA:	201675
ANDA Sponsor:	Mylan Technologies
Reference Listed Drug:	Vivelle-Dot® extended release film (NDA 020538, approved 1/8/99)
RLD Sponsor:	Novartis Pharmaceuticals Corporation
Reviewer:	Lolita A. Lopez, M.D., Medical Officer Division of Clinical Review, Office of Generic Drugs (OGD)
Secondary Reviewer:	James L. Osterhout, Ph.D. Division of Clinical Review, OGD
	John R. Peters, M.D., Director Division of Clinical Review, OGD
To:	Guohua Li Chemistry Division I
Reason for Consult:	CMC is requesting a Pharm/Tox Review for the Firm's Toxicology data to justify if the specifications for (b) (4) are acceptable in Estradiol Transdermal System. (b) (4) . DCR is requested to review the Firm's Safety Assessment for Residual (b) (4) in Estradiol TDS and provide comment if these levels are safe for human use.
Materials Reviewed:	1. ANDA 201675 SD15 submission (in DARRTS) dated 8/15/13 2. ANDA 201675 Complete Response letter to the sponsor dated 5/28/13 and sponsor's response dated 8/15/13 3. Various Pham/Tox Databases and Published Medical Literature 4. Chemistry Reviews for ANDAs 75182 & 75115, NDA 20538 5. DMF (b) (4) (Type IV) Review dated 1/12/2011 & 4/7/11
Date of Submission: **Date Consult Received:**	8/15/13 11/7/13
Date of Completion:	2/12/14
Conclusion:	Based on the review of available pharmacology and toxicity information for the residuals (b) (4) appears reasonably safe for human use under the prescribed use conditions. See details in our Recommendations below.

1 Executive Summary:

Chemistry Division I is requesting a Pharm/Tox Review for the Firm's Toxicology data to justify if the specifications for [redacted] are acceptable in the proposed Estradiol Transdermal System (TDS). [redacted] DCR is requested to review the Firm's Safety Assessment for residual [redacted] in Estradiol TDS and provide comment if these levels are safe for human use.

Mylan Pharmaceuticals, Inc. (sponsor) submitted ANDA 201675 on 04/26/2010 for a generic formulation of Vivelle-Dot® TDS (RLD) for twice weekly use. One of the components of the proposed product is [redacted] typically used in transdermal drug delivery systems. Mylan states each patch may contain up to [redacted] Considering the potential maximum concentration of the residual materials in the proposed product, the maximal daily exposure to these materials based upon a 3.5 day wear period and assuming 100% dermal absorption would be not more than [redacted]. For a 50 kg individual, these daily doses would be [redacted] Note that the RLD contains different adhesive system, [redacted] (Tables 5 and 6). Mylan was required to submit toxicology data or a justification as to why the limits for the [redacted] impurities, [redacted] should be considered acceptable.

Mylan provided a safety assessment and written qualification in support of specification limits for [redacted] in their proposed product, and information relevant to a safety evaluation of [redacted] which includes published toxicity data obtained from investigations in experimental animal models and also reports from workers occupationally exposed to [redacted] DCR also conducted a search of the various databases including Phar/Tox databases and published medical literature for safety-related information on [redacted] The FDA's inactive ingredient database and DARRTS were also searched for previously approved products that contain the inactive ingredient, [redacted]

2 Recommendation:

Based on the review of available data and safety information, the amount of the residuals, [redacted] appears reasonably safe for use in humans under the prescribed use conditions. [redacted] It has the same indication, mode of delivery, and intended population as the proposed product. DCR has is no reason to believe that the proposed product will be less safe than its RLD or Mylan's currently marketed Estradiol TDS once weekly use. Human irritation studies should demonstrate that the proposed product is not more irritating to the skin when compared to its RLD.

The maximal daily exposure to [redacted] based upon a 3.5 day wear period and assuming 100% dermal absorption would be [redacted] Based

[1] Sponsor's ANDA 201675 SD 15 submission dated 8/15/13 Mylan's response to FDA comment #3.

upon the available data, the specifications of an [redacted] in the proposed Estradiol TDS are reasonably justified.

3 Regulatory Background:

Estradiol Transdermal System (TDS), marketed under the brand name Vivelle-Dot®, was first approved on 1/08/1999 under NDA 020538 (sponsor Novartis). Vivelle-Dot® contains estradiol in a multipolymeric adhesive and is designed to release estradiol continuously upon application to intact skin. It is available in five dosage strengths for twice weekly use: 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day. To use, Estradiol TDS is placed on a clean, dry area of the trunk of the body including the abdomen or buttocks. Indications are for:

- Treatment of moderate to severe vasomotor symptoms associated with the menopause.
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.
- Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
- Prevention of postmenopausal osteoporosis.

On 4/26/2010, Mylan submitted Estradiol TDS under ANDA 201675 for a generic formulation of Vivelle-Dot® for twice weekly use in the following dosage strengths: 0.025 mg/day (2.5 cm^2), 0.0375 mg/day (3.75 cm^2), 0.05 mg/day (5 cm^2), 0.075 mg/day (7.5 cm^2), and 0.1 mg/day (10 cm^2). On 12/20/11, a correspondence was sent to the sponsor regarding chemistry comments on the minor deficiencies of the application. One of the deficiencies was to establish suitable acceptance criteria for the [redacted] impurities in the [redacted] in the final drug product specification (see letter entered in DARRTS). On 6/15/12, the sponsor amended their application and addressed FDA's comments on the above impurities and other issues, see ANDA 201675 SD11 submission entered in DARRTS). The Division of Chemistry consulted OND's Division of Reproductive and Urology Products[2] Pharm/Tox if the proposed limits of [redacted] were acceptable (Consult No: 2012-0724 entered in DARRTS). Below are the consult response comments, conclusion and recommendations by OND Pharm/Tox reviewer K. Raheja dated 12/3/12:

> **"Reviewer comments and conclusion:** Mylan proposed specifications of [redacted] in the Estradiol Transdermal System (Twice Weekly). No toxicity data for these impurities has been provided. Toxicity data needs to be submitted and reviewed before the proposed limits can be assessed.
>
> **Reviewer' recommendations:** Specification limits for [redacted] have been proposed. No toxicology data were submitted with the application. Please submit toxicity data or a justification as to why these limits should be considered acceptable."

On 5/28/13, the application received a Complete Response (CR) letter from OGD due to deficiencies regarding product quality, bioequivalence, and clinical issues (see Complete Letter entered in DARRTS). One of the deficiencies listed in the CR letter (under Product Quality A.3)

[2] Now Division of Reproductive and Urology Products (DBRUP)

was the necessity to submit toxicology data or a justification as to why the limits for [redacted] should be considered acceptable.

On 8/15/2013, the Mylan amended their application to address FDA's CR letter (ANDA 201675, SD 15 in DARRTS). The submission included toxicology data to justify the specifications for [redacted] in the finished product. Below is Mylan's response to FDA's comment #3.

> FDA COMMENT 3:
> The following deficiency is based on comments from initial consult to FDA's Pharmacology/Toxicology division: Please submit toxicology data or a justification as to why the limits for [redacted] should be considered acceptable.
>
> MYLAN RESPONSE 3:
> A complete Safety Assessment for Residual [redacted] in Estradiol Transdermal Systems is included in Section 3.3. This safety assessment supports the current limit of [redacted] in the finished product. In the case of [redacted] a Threshold of Toxicological Concern (TTC) based exposure level of [redacted] is applicable as a threshold considered to be associated with negligible risk (ICH 2013). Therefore, the level of residual [redacted] is being reduced from [redacted] The revised 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day.

On 11/7/13 the Chemistry Division consulted DCR to review the sponsor's safety assessment for residual [redacted] in the product, and to provide comment if these levels are safe for human use.

3.1 DARRTS Listings for This Product:

In DARRTS, there are currently 8 approved NDAs for Estradiol TDS (Table 1), and 5 approved and 5 pending ANDAs (Table 2); withdrawn ANDAs are not included. There are 22 commercial INDs (Table 3) listed for Estradiol TDS submitted to the Center for Drug Development and Research/Office of Drug Evaluation III/Division of Bone, Reproductive and Urologic Products (CDER/ODE III/DBRUP).

Table 1: DARRTS - List of NDAs for Estradiol Transdermal System

Application Type/No.	Product Name	Submitter	Dosage Form	Responsible Organization	Current Status	Status Date
NDA-020538	VIVELLE-DOT	NOVARTIS	FILM, CONTROLLED RELEASE	CDER/ODEIII/DBRUP	Approved	07/31/1996
NDA-021674	MENOSTAR ETS*	BAYER	PATCH, CONTROLLED RELEASE	CDER/ODEIII/DBRUP	Approved	06/08/2004
NDA-021167	VIVELLE ETS*	NOVARTIS	PATCH, CONTROLLED RELEASE	CDER/ODEIII/DBRUP	Approved	08/16/2000
[redacted]						

Application Type/No.	Product Name	Submitter	Dosage Form	Responsible Organization	Current Status	Status Date
	[redacted] (b) (4)					
NDA-021310	ALORA ETS*	WATSON	PATCH, CONTROLLED RELEASE	CDER/ODEIII/DBRUP	Approved	04/05/2002
NDA-020375	CLIMARA	BAYER	FILM, CONTROLLED RELEASE	CDER/ODEIII/DBRUP	Approved	12/22/1994
NDA-021048	ETS* (E2 III TS)	ORTHO MCNEIL	FILM, CONTROLLED RELEASE	CDER/ODEIII/DBRUP	Withdrawn FR Effective	09/13/2000
NDA-203752	Minivelle (estradiol)	NOVEN	FILM	CDER/ODEIII/DBRUP	Approved	10/29/2012

* ETS-Estradiol Transdermal System

Source: CDER's Document Archiving, Reporting & Regulatory Tracking System (DARRTS), NDA application search, keyword Estradiol Transdermal System, 1/14/2014

Table 2: DARRTS – List of ANDA Estradiol Transdermal System

Application Type/Number	Product Name	Submitter	Dosage Form	Responsible Organization	Current Status	Status Date
ANDA-075233	ESTRADIOL	MYLAN	FILM, CONTROLLED RELEASE	CDER/OGD	Approved	02/24/2000
ANDA-090719	LEVONORGESTREL; ETHINYL ESTRADIOL	NOVAST	TABLET, FILM COATED	CDER/OGD	Approved	12/29/2010
ANDA-091440	LEVONORGESTREL; ETHINYL ESTRADIOL	LUPIN LTD	TABLET, FILM COATED	CDER/OGD	Approved	10/23/2012
ANDA-091105	NORGESTREL; ETHINYL ESTRADIOL	NOVAST	TABLET (IMMED./COMP. RELEASE), FILM COATED	CDER/OGD	Approved	03/28/2012
ANDA-075182	ESTRADIOL	MYLAN	FILM, CONTROLLED RELEASE	CDER/OGD	Approved	02/24/2000
ANDA-090716	LEVONORGESTREL; ETHINYL ESTRADIOL	NOVAST	TABLET (IMMED./COMP. RELEASE), FILM COATED	CDER/OGD	Complete Response	12/13/2013
[redacted] (b) (4)						
ANDA-200910	ETHINYL ESTRADIOL; NORELGESTROMIN	MYLAN	FILM, CONTROLLED RELEASE	CDER/OGD	Pending	08/21/2013
[redacted] (b) (4)						

CDER/OGD- Center for Drug Development and Research/Office of Generic Drugs

Source: CDER's Document Archiving, Reporting & Regulatory Tracking System (DARRTS), ANDA application search, keyword Estradiol Transdermal System, 1/24/2014

3.2 Current Guidances/Draft Guidances:

There are three Draft Guidances[3] listed for Estradiol TDS, Extended Release published on November 2010. One of the draft guidances is for Estradiol TDS worn for 7 days and two are for those worn every 3.5 days, the latter are listed below.

(1) Estradiol TDS 0.1 mg/24 hr and 0.025 mg/24 hr

Active ingredient: Estradiol
Form/Route: Film, Extended Release/Transdermal
Recommended studies: 2 studies

1. Type of study: Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints and Adhesion Study
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.1 mg/24 hr
   Subjects: Healthy, non-smoking, postmenopausal women with no contraindication to estrogen therapy
   Additional comments:
   - The transdermal patch should be applied to clean, dry, intact, healthy skin on the lower abdomen below the waistline, as recommended in the approved reference listed drug (RLD) labeling, and worn for 3.5 days (84 hours).
   - An average baseline correction is obtained by averaging the 3 pre-application sampling times (-48, -24 and 0 hours).
   - A washout period of 7 days after removal of the Estradiol transdermal patch is recommended.
   - Observations and rating of skin adhesion should be documented during this study.
2. Type of study: Skin Irritation, Sensitization and Adhesion
   Study Design: Randomized, evaluator-blinded, in vivo within-subject repeat test
   Strength: 0.025 mg/24 hr
   Subjects: Healthy, non-smoking, postmenopausal women with no contraindication to estrogen therapy
   Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Estradiol in plasma (PK study only)
Bioequivalence based on (90% CI): Estradiol, using both baseline corrected and uncorrected data (PK study only)
Waiver request of in vivo testing: 0.05 mg/24 hr may be considered for a waiver of in vivo bioequivalence testing based on (1) acceptable bioequivalence studies on the 0.1 mg/24 hr strength, (2) acceptable dissolution testing of both strengths, and (3) proportional similarity in the formulations.
Dissolution test method and sampling times:
Please note that a Dissolution Methods Database is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

In addition to the method above, for transdermal systems, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatuses for transdermal systems in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary.

[3] Bioequivalence Recommendations for Specific Products: Draft Guidances for Estradiol Transdermal Film, Extended Release http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081318 htm, accessed 1/21/2014.

Please include early sampling times of 0.5, 1, 2, and 4 hours and continue every 2 hours until 24 hours and until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Additional comments regarding the skin irritation, sensitization and adhesion study: see Draft Guidance for a complete list 40 comments.

(2) Estradiol TDS 0.1 mg/24 hr and 0.05 mg/24 hr

Active ingredient: Estradiol
Form/Route: Film, Extended Release/Transdermal
Recommended studies: 2 studies

1. Type of study: Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints and Adhesion Study
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.1 mg/24 hr
   Subjects: Healthy, non-smoking, postmenopausal women with no contraindication to estrogen therapy
   Additional comments:
   - The transdermal patch should be applied to clean, dry, intact, healthy skin on the lower abdomen below the waistline, as recommended in the approved reference listed drug (RLD) labeling, and worn for 3.5 days (84 hours).
   - An average baseline correction is obtained by averaging the 3 pre-application sampling times (-48, -24 and 0 hours).
   - A washout period of 7 days after removal of the Estradiol transdermal patch is recommended.
   - Observations and rating of skin adhesion should be documented during this study.
2. Type of study: Skin Irritation, Sensitization and Adhesion Study
   Design: Randomized, evaluator-blinded, in vivo within-subject repeat test
   Strength: 0.05 mg/24 hr
   Subjects: Healthy, non-smoking, postmenopausal women with no contraindication to estrogen therapy
   Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Estradiol in plasma (PK study only)
Bioequivalence based on (90% CI): Estradiol, using both baseline corrected and uncorrected data (PK study only)
Waiver request of in vivo testing: 0.05 mg/24 hr may be considered for a waiver of in vivo bioequivalence testing based on (1) acceptable bioequivalence studies on the 0.1 mg/24 hr strength, (2) acceptable dissolution testing of both strengths, and (3) proportional similarity in the formulations.
Dissolution test method and sampling times:
Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

In addition to the method above, for transdermal systems, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatuses for transdermal systems in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 0.5, 1, 2, and 4 hours and continue every 2 hours until 24 hours

and until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Additional comments regarding the skin irritation, sensitization and adhesion study: *see Draft Guidance for a complete list 40 comments.*

3.3 Orange Book:

In the Orange book, there are currently 30 marketed prescription entries for single ingredient Estradiol Transdermal System (Table 3); there are five entries under the proprietary name Vivelle-Dot (sponsor: Novartis). There are no unexpired exclusivity or patents for the RLD listed as of 1/16/2014 in the Orange Book database for each of the approved Estradiol TDS (Table 3).

Table 4: Orange Book - Currently Marketed Rx Entries for Estradiol Transdermal System

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N203752		No	ESTRADIOL	FILM, ER*; TRANSDERMAL	0.0375MG/24HR	MINIVELLE	NOVEN
N203752		No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.05MG/24HR	MINIVELLE	NOVEN
N203752		No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.075MG/24HR	MINIVELLE	NOVEN
N203752		Yes	ESTRADIOL	FILM, ER; TRANSDERMAL	0.1MG/24HR	MINIVELLE	NOVEN
N021674		Yes	ESTRADIOL	FILM, ER; TRANSDERMAL	0.014MG/24HR	MENOSTAR	BAYER
N020655	BX	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.025MG/24HR	ALORA	WATSON LABS
N020655	BX	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.05MG/24HR	ALORA	WATSON LABS
N020655	BX	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.075MG/24HR	ALORA	WATSON LABS
N020655	BX	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.1MG/24HR	ALORA	WATSON LABS
N020538	BX	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.025MG/24HR	VIVELLE-DOT	NOVARTIS
N020538	BX	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.0375MG/24HR	VIVELLE-DOT	NOVARTIS
N020538	AB1	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.05MG/24HR	VIVELLE-DOT	NOVARTIS
N020538	BX	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.075MG/24HR	VIVELLE-DOT	NOVARTIS
N020538	AB1	Yes	ESTRADIOL	FILM, ER; TRANSDERMAL	0.1MG/24HR	VIVELLE-DOT	NOVARTIS
N020375	AB2	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.025MG/24HR	CLIMARA	BAYER HLTHCARE
N020375	AB	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.0375MG/24HR	CLIMARA	BAYER HLTHCARE

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N020375	AB2	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.05MG/24HR	CLIMARA	BAYER HLTHCARE
N020375	AB	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.06MG/24HR	CLIMARA	BAYER HLTHCARE
N020375	AB2	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.075MG/24HR	CLIMARA	BAYER HLTHCARE
N020375	AB2	Yes	ESTRADIOL	FILM, ER; TRANSDERMAL	0.1MG/24HR	CLIMARA	BAYER HLTHCARE
N020323	AB1	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.05MG/24HR	VIVELLE	NOVARTIS
N020323	AB1	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.1MG/24HR	VIVELLE	NOVARTIS
N019081	BX	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.05MG/24HR	ESTRADERM	NOVARTIS
N019081	BX	Yes	ESTRADIOL	FILM, ER; TRANSDERMAL	0.1MG/24HR	ESTRADERM	NOVARTIS
A075182	AB2	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.025MG/24HR	ESTRADIOL	MYLAN
A075182	AB	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.0375MG/24HR	ESTRADIOL	MYLAN
A075182	AB2	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.05MG/24HR	ESTRADIOL	MYLAN
A075182	AB	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.06MG/24HR	ESTRADIOL	MYLAN
A075182	AB2	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.075MG/24HR	ESTRADIOL	MYLAN
A075182	AB2	No	ESTRADIOL	FILM, ER; TRANSDERMAL	0.1MG/24HR	ESTRADIOL	MYLAN

ER-Extended Release

Source: Orange Book Online (http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm) reviewer search for Estradiol Transdermal System, 1/16/2014.

3.4 RLD Formulation:

The RLD, Vivelle-Dot is supplied in five dosage strengths: 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day. Below is a tabulated component and composition of the RLD.

Table 5: Component and Composition of the RLD (Vivelle-Dot®)

RLD	mg per system				
Ingredient	0.025mg/day	0.0375mg/day	0.05mg/day	0.075mg/day	0.1mg/day
Estradiol (b) (4)	0.390	0.585	0.780	1.17	1.56
(b) (4) acrylic adhesive (b) (4)	(b) (4)				
(b) (4) silicone					
Oleyl alcohol					
Dipropylene glycol					
Povidone, USP					
(b) (4)					
(b) (4)					

Source: CMC review by Xihao Li, Ph.D., ANDA 201-675 p.41 entered in DARRTS on 2/25/13.

Table 6: Composition and Pharmaceutical Function of Adhesive Matrix Components of Mylan's Estradiol Transdermal System (Twice-Weekly)

Components	Pharmaceutical Function	% w/w	mg per system				
			0.025 mg/ day	0.0375 mg/ day	0.05 mg/ day	0.075 mg/ day	0.1 mg/ day
Active Ingredient							
Estradiol (b) (4) USP, (b) (4)	Active Ingredient	(b) (4)	0.41	0.62	0.82	1.23	1.64
Inactive Ingredients							
Oleyl Alcohol, (b) (4) (b) (4)	(b) (4)						
Dipropylene Glycol (b) (4)							
Povidone (b) (4) (b) (4)							
Silicone Adhesive (b) (4)	Adhesive	(b) (4)					
Acrylic Adhesive (b) (4)	Adhesive						
(b) (4)	(b) (4)						
Theoretical Total Matrix[5]		(b) (4)					
Components of the Delivery and Packaging System							
Polyolefin Film (b) (4)	Backing	(b) (4)					
Brown Ink (b) (4)	Imprinting Ink						
(b) (4) Polyester Film (b) (4)	Oversized Release Liner						

Source: CMC review by Xihao Li, Ph.D., ANDA 201-675 p.40 entered in DARRTS on 2/25/13.

Reviewer Comment: *The proposed product is also in a film extended release transdermal system formulation that will be supplied in the same (5) dosage strengths as the RLD. According to the CMC Review by Xihao Li, Ph.D entered in DARRTS on 12/20/11 and 2/25/13, the ANDA products have the same sizes as the RLD. The component, composition and excipients of the ANDA are similar to that of the RLD.* (b) (4)

4 Label:

The current product label for the RLD Vivelle-Dot was approved on 5/20/2013 (NDA 020538/S-028, S-029, S-030). There is a black box warning for this product regarding increased risk of endometrial cancer, cardiovascular disorders, probable dementia and breast cancer.

Most of the information provided in this section is taken from the latest approved RLD label; see label for the full prescribing information and details.

4.1 Indications:

Estradiol Transdermal System is indicated for the:

- Treatment of moderate to severe vasomotor symptoms due to menopause.
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
- Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
- Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

  The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg per day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400 to 800 IU per day may also be required to ensure adequate daily intake in postmenopausal women.

4.2 Usual dosage:

See section 4.2 and 4.5.

4.3 Maximum dose:

See section 4.2 and 4.5.

4.4 Initial dosage:

Patients should be started at the lowest dose. The lowest effective dose of Vivelle-Dot has not been determined for any indication.

- For treatment of moderate to severe vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, start therapy with Vivelle-Dot 0.0375 mg per day applied to the skin twice weekly.
- For the prevention of postmenopausal osteoporosis, start therapy with Vivelle-Dot 0.025 mg per day applied to the skin twice weekly.

The dosage may be adjusted as necessary. Reproductive system-associated adverse events were encountered more frequently in the highest dose group (0.1 mg per day) than in other active treatment groups or in placebo-treated patients.

In women not currently taking oral estrogens or in women switching from another estradiol transdermal therapy, treatment with Vivelle-Dot may be initiated at once. In women who are currently taking oral estrogens, treatment with Vivelle-Dot should be initiated 1 week after withdrawal of oral hormone therapy, or sooner if menopausal symptoms reappear in less than 1 week.

4.5 Maintenance dosage:

Vivelle-Dot may be given continuously in patients who do not have an intact uterus. In those patients with an intact uterus, Vivelle-Dot may be given on a cyclic schedule (for example, 3 weeks on drug followed by 1 week off drug).

4.6 Contraindications:

Vivelle-Dot is contraindicated in women with any of the following conditions:

1) Undiagnosed abnormal genital bleeding.
2) Known, suspected or history of breast cancer.
3) Known or suspected estrogen-dependent neoplasia.
4) Active DVT, PE, or a history of these conditions.
5) Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions
6) Known anaphylactic reaction or angioedema or hypersensitivity to Vivelle-Dot.
7) Liver impairment or disease.
8) Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.
9) Known or suspected pregnancy.

4.7 Significant Warnings and Precautions:

BOXED WARNING
The following information is listed in the boxed warning for Vivelle-Dot:

Estrogen-Alone Therapy

Endometrial Cancer:
There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Cardiovascular Disorders and Probable Dementia:
Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or Dementia.

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia:
Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia.

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo.

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

Breast Cancer:
The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast

cancer.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE plus MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

WARNINGS
The following are additional warnings listed in the label:

1) Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.
Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 womenyears). The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

b. Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on CHD events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo.

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women less than 10 years since menopause (8 versus 16 per 10,000 women-years).

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased

risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5.

In postmenopausal women with documented heart disease (n = 2,763, average 66.7 years of age), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open-label extension of HERS, HERS II. Average followup in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in the HERS, the HERS II, and overall.

c. Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 womenyears), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women years). The increase in VTE risk was demonstrated during the first 2 years. Should a VTE occur or be suspected, estrogen-alone should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. (See CLINICAL STUDIES.) Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2) Malignant Neoplasms

a. Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is

discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogenalone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg)-alone was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80).

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA.

In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 per cent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA 92.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade, and hormone receptor status did not differ between the groups.

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In

addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

c. Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies and some report no association.

3) Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo. After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years.

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women aged 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women.

4) Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5) Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6) Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

7) Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

PRECAUTIONS

The following are listed General precautions in the label:

1. Addition of a progestin when a woman has not had a hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

2. Elevated blood pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

3. Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

4. Hepatic impairment and/or past history of cholestatic jaundice

Although transdermally administered estrogen therapy avoids first-pass hepatic metabolism, estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

5. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be

influenced by this factor, such as cardiac or renal impairment, warrant careful observation when estrogen-alone is prescribed.

7. Hypocalcemia
   Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen induced hypocalcemia may occur.

8. Exacerbation of endometriosis
   A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

9. Exacerbation of other conditions
   Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraines, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

4.8 Adverse Reactions:

Table 7 is a list the most commonly reported adverse reactions reported with Vivelle-Dot therapy during clinical trials.

Table 7: Summary of Most Frequently Reported AEs/Medical Events Regardless of Relationship Reported at a Frequency ≥5%

	Vivelle 0.025 mg/day† (N=47) N (%)	Vivelle 0.0375 mg/day† (N=130) N (%)	Vivelle 0.05 mg/day† (N=103) N (%)	Vivelle 0.075 mg/day† (N=46) N (%)	Vivelle 0.1 mg/day† (N=132) N (%)	Placebo (N=157) N (%)
Gastrointestinal disorders						
Constipation	2 (4.3)	5 (3.8)	4 (3.9)	3 (6.5)	2 (1.5)	4 (2.5)
Dyspepsia	4 (8.5)	12 (9.2)	3 (2.9)	2 (4.3)	0	10 (6.4)
Nausea	2 (4.3)	8 (6.2)	4 (3.9)	0	7 (5.3)	5 (3.2)
General disorders and administration site conditions* **						
Influenza-like illness	3 (6.4)	6 (4.6)	8 (7.8)	0	3 (2.3)	10 (6.4)
Pain NOS*	0	8 (6.2)	0	2 (4.3)	7 (5.3)	7 (4.5)
Infections and infestations						
Influenza	4 (8.5)	4 (3.1)	6 (5.8)	0	10 (7.6)	14 (8.9)
Nasopharyngitis	3 (6.4)	16 (12.3)	10 (9.7)	9 (19.6)	11 (8.3)	24 (15.3)
Sinusitis NOS*	4 (8.5)	17 (13.1)	13 (12.6)	3 (6.5)	7 (5.3)	16 (10.2)
Upper respiratory tract infection NOS*	3 (6.4)	8 (6.2)	11 (10.7)	4 (8.7)	6 (4.5)	9 (5.7)
Investigations						
Weight increased	4 (8.5)	5 (3.8)	2 (1.9)	2 (4.3)	0	3 (1.9)
Musculoskeletal and connective tissue disorders						
Arthralgia	0	11 (8.5)	4 (3.9)	2 (4.3)	5 (3.8)	9 (5.7)
Back pain	4 (8.5)	10 (7.7)	9 (8.7)	4 (8.7)	14 (10.6)	10 (6.4)
Neck pain	3 (6.4)	4 (3.1)	4 (3.9)	0	6 (4.5)	2 (1.3)
Pain in limb	0	10 (7.7)	7 (6.8)	2 (4.3)	6 (4.5)	9 (5.7)
Nervous system disorders						
Headache NOS*	7 (14.9)	35 (26.9)	32 (31.1)	23 (50.0)	34 (25.8)	37 (23.6)
Sinus headache	0	12 (9.2)	5 (4.9)	5 (10.9)	2 (1.5)	8 (5.1)
Psychiatric disorders						
Anxiety NEC**	3 (6.4)	5 (3.8)	0	0	2 (1.5)	4 (2.5)
Depression	5 (10.6)	4 (3.1)	7 (6.8)	0	4 (3.0)	6 (3.8)
Insomnia	3 (6.4)	6 (4.6)	4 (3.9)	2 (4.3)	2 (1.5)	9 (5.7)
Reproductive system and breast disorders						
Breast tenderness	8 (17.0)	10 (7.7)	8 (7.8)	3 (6.5)	17 (12.9)	0
Dysmenorrhea	0	0	0	3 (6.5)	0	0
Intermenstrual bleeding	3 (6.4)	9 (6.9)	6 (5.8)	0	14 (10.6)	7 (4.5)
Respiratory, thoracic and mediastinal disorders						
Sinus congestion	0	4 (3.1)	3 (2.9)	3 (6.5)	6 (4.5)	7 (4.5)
Vascular disorders						
Hot flushes NOS*	3 (6.4)	0	3 (2.9)	0	0	6 (3.8)
Hypertension NOS*	2 (4.3)	0	3 (2.9)	0	0	2 (1.3)

† Represents milligrams of estradiol delivered daily by each system
* NOS represents not otherwise specified
** NEC represents not elsewhere classified
*** Application site erythema and application site irritation were observed in a small number of patients (3.2% or less of patients across treatment groups.)

4.9 Drug Interactions:

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's wort (Hypericum perforatum) preparations, phenobarbital, carbamazepine and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

4.10 Pregnancy Category:

Vivelle-Dot is contraindicated in women known or suspected pregnant (see section 4.6), and should not be used during pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

4.11 Off-Label Uses:

Off-label use of estradiol products including Vivelle-Dot are gender identity disorder (male-to-female transsexual), menstrual migraine, mental distress, postpartum depression, and urinary tract infectious disease (prophylaxis)[4]

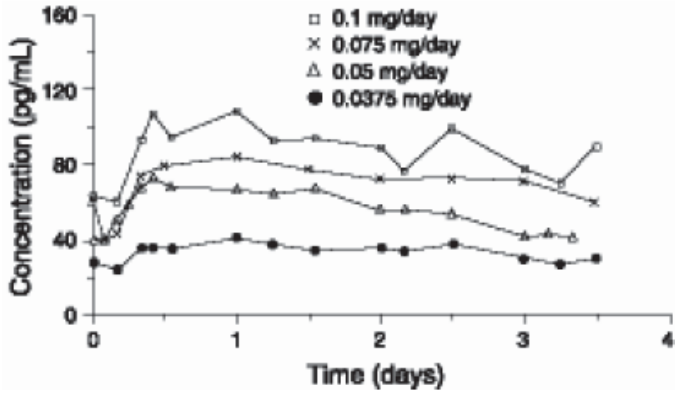
4.12 Pharmacokinetics:

Absorption
In a multiple-dose study consisting of three consecutive system applications of the original formulation [Vivelle (estradiol transdermal system)] which was conducted in 17 healthy, postmenopausal women, blood levels of estradiol and estrone were compared following application of these units to sites on the abdomen and buttocks in a crossover fashion. Systems that deliver nominal estradiol doses of approximately 0.0375 mg per day and 0.1 mg per day were applied to abdominal application sites while the 0.1 mg per day doses were also applied to sites on the buttocks. These systems increased estradiol levels above baseline within 4 hours and maintained respective mean levels of 25 and 79 pg/mL above baseline following application to the abdomen; slightly higher mean levels of 88 pg/mL above baseline were observed following application to the buttocks. At the same time, increases in estrone plasma concentrations averaged about 12 and 50 pg/mL, respectively, following application to the abdomen and 61 pg/mL for the buttocks. While plasma concentrations of estradiol and estrone remained slightly above baseline at 12 hours following removal of the systems in this study, results from another study show these levels to return to baseline values within 24 hours following removal of the systems.

[4] Micromedex Online: http://www micromedexsolutions.com/micromedex2/librarian search term Vivelle-dot/estradiol, accessed 1/17/2014.

Figure 1 illustrates the mean plasma concentrations of estradiol at steady-state during application of these patches at four different dosages.

Figure 1: Steady-State Estradiol Plasma Concentrations for Systems Applied to the Abdomen
Nonbaseline-corrected Levels



Vivelle-Dot (estradiol transdermal system), the revised formulation with smaller system sizes, was shown to be bioequivalent to the original formulation, Vivelle (estradiol transdermal system), used in the clinical trials.

Distribution
No specific investigation of the tissue distribution of estradiol absorbed from Vivelle-Dot in humans has been conducted. The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone-binding globulin (SHBG) and albumin.

Metabolism
Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver by Cytochrome 450 isoforms CYPIA2 and CYP3A4. Estradiol undergoes further metabolism to sulfate and glucuronide conjugates. Estradiol and its metabolites are glucuronidated by UGT1A1 and UGT2B7. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion
Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The half-life values calculated after dosing with the Vivelle-Dot ranged from 5.9 to 7.7 hours. After removal of the transdermal systems, serum concentrations of estradiol and estrone returned to baseline levels within 24 hours.

4.13 Mechanism of Action:

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

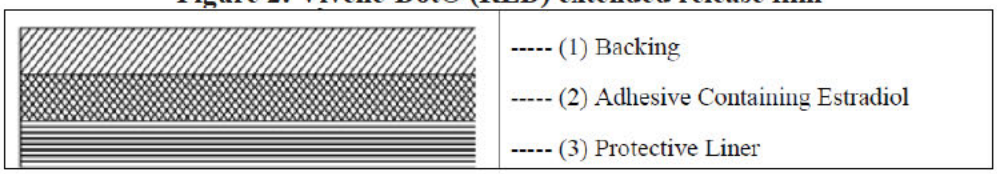
Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

5 Discussion:

The RLD, Vivelle-Dot® TDS (patch) contains estradiol in a multipolymeric adhesive designed to release estradiol continuously upon application to intact skin. This extended release film is comprised of three layers (Figure 2); proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin film (2) an adhesive formulation containing estradiol, acrylic adhesive, silicone adhesive, oleyl alcohol, NF, povidone, USP and dipropylene glycol, and (3) a polyester release liner which is attached to the adhesive surface and must be removed before the system can be used. The active component of the system is estradiol, and the remaining components of the system are pharmacologically inactive.

Figure 2: Vivelle-Dot® (RLD) extended release film



Mylan (sponsor) is proposing to market an Estradiol TDS designed to be the therapeutic equivalent of Novartis' Vivelle-Dot® TDS for twice weekly use. One of the components of the proposed transdermal drug delivery system is (b) (4) typically used in transdermal drug delivery systems. (b) (4) .

Reviewer Comment:As mentioned earlier in this review, note that the (b) (4) used in the RLD is listed as (b) (4) while that of the ANDA is (b) (4) See Tables 5 and 6.

A DMF (b) (4) review for (b) (4) by C. Strasinger, Ph.D. [6] stated:

[5] Sponsor's ANDA 201675 SD 15 submission dated 8/15/13 Mylan's response to FDA comment #3.
[6] DMF (b) (4) (Type IV) Review by C. Strasinger, Ph.D. entered in DARRTS on 1/12/2011.

- [redacted] The level of by-product remaining in the [redacted] will depend on the conditions of use. The actual levels can only be determined by the drug product manufacturer, as drying temperatures, oven air flow, line speed, coating thickness and formulation details will affect final ppm levels.
- [redacted] is classified as a primary irritant and mutagen; however there is no toxicological data on long term dermal exposure to [redacted] is found in many foods, human serum and as a contaminant in food, pharmaceutical and cosmetic preservatives. The boiling point of [redacted] remaining in a transdermal patch would be dependant on conditions of use including, [redacted] drying temperature, oven air flow, line speed, coating thickness and formulation details.

As mentioned in section 3 of this review, in the ANDA CR letter sent to the sponsor (Mylan) on 5/28/13, one of the deficiencies listed (under Product Quality A.3) was the need to submit toxicology data or a justification as to why the limits for the [redacted] impurities, [redacted] should be considered acceptable.

In a submission dated 8/15/13, Mylan explained that although these residual materials are observed in the [redacted], [redacted] of the Estradiol Transdermal System [redacted]. Mylan provided information relevant to the safety evaluation of [redacted] that included published toxicity, genotoxicity, and carcinogenicity data obtained from investigations in experimental animal models, and reports from workers occupationally exposed to [redacted]

[redacted]

[redacted]

[7] Pohanish, Richard P. (2008). Sittig's Handbook of Toxic and Hazardous Chemicals and Carcinogens [redacted]. William Andrew Publishing. Online version: http://app.knovel.com/hotlink/toc/id:kpSHTHCC07/sittigs-handbook-toxic, accessed 1/31/14

[redacted]

[redacted] is reported to cause adverse effects following exposure via inhalation, ingestion, dermal or eye contact. [redacted] Short-term exposure may cause headache, sensation of pressure in the head, dizziness, nausea, vomiting, peculiar taste, respiratory distress, fatigue, convulsions, and unconsciousness. [10,11]

Reviewer Comment: *A search of the FDA's inactive ingredient database[12] for [redacted] did not yield any result. However, a search of the same database for [redacted] yielded 11 items, one of these is [redacted]. The database list [redacted] on 10/10/04. A DARRTS search confirms that [redacted] Annual Report from 2012 to 2013.*

A Micromedex search for [redacted] resulted in two items on reproductive risk, both listing [redacted] article. A search of the term [redacted] on the International Program on Chemical Safety website[15] yielded brief description on acute hazards symptoms, prevention, spillage disposal etc.

Sponsor's Summary Safety Assessment of [redacted]

[redacted] has been studied in animal species. Acute toxicity studies demonstrated [redacted] is moderately toxic across species using various routes of administration. Following oral administration, histopathological findings included congestion or edema of brain, injury to stomach, and minute hemorrhages in lungs and thymus. Mylan states since Estradiol TDS is intended for chronic use; results from oral repeat-dose toxicology studies in rats and dogs were used to establish safety margins for [redacted]

[redacted] up to 10 mg/kg/day in which the liver was identified as a target organ, liver effects included significant increases in relative/absolute weights (≥ 3 mg/kg/day) and enlarged

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[redacted]

[12] FDA's Inactive Ingredient Database search for [redacted] ttp://intranetapps.test.fda.gov/scripts/iig/getiig.cfm accessed 1/31/14

[redacted]

[15] International Program on Chemical Safety http://www.inchem.org/ accessed 2/4/14.

[redacted]

hepatocytes in the centrilobular and midzonal regions at 10 mg/kg/day. A NOAEL of 1 mg/kg/day was established for rats based upon increased liver weight at 3 mg/kg/day. Findings in dogs administered (b) (4) up to 3 mg/kg/day for 90 days were limited to increases in relative liver weights in male and females, and slight suppression in body weights in females at 3 mg/kg/day. The increase in liver weight is not considered adverse which is supported by the lack of clinical chemistry or histopathological findings. Mylan states the NOAEL in dogs is 3 mg/kg/day based upon the slight decrease in body weights in females.

(b) (4) was not shown to be mutagenic in in-vitro assays with Salmonella typhimurium and mouse lymphoma cells (L5178Y TK-/+), and literature search did not identify a mutagenic or carcinogenic alert for (b) (4) An oral reproductive and developmental toxicology study demonstrated that (b) (4) was toxic to the dams and was teratogenic at ≥ 10 mg/kg.

There is no data available on long-term exposure, carcinogenicity, mutagenicity, genotoxicity and reproduction toxicity. In humans, acute occupational exposure (inhalation) of (b) (4) resulted in unconsciousness and convulsions[17]; however, no exposure levels were reported. Absorption of (b) (4) following oral administration is also not known, but is assumed to be well-absorbed based upon the relative low molecular weight (b) (4)

Mylan explains based upon the total mass (b) (4) of the drug and adhesive matrix components in the 0.1 mg/day patch (maximum daily dose for Estradiol TDS), each patch may contain up to (b) (4) (b) (4) Mylan calculated (below) the permissible daily exposure (PDE) values for a 50 kg subject for (b) (4) (Table 8). Based on these calculations, safety margins of ~16- and 61-fold exist at the requested specification levels for the (b) (4) (for a 50 kg individual) for rat and dog, respectively. Mylan concludes that the requested specification limits of Not More Than (b) (4) in the Estradiol TDS is reasonably justified, posing minimal risk to human subjects under the prescribed use conditions. When considering the potential maximum concentration of the residual materials in the final product, the maximal daily exposure to these materials based upon a 3.5 day (twice weekly) wear period and assuming 100% dermal absorption would be not more than (b) (4)

Mylan adds (b) (4) (b) (4)

(b) (4)

Below is Mylan's calculation of the permissible daily exposure (PDE) values for a 50 kg subject.

PDE = (NOAEL) ÷ (F1xF2xF3xF4xF5xF6)

F1 = A factor to account for extrapolation between species
- F1 = 2 for extrapolation from dogs to humans
- F1 = 5 for extrapolation from rats to humans

F2 = A factor of 10 to account for variability between individuals

F3 = A variable factor to account for toxicity studies of short-term exposure
- F3 = 10 for a < 2 year study in dogs
- F3 = 5 for a 3 month study in rodents

F4 = A factor that may be applied in cases of severe toxicity
- A NOEL/NOAEL was established

F5 = A variable factor that may be applied if the no-effect level was not established
- A NOEL/NOAEL was established

F6 = Factor to address any remaining uncertainties
- F6 = 3
  - Although detailed oral bioavailability studies were not performed in rats or dogs with (b) (4) systemic exposure was indirectly demonstrated based upon the observed toxicities (liver, kidney) following oral administration of (b) (4) over a 90 day dosing period. Assuming that the integrity of the skin is maintained and not compromised, absorption through the skin is generally lower than or, at most, equivalent to, absorption through the GI tract. However, for conservatism, an additional factor of 3 is included in the calculation to account for the potential differences in bioavailability between dermal and oral exposures.

PDE (at 50 kg) = Permissible daily exposure for a 50 kg subject

Max Daily Exposure = Maximum potential daily (b) (4) exposure based upon the "not more than" levels proposed for (b) (4) in the Mylan's Estradiol Transdermal System USP.

Safety margin = PDE (at 50 kg) ÷ Max Daily Exposure

Table 8: Mylan's Calculation of PDE for (b) (4) (ANDA 201-675)

Species	Rat	Dog
NOEL/NOAEL	1 mg/kg/day	3 mg/kg/day
F1	5	2
F2	10	10
F3	5	10
F4	1	1
F5	1	1
F6	3	3
PDE	1.3 µg/kg/day	5 µg/kg/day
PDE (at 50 kg)	66.7 µg/day	250 µg/day
Max Daily Exposure	4.1 µg/day	4.1 µg/day
Safety Margin	16-fold	61-fold

PDE-Permissible daily exposure

Reviewer Comments:
Using Mylan's NOAEL values of 1 mg/kg/day for rats and 3 mg/kg/day based on rat and dog studies, respectively, the safety margin is calculated as 16-fold and and 61-fold.

[redacted] *considers the liver to be the target organ, and considers the NOAEL for liver effects in both species is 1 mg/kg bw/day* [redacted] *administered during 90 days.*

[redacted] *concluded that the statistical increase in the liver-to-body weight ratio may be a result from the observed decrease in body weights, particularly in females. The absence of correlative clinical chemistry or histopathological findings supports this conclusion and indicates that the liver is not a target organ. A slight increase in SCN- blood levels was produced at 3 mg/kg/day. Mylan considers the NOAEL for this study was 3 mg/kg/day based upon the slight decrease in body weights in females.*

[redacted] *NOAEL of 1 mg/kg/day for dog species is used, the calculation of the safety margin is reduced to 19.5 fold. Nonetheless, a safety margin of 16-fold and 19.5 fold for* [redacted] *based on rat and dog studies (respectively) appear reasonable.*

[redacted]

[redacted] and a very reactive compound. It is a chemical intermediate used chiefly in the manufacture of sorbates, solvents, and, to a lesser extent, pharmaceutical products and aroma chemicals.[19] It is an important environmental pollutant formed during combustion of carbon-containing fuels and other materials (e.g., burning wood in fireplaces, and cigarette smoking)[20]. Data indicate that humans are permanently exposed to this compound via different routes to a strongly varying extent.[21] Strongly varying concentrations of [redacted] re reported to occur in food and alcoholic beverages, e.g., fish (71–1000 µg/kg), meat (10–270 µg/kg), fruits

[redacted]

[21] Agency for Toxic Substances and Disease Registry (ATSDR) http://www.atsdr.cdc.gov/ accessed 2/3/14

and vegetables (1-100 µg/kg), wine (0.3–1.24 mg/liter) or whisky (30–210 µg/liter). (b) (4) (b) (4) [redacted] ve (b) (4) (b) (4) (b) (4)[23]

There is little experience with acute overexposures in humans. It is reported to be highly toxic by the inhalation, dermal, and oral routes, and is very irritating to eyes, skin, and mucous membranes. Corneal damage may occur; respiratory irritation and delayed pulmonary edema are possible, and allergic contact dermatitis may be seen. (b) (4) is a genotoxin and animal carcinogen; seizures have been seen in experimental animals only. The minimum lethal exposure is not well established. Its extreme irritant properties prevent voluntary exposure to dangerous concentrations. Lacrimation occurs within 30 seconds at 4.1 ppm. Eye and upper respiratory tract irritation occur after 10 minutes of exposure to 10 ppm and within seconds to 45 ppm. Skin irritation occurs at concentrations greater than 0.12%. [24,25]

Reviewer Comment: *A search of the FDA's inactive ingredient database[26] for* (b) (4) *and its synonyms did not yield any result.*

Sponsor's Summary Safety Assessment of (b) (4)

In rats, following oral administration, (b) (4) was readily absorbed and extensively metabolized primarily to 3-hydroxy-1-methylpropylmercapturic acid and to a lesser extent 2-carboxy-1-methylethylmerpaturic acid[27]; a similar metabolic profile was noted in humans[28]. Acute toxicology studies performed in mouse, rat, guinea pig, and rabbit demonstrated tha (b) (4) was moderately toxic following oral, inhalation, and dermal administration. Observed oral LD50 values in rats ranged from 174-300 mg/kg. Mortality was produced early following dosing (within 24 hour). Following oral gavage, clinical observations in rats included lethargy, salivation, ataxia, lacrimation, soft feces, and squinted eyes. Additional findings included increased pulse rate and cyanosis. Although

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(b) (4) [redacted]

[24] Micromedex 2.0 http://www.micromedexsolutions.com/micromedex2/librarian search term (b) (4) accessed 1/24/14.

[25] Center for Disease Control website. http://www.cdc.gov/niosh/idlh/123739.html search term (b) (4) accessed 1/24/14.

[26] FDA's Inactive Ingredient Database search for (b) (4) (b) (4) (b) (4)

[27] ECHA. 1985b. Exp Key Basic Toxicokinetics.003. European Chemicals Agency. 1985. Available at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9ea76f1d-cdae-42b5-e044-00144f67d031/AGGR-82ea7cb9-18aa-428a-b3be-62eb780f85d7_DISS-9ea76f1d-cdae-42b5-e044-00144f67d031.html#AGGR-82ea7cb9-18aa-428a-b3be-62eb780f85d7

(b) (4) [redacted]

experimental details were not provided, in humans, irritation of the respiratory tract mucosa has been shown following extended exposure (duration not indicated) at 4.1 ppm[29]. Observed dermal LD50 values in guinea pigs ranged from 26-30 mg/kg (4 days) and 300 mg/kg (2 or 24 hour). In rabbits, the LD50 value was 322 mg/kg (duration not provided). Clinical observations included necrosis, edema, and erythema.

Oral repeat dose toxicology studies were performed in mice and rats up to 13 weeks. In a study in mice (n = 5 per sex) (b) (4) was administered from 18.75 to 300 mg/kg by oral gavage for 2 weeks (b) (4) [30]. Clinical observations, body weight, organ weights, gross observations, and histopathology were evaluated. Animals at 300 mg/kg and 8/10 animals at the 150 mg/kg dose died during the first week of dosing. The NOAEL established for this study was 18.75 mg/kg/day. In a similar 2 week oral toxicity study in rats, a significant incidence of mortality was observed within the first week of treatment at 300 (all animals) and 150 (9/10) mg/kg/day. No compound-related deaths occurred at ≤ 75 mg/kg/day. Decreased body weight at the study's termination was observed in male and females animals at 75 mg/kg/day. A significant decrease in heart and lung weights of females was produced at 75 mg/kg/day. Similar to mice, the stomach was identified as the primary target organ. Necropsy findings included inflammation, edema, and hemorrhage of the forestomach ≥ 18.75 mg/kg/day. Forestomach hyperplasia, inflammation, and ulceration were produced in a high proportion (numbers not provided) of animals at ≥ 18.75 mg/kg/day. A NOAEL was not established for this study.

In a study by (b) (4) [31], (b) (4) was administered orally to male and female mice and rats (n = 10 per sex) up to 40 mg/kg/day for 13 weeks. Clinical observations, body weight, organ weights, gross observations, and histopathology were evaluated. No mortality or significant clinical signs were produced at any dose level. Findings were limited to epithelial hyperplasia of the forestomach at 40 mg/kg/day. The NOAEL for hyperplasia and inflammation of the forestomach for both male and female mice was considered to be 20 mg/kg/day. In rats, mortality (incidence not reported) was produced at ≥ 5 mg/kg/day. A significant decrease in body weight in males was reported at the terminal sacrifice at 40 mg/kg/day. Several changes in organ weights and hematology/clinical chemistry were observed, but were not dose-dependent or considered to be of toxicological significance. Thickening of the forestomach and nodules were noted at necropsy in male and females rats at ≥ 20 mg/kg/day. Hyperplasia of the forestomach epithelium was produced in male and female rats at ≥ 10 mg/kg/day. Forestomach hyperkeratosis, ulcers, and necrosis were also seen in rats at 40 mg/kg/day. Additionally, acute inflammation in the nasal cavity was observed in rats at ≥ 20 (males) and 5 (females) mg/kg/day. The NOAEL was considered to be 2.5 mg/kg/day for both male and female rats for histopathological findings in stomach and nasal cavity.

(b) (4) was shown to be mutagenic in Salmonella typhimurium TA100 when tested using a modified liquid suspension protocol, and was clastogenic in vitro in Chinese hamster ovary cells and in mouse bone marrow and spermatocytes following intraperitoneal injection (b) (4)

(b) (4)

(b) (4) A statistically significant increase in the incidence of hepatocellular neoplasms at 1.8 mg/kg/day was produced in male rats when administered (b) (4) in the drinking water for 2 year (b) (4) [32]. Bladder tumors were also noted in rats at this dose. While the production of tumors following (b) (4) administration is certainly plausible given the detection of (b) (4) as a mutagen the lack of a dose-response calls the results somewhat into question. The neonatal mouse bioassay provided exposure to (b) (4) only during two days of the mouse lifetime and only at low doses which does not permit an accurate evaluation of (b) (4) carcinogenic potential (b) (4)

The International Agency for Research on Cancer (IARC)[33] reviewed available evidence for the carcinogenicity of (b) (4) and available genotoxicity data. IARC concluded that there is inadequate evidence in humans and experimental animals for the carcinogenicity of (b) (4) is not classifiable as carcinogenic to humans (Group 3).[34]

Mylan that based upon the available studies and the IARC review, the ability of (b) (4) to cause tumors with long-term exposure remains undetermined, and the potential adverse effects of dermal contact with (b) (4) remain poorly characterized.

Reviewer Comment: *The sponsor also made reference to the results from irritation and sensitization study performed with Mylan's Estradiol Transdermal System, USP (twice-weekly) (0.025 mg/day). Although the results of that study are a subject of a different review, it is important to demonstrate from these irritation/sensitization studies that the product that it is not more irritating than the RLD.*

(b) (4) (b) (4) *According to the most recent Annual Report, current drug substance specification, the product contains* (b) (4) (b) (4) [35]. *The proposed Estradiol TDS contains up to* (b) (4) *it should be noted that this amount is much less than that of Nitroglycerin Transdermal System of* (b) (4)

Mylan concluded that (b) (4) demonstrated genotoxicity (positive for mutagenicity, clastogenicity), and based upon this, an exposure level of 1.5 µg/day for lifetime exposures is considered applicable as a risk threshold level thought to pose negligible safety concerns, and used ICH M7 Guideline 2013 as a reference. Mylan concluded that the requested specification limits of Not More Than (b) (4) in Estradiol TDS is reasonably justified, posing minimal risk to human subjects under the prescribed use conditions.

Sponsors Overall Summary

Based upon the total mass (b) (4) of the drug and (b) (4) components in the 0.1 mg/day patch (maximum daily dose) each patch may contain up to (b) (4)

(b) (4)

(b) (4)

[redacted] Considering the potential maximum concentration of the residual materials in the final product, the maximal daily exposure to these materials based upon a 3.5 day wear period and assuming 100% dermal absorption would be not more than [redacted] For a 50 kg individual, these daily doses would equate to approximately [redacted]

Reviewer's Overall Summary and Comments:

- *Mylan (sponsor) is proposing to market an Estradiol TDS designed to be the therapeutic equivalent of Novartis' Vivelle-Dot® TDS for twice weekly use. One of the components of the proposed transdermal drug delivery system is* [redacted].

- [redacted] *is reported to be a neurotoxicant. Uptake occurs after inhalation and through the skin, and is reported to cause adverse effects following exposure via inhalation, ingestion, dermal or eye contact; however, no quantitative data are available. In humans, accidental occupational exposure to* [redacted] *by inhalation caused unconsciousness with convulsions. Short-term exposure may cause headache, sensation of pressure in the head, dizziness, nausea, vomiting, peculiar taste, respiratoty distress, fatigue, convulsions, and unconsciousness. There is no data available for* [redacted] *on long-term exposure, carcinogenicity, mutagenicity, genotoxicity and reproduction toxicity.*

- *A review of DMF* [redacted] *by C. Strasinger states* [redacted] *is classified as a primary irritant and mutagen; however there is no toxicological data on long term dermal exposure to* [redacted] *is found in many foods, human serum and as a contaminant in food, pharmaceutical and cosmetic preservatives….*[36]

- *Humans are permanently exposed to* [redacted] *in varying extent via different routes from environmental pollutants, food (e.g., fish, meat, fruits, vegetables), alcoholic beverages (e.g. beer and wine), synthesis of tocopherol (vitamin E), etc.*[37, 38] *Most recently, an article quantitated the presence of* [redacted][39]

- [redacted]
  - [redacted]

[36] DMF [redacted] (Type IV) Review by C. Strasinger, Ph.D. entered in DARRTS on 1/12/2011

[redacted]

[redacted] *The indication and target population of this product is similar as that of the proposed product.* [redacted] *and so far, there has been no evidence that these patches have been less safe compared to its RLD.*

- [redacted] *and is indicated for the prevention of angina pectoris due to coronary artery disease. This product contains* [redacted] *this amount is much less than that of Nitroglycerin TDS.*

- *The International Agency for Research on Cancer (IARC) reviewed available evidence for the carcinogenicity of* [redacted] *and available genotoxicity data. IARC concluded that there is inadequate evidence in humans and experimental animals for the arcinogenicity of* [redacted] *is not classifiable as carcinogenic to humans.*[40]

- *The ICH M7 Draft Consensus Guideline (also FDA's Draft Guidance) dated 2/6/2013: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, section 7.1 states "A TTC [Threshold of Toxicological Concern]-based acceptable intake of a mutagenic impurity of 1.5 µg per person per day is considered to be associated with a negligible risk (theoretical excess cancer risk of <1 in 100,000 over a lifetime of exposure) and can in general be used for most pharmaceuticals as a default to derive an acceptable limit for control. This generic approach would usually be used for mutagenic impurities present in pharmaceuticals for long-term treatment (>10 years) and where no carcinogenicity data are available…."*

  The sponsor's requested specification limits for [redacted] *in the proposed Estradiol TDS* [redacted] *1.5 µg per person per day level listed in the ICH M7 Draft Consensus Guideline. Based on this,* [redacted] *appears reasonably justified, and appears to pose minimal risk to hu er the prescribed use conditions.*

- *The sponsor also made reference to the results from irritation and sensitization study performed with Mylan's Estradiol Transdermal System, USP (twice-weekly) (0.025 mg/day). Although the results of that study are a subject of a different review, it is important to demonstrate from these irritation/sensitization studies that the proposed product that it is not more irritating than the RLD.*

- *Although the Pharmacology and Toxicology data did not meet all the requirements listed in the Guidance for Industry, Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*[41]*, available information appears adequate enough to make a safety assessment on the residual amounts of* [redacted]

[40] International Agency for Research on Cancer (IARC). http://www.iarc fr/ search term [redacted] accessed 2/5/14.

[41] Guidance for Industry, Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf

6 Conclusions and Recommendations:

Based on the review of available data and safety information, the amount of the residuals, (b) (4) (b) (4), appears reasonably safe for use in humans under the prescribed use conditions. (b) (4) (b) (4) It has the same indication, mode of delivery, and intended population as the proposed product. DCR has is no reason to believe that the proposed product will be less safe than its RLD or Mylan's currently marketed Estradiol TDS once weekly use. Human irritation studies should demonstrate that the proposed product is not more irritating to the skin when compared to its RLD.

The maximal daily exposure to (b) (4) based upon a 3.5 day wear period and assuming 100% dermal absorption would be (b) (4). Based upon the available data, the specifications of an (b) (4) (b) (4) for a 3.5 day wear period) and an (b) (4) for a 3.5 day wear period) in the proposed Estradiol TDS are reasonably justified.

Based on Mylan's calculated permissible daily exposure (PDE) values for (b) (4) the safety margins of approximately 16- and 61-fold exist at the requested specification levels for the (b) (4) (for a 50 kg individual) for rat and dog, respectively. The requested specification limits of Not More Than (b) (4) in the proposed Estradiol TDS is reasonably justified. In DCR's opinion, this amount poses minimal risk to human subjects under the prescribed use conditions.

The sponsor's requested specification limits for (b) (4) (b) (4) in the proposed Estradiol TDS (b) (4) the 1.5 µg per person per day level listed in the ICH M7 Draft Consensus Guideline. Therefore, (b) (4) appears reasonably justified, and appears to pose minimal risk to human subjects under the prescribed use conditions.

The International Agency for Research on Cancer (IARC)[42] review of available evidence for the carcinogenicity of (b) (4) and available genotoxicity data concluded that there is inadequate evidence in humans and experimental animals for the carcinogenicity of (b) (4). (b) (4) is not classifiable as carcinogenic to humans. The sponsor's requested specification limits for (b) (4) (b) (4) in the proposed Estradiol TDS (b) (4) the 1.5 µg per person per day level listed in the ICH M7 Draft Consensus Guideline: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. Based on this, (b) (4) appears reasonably justified, and appears to pose minimal risk to human subjects under the prescribed use conditions.

(b) (4) of previously approved generic produc

- (b) (4) (b) (4) and so far, there has been no evidence that these patches have been less safe compared to its RLD.

[42] International Agency for Research on Cancer (IARC). http://www.iarc.fr/ search term (b) (4), accessed 2/5/14.

- [redacted] and is indicated for the prevention of angina pectoris due to coronary artery disease. This product contains [redacted]

Conclusions:

- Based on the review of available data and safety information, the amount of the residuals, [redacted] appears reasonably safe for use in humans under the prescribed use conditions.
- Human irritation studies should demonstrate that the proposed product is not more irritating to the skin when compared to its RLD.
- The maximal daily exposure to [redacted] based upon a 3.5 day wear period and assuming 100% dermal absorption would be [redacted]
- Based upon the available data, the specifications of an [redacted] for a 3.5 day wear period) and an [redacted] for a 3.5 day wear period) in the proposed Estradiol TDS are reasonably justified.

References:

1) Agency for Toxic Substances and Disease Registry (ATSDR): http://www.atsdr.cdc.gov/

2) (b) (4)

3)

4) (b) (4)

5)

6) Concise International Chemical Assessment Document (b) (4) http://www.inchem.org/documents/cicads/cicads/cicad (b) (4)

7) DARRTS In-use labeling for Estradiol Transdermal System Continuous Delivery, USP (once weekly) ANDA 75182, revised 10/2012.

8) Division of Standards Development and Technology Transfer: http://www.cdc.gov/niosh/docs/81-123/pdfs/0604.pdf

9) (b) (4)

10) DMF (b) (4) (Type IV) Reviews by C. Strasinger, Ph.D. entered in DARRTS on 1/12/2011, and 4/7/11.

11) (b) (4)

12) European Chemicals Agency (ECHA): http://www.echa.europa.eu/

13) FDA's Inactive Ingredient Guide. http://intranetapps.test.fda.gov/scripts/iig/

(b) (4)

15) Handbook of Pharmaceutical Excipients: http://www.medicinescomplete.com/mc/excipients/current/

16) [redacted]

17) [redacted]

18) International Program on Chemical Safety (IPCS Inchem): http://www.inchem.org/ accessed 2/4/14.

19) [redacted]

20) Micromedex - http://www.micromedexsolutions.com/micromedex2/librarian/

21) National Toxicology Program (NTP NIEHS): http://ntp.niehs.nih.gov/

22) [redacted]

23) Occupational safety and health guideline for [redacted] U.S. Dept of Health and Human Svcs. Public Health Service Centers for Disease Control National Institute for Occupational Safety and Health.

24) Pohanish, Richard P. (2008). Sittig's Handbook of Toxic and Hazardous Chemicals and Carcinogens [redacted]. William Andrew Publishing. Online version: http://app.knovel.com/hotlink/toc/id:kpSHTHCC07/sittigs-handbook-toxic accessed 1/31/14.

25) United States Environmental Protection Agency, Integrated Risk Information System (EPA IRIS): http://www.epa.gov/IRIS/

26) United States National Library of Medicine Toxicology Data Network (Toxnet): http://toxnet.nlm.nih.gov/

27) [redacted]

28) World Health Organization (WHO): http://www.who.int/en/

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/s/

LOLITA A LOPEZ
02/24/2014

JAMES L OSTERHOUT
02/24/2014

JOHN R PETERS
02/25/2014

Review of Skin Irritation, Sensitization and Adhesion Studies

ANDA #201675

Estradiol Transdermal System, USP 0.025 mg/day; 0.0375 mg/day; 0.05 mg/day; 0.075 mg/day and 0.1 mg/day
Mylan Technologies, Inc.

Nicole Lee, Pharm.D.
Division of Clinical Review

Dates of submissions reviewed:
April 26, 2010;
September 10, 2010 (amendment)

Table of Contents

Review of Skin Irritation, Sensitization and Adhesion for ANDA 201675

Executive Summary

Estradiol Transdermal System, 0.025 mg/day (NDA 020538, Vivelle-Dot®, approved 01/08/1999, Novartis) is indicated for:
1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

Mylan Pharmaceuticals, Inc. (Sponsor) submitted ANDA 201675 on 04/26/2010 for a generic formulation of Vivelle-Dot®. This review focuses on the studies submitted to ensure that the skin irritation and sensitization potential of Mylan's generic Estradiol Transdermal System are no greater than those of the RLD and that the generic product adheres to the skin as well as the RLD over the intended duration of wear.

Mylan Pharmaceuticals, Inc. (Mylan) conducted study #EDOT-0908 for skin adhesion, irritation and sensitization. Study #EDOT-0908 was an open-label, multiple dose, randomized application site, two-treatment, three-phase, one-period study investigating the adhesion, cumulative induction of dermal irritation and contact sensitization by repetitive applications of the transdermal delivery system to the same skin sites. This study was initiated with two hundred twenty-eight (228) subjects, and 221 subjects completed the study.

According to the FDA statistical review, this study suggests that Mylan's Estradiol Transdermal System is, in fact, more irritating than the RLD system and fails to demonstrate that it adheres as well as the RLD. The data shows that the test product has no more potential to cause sensitization than that expected with use of the reference listed product Vivelle-Dot®.

I. Approval Recommendation

The data submitted to ANDA 201675, for irritation, sensitization and adhesion of Mylan's Estradiol Transdermal System are **not** adequate to demonstrate that it is no more irritating than the RLD system and **does not demonstrate** that it adheres as well as the RLD. The data shows that the test product has no greater potential to cause sensitization than the reference listed drug (RLD), Vivelle Dot®. This application is therefore **not** recommended for approval from a clinical bioequivalence perspective.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Study #EDOT-0908 was a open-label, multiple dose, randomized application site, two-treatment, three-phase, one-period study of Mylan's Estradiol Transdermal System vs. the reference listed drug, Vivelle Dot® for adhesion, irritation potential and sensitization potential.

Treatments Administered:
One patch of Treatment A and One patch of Treatment B

A. Estradiol Transdermal System, 0.025mg, Lot No: R6A0028, Mfg Date: August 2009, Mylan Pharmaceuticals, Inc.
B. Vivelle-Dot® transdermal system, 0.025 mg/day, Lot No: 36393, Exp. Date: Oct 2010, Manufactured by: Novartis Pharmaceutical Corporation

The study was initiated with 228 healthy postmenopausal female volunteers in order to assess the cumulative dermal irritation and induction of contact sensitization by repetitive placement of the transdermal delivery system treatments to the skin. Both treatments (Mylan estradiol transdermal system and Vivelle-Dot® transdermal system) were placed simultaneously (total dose 0.05 mg/day) on each volunteer for a 3.5-day wear cycle per application over a total of 6 applications (21 days). This induction phase was followed by a 14-day rest period and a subsequent 48-hr Challenge phase, which was followed by 3 days of observation and irritation evaluation..

Subjects received a 0.025 mg/day estradiol transdermal system (Mylan) and a 0.025 mg/day Vivelle- Dot® transdermal system simultaneously applied to a clean, dry area of the skin on the abdomen according to the randomization scheme. Patches were applied for a 3.5-day wear cycle per application with a total of 6 applications during the Induction phase (21 days), followed by a 14-day Rest phase. Following the Rest Phase, one Challenge application of a 0.025 mg/day estradiol transdermal system (Mylan) and a 0.025 mg/day Vivelle Dot® Transdermal system was simultaneously applied to a clean, dry area of the skin on the abdomen (naïve site) for a 48-hour period according to the randomization scheme described.

B. Comparative Irritation

Mylan's norelgestromin/ethinyl estradiol transdermal system appears to be **more irritating** than the RLD.

The firm made a modification of the statistical plan due to the nature of the data (both the absolute means, and respective difference between the Test and Reference, are very well below the clinical sensitivity (irritation score of 1) utilized in this study). Based on this new plan, they state that their patch can be considered no more irritating than Vivelle-Dot® Transdermal System as the upper one-sided 95% confidence bound on μ_T-μ_R was less than 0.25.

According to the sponsor, the majority of scores for both patches were less than or equal to a score of 1 (96.5% for test and 98% for reference), the test patch had a significantly greater

number of scores equal to 3 (10 for the test and 1 for the reference) and a greater number of scores equal to 7 (3 for the test and 0 for the reference). In addition, the number of patients with the frequency of mean cumulative irritation score greater than one was 8 for the test and 3 for the reference. There were three subjects (Nos. 157, 192 and 203) who had their test sites moved due to irritation for the test patch. Subject 157 had the test site moved for patches 5 & 6; Subject 192 had the test site moved for patches 5 & 6; and Subject 203 had the test site moved for patches 5 & 6.

According to the FDA statistical analyses, the 95% upper confidence bounds (CB) for the adjusted mean difference (μ_T -1.25μ_R) was greater than zero (0.047) for irritation. The least mean cumulative score for irritation was 0.1925 for the test and 0.1495 for the reference. In addition, the 95% upper confidence bound for difference in proportions of test versus reference based on the dichotomized irritation score was at most 4.7% with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1 or 3.

C. Comparative Sensitization

The sponsor states that no evidence of a sensitization reaction was observed in their study. An edematous reaction score of "3" or greater that was characterized by a crescendo evolution of the reaction over 72-hours post-removal of the Challenge Phase was considered potentially sensitized by the sponsor. No re-challenge was performed.

According to the raw irritation data, no subject was considered potentially sensitized using the OGD's analysis of sensitization also.

According to the FDA statistical analysis, the test might exceed the reference by at most 1.9 percentage points based on the 95% upper confidence bound for the difference in sensitization rates.

D. Comparative Adhesion

According to the FDA statistical analysis, the 95% upper confidence bound (CB) for the adjusted mean difference (μ_T -1.25μ_R) was greater than zero (0.015). **Thus, the test product was found to be inferior to the reference.** Based on the 95% upper confidence bound for the difference in detachment rates of greater than or equal to 10% detached (score≥1), the test might exceed the reference by at most 3.2 percentage points for the mean of the adhesion score.

E. Adverse Events

Out of 228 subjects enrolled into the study, 166 (72.8%) subjects experienced a total of 527 adverse events (AEs) over the course of the study. The majority of the adverse events were mild in severity. Most of the adverse events were definitely related to the study medications. There were 2 serious adverse events, which were considered probably related to the study medication.

III. Design and Formulation

Schematic diagram of Generic Transdermal System design (per sponsor):

Backing Film (1)	
Adhesive Matrix (2)	
Slit Release Liner (3)	Slit Release Liner (3)

Mylan's Estradiol Transdermal Systems USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice-Weekly) are transdermal drug delivery systems of identical composition and the product strength is determined by the patch size. They are matrix "solution" transdermal systems in which the estradiol active ingredient is dissolved in a solid adhesive matrix. The figure above is a schematic representation of Mylan's Estradiol Transdermal System USP (Twice-Weekly), which is designed to be therapeutically equivalent to Novartis' Vivelle-Dot® transdermal system. Proceeding from the visible surface towards the surface attached to the skin, these layers are (1) a translucent polyolefin backing film printed with brown ink, (2) an adhesive formulation containing estradiol USP, silicone adhesive, acrylate adhesive, dipropylene glycol, povidone, oleyl alcohol, and (3) an oversized slit polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.

Reviewer's comments*: The RLD uses a DOT Matrix delivery system which is comprised of a protective backing, one layer containing both evenly distributed estradiol and a silicone adhesive, and a removable liner. This is the same design as the Test product.*

Sizing

Drug product	0.025 mg/day	0.0375 mg/day	0.05 mg/day	0.075 mg/day	0.1 mg/day
RLD	2.5 cm^2	3.75 cm^2	5.0 cm^2	7.5 cm^2	10.0 cm^2
Test product	2.5 cm^2	3.75 cm^2	5.0 cm^2	7.5 cm^2	10.0 cm^2

Test Formulation

Components	% w/w	mg/patch (0.025 mg/day)	mg/patch (0.0375 mg/day)	mg/patch (0.05 mg/day)	mg/patch (0.075 mg/day)	mg/patch (0.1 mg/day)	Pharmaceutical Function
Estradiol (b) (4) USP, (b) (4)	(b) (4)	0.41	0.62	0.82	1.23	1.64	Active ingredient
Oleyl alcohol, (b) (4)		(b) (4)					(b) (4)
Dipropylene glycol							
Povidone (b) (4)							
Silicone Adhesive							Adhesive

(b) (4)							
Acrylic Adhesive	(b) (4)						Adhesive
(b) (4)							(b) (4)

Composition of Other components of Estradiol Transdermal System

Components	mg/patch (0.025 mg/day)	Pharmaceutical function
Polyolefin film	(b) (4)	backing
Brown ink		Imprinting ink
(b) (4) polyester film		Oversized release liner

Reference Formulation[1]

Component	mg/patch (0.025 mg/day)	mg/patch (0.0375 mg/day)	mg/patch (0.05 mg/day)	mg/patch (0.075 mg/day)	mg/patch (0.1 mg/day)	Function
Estradiol	0.390	0.585	0.780	1.17	1.56	Active ingredient
(b) (4) (b) (4) acrylic adhesive	(b) (4)					Adhesive
(b) (4) (b) (4) silicone						Adhesive
Oleyl alcohol						(b) (4)
Dipropylene glycol						
Povidone, USP						
(b) (4)						

[1]**Data from chemistry review dated 12/20/2011**

(b) (4).

Reviewer's comments: *The test product is quantitatively and qualitatively very similar to the RLD, although it is not a q/1q2 patch. In addition, the test patches are the same size as the RLD patches for all dose strengths. Currently, the Chemistry Reviewer has requested two separate Pharm/Tox reviews (10/17/2012). One is based on the excipient* (b) (4) (b) (4) *than the IIG list of 57.14 mg and the other is based on the limits of* (b) (4) *impurities found in the excipients used in the drug product* (b) (4)

[redacted] In a response dated 12/10/2013, the Pharm/Tox reviewer stated that the information provided and reviewed suggests that Mylan's Estradiol Transdermal System, USP (Twice Weekly) 0.1 mg/day that contains [redacted] is safe for human use. In a separate response dated 12/10/2013, the Pharm/Tox reviewer states that the toxicity of [redacted] was reviewed [redacted] which suggested no significant safety risk for its human use. However, Mylan's proposed specifications for [redacted] contained no toxicity data for these impurities. Toxicity data needs to be submitted and reviewed before the proposed limits can be assessed.

Clinical Review

I. Introduction and Background

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women. Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue. Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

A. Drug Established Name, Drug Class

Established Name: Estradiol Transdermal System
Drug Class: Transdermal Hormonal Patch

B. Trade Name of Reference Drug, NDA number, Date of approval, Approved Indication(s), Dose, Regimens

Reference Drug: Vivelle-Dot® Transdermal System, Novartis Pharmaceutical Corporation
NDA number: 020538
Date of Approval: January 8, 1999
Approved Indication(s): Vivelle-Dot® is indicated for
1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.

2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

Dosing Regimen: The adhesive side of Vivelle-Dot® (estradiol transdermal system) should be placed on a clean, dry area of the abdomen. Vivelle-Dot should not be applied to the breasts. Vivelle-Dot should be replaced twice weekly. The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. In the event that a system should fall off, the same system may be reapplied. If the same system cannot be reapplied, a new system should be applied to another location. In either case, the original treatment schedule should be continued. If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. The new patch should be applied on the original treatment schedule. The interruption of treatment in women taking Vivelle-Dot might increase the likelihood of breakthrough bleeding, spotting and recurrence of symptoms.

C. Regulatory Background

No other ANDAs have previously been approved for this product.

DARRTS list the following submissions for Estradiol Transdermal System (RLD Vivelle-Dot®)

(b) (4)

[redacted]

Controls/Protocols

There are 8 protocols listed in the Office of Generic Drugs (OGD) database:

Protocol No.	Drug Name	Firm	Completed Date	Comments
93-021	Estradiol Patch	(b) (4) [redacted]	12/6/1993	No letter
99-006	Estradiol Patch		04/20/1999	2 protocols
06-049	Estradiol Transdermal Patch		10/31/2007	

06-059	Estradiol Transdermal Patch	(b) (4)	03/22/2012	Skin irritation, sensitization, and adhesion study. DCR comments faxed to firm in letter dated 3/22/2012
95-141	Estradiol Patch		02/11/1996	
97-021	Estradiol Patch		03/06/1998	
96-068	Estradiol Patch		11/21/1997	See also P96-056
95-142	Estradiol Patch		02/11/1996	
96-056	Estradiol patch		11/21/1997	Replaced by 96-068

There are 36 controls listed in the OGD database:

Control No.	Title	Description	Status	From
00-339	Estradiol Transdermal System	Estradiol Transdermal System Skin Irritation/Sensitization Studies	Closed (10/10/2000)	(b) (4)
(b) (4)				
00-540	Estradiol Patches	BE study, Estradiol patches against Climara (once a week)	Closed (5/29/2001)	
01-014	Estradiol Patch	BE study, Estradiol patches against Climara (Once a week)	Closed 1/23/2001	
01-020	Estradiol Patch	LTS Estradiol-TTS (Generic) Request for FDA Opinion	Closed 11/7/2001	

01-238	Estradiol Transdermal	Congressional Inquiry from Rep. Tiberi. Regarding generic drug distribution and laws governing testing	Closed 5/15/2001	CDER Exec. OPS
01-397	Estradiol Transdermal	Estradiol Transdermal	Closed 7/31/2001	Exec OPS
01-516	Ethinyl Estradiol	Request for Regulatory Opinion	Closed 12/6/2001	(b) (4)
01-557	Estradiol Transdermal	Skin irritation study questions	Closed 1/22/2002	
02-074	Estradiol Transdermal System	Petitioners request that FDA change the therapeutic equivalence code for Mylan's estradiol transdermal system from A-rated to B-rated	Closed 10/22/2004	Berlex and 3M
02-244	Estradiol TDS-Mylan	Adhesion Problems Referral to TIACC	Closed 5/8/2003	DQRS
02-314	Estradiol Transdermal System	Estradiol Transdermal System Continuous delivery for twice weekly applications 0.25, 0.0375, 0.05, 0.075, 0.4mg/estradiol/day	Closed 6/10/2002	(b) (4)
02-335	Estradiol TDS	Estradiol Transdermal System Continuous delivery for twice weekly application 0.25, 0.0375, 0.05, 0.075, 0.1mg/estradiol/day	Closed 4/13/2005	
04-008	Estradiol Transdermal Film	Bioequivalence Study	Closed 9/2/2005	
05-1478	Estradiol Transdermal Therapeutic System	Question relating to formulation and clinical development	Closed 2/23/2006	
06-1420	Estradiol Transdermal System	BE requirements	Closed 4/4/2007	

				(b) (4)
06-1693	Estradiol Transdermal Patch	Requesting guidance regarding bioequivalence	Closed 11/29/2010	
07-0511	Estradiol Transdermal System	Request for BE and Dissolution Recommendations	Closed 5/16/2007	
07-1418	Estradiol Film Extended Release Transdermal	Requesting suggested in-vitro study method and bioequivalence recommendations.	Closed 11/29/2010	
07-1453	Estradiol Transdermal Patches	Requesting guidance for performing the cumulative irritation and skin sensitization tests.	Closed 11/29/2010	
07-1540	Estradiol Transdermal Systems	Seeking clarification on agency's BE requirements.	Closed 11/10/2010	
08-0233	Estradiol Transdermal Patch	BE studies and guidance.	Closed 11/29/2010	
08-0525	Estradiol Extended Release Transdermal Film	BE and dissolution method recommendations	Closed 11/29/2010	
08-0778	Estradiol transdermal system	Request recommendations for required bioequivalence studies, skin irritation/sensitization studies, dissolution testing & apparent dose requirements.	Closed 11/29/2010	
08-0786	Estradiol Film Extended Release	Requesting BE recommendations	Closed 11/29/2010	
08-0819	Estradiol film extended release	Requesting bioequivalence study for a generic version of their product.	Closed 11/10/2010	
92-175	Letter from Dr. (b) (6) (b) (4) (b) (4) re estradiol	Requesting teleconference as a follow up to 9/16/92 meeting which dis-cussed the design of	Open	

		bioequivalence studies comparing (b) (4) transdermal estradiol		
97-297	Drug Estradiol Transdermal	Requesting preliminary review of ANDA 75-182 for Estradiol Transdermal System, 0.1 mg/day by Bertek, Inc.	open	Bertek, Inc.
97-392	Drug: Estradiol Transdermal System (75-182 & 75-233)	Request for a t-con to discuss: the existing data on Climara obtained through FOI regarding the similarity of single and multiple- dose profiles	Closed 1/28/1998	Bertek (Mylan)
98-130	Drug: Transdermal Estradiol Patch	Requesting guidance on the bioequivalence requirements.	Open	(b) (4)
98-230	Drug: Estradiol Transdermal, Climara	6-12-98 CPs requesting: 1) stay of approval based on Climara, 2)refuse to recieve or AP any ANDA unless: a) use of best method to demo rate & extent o	Closed 3/17/2000	
98-285	Drug: Estradiol TDS	Would like to start pivotal bioequivalence studies, but has a few questions. (Please see attached)	Closed 6/24/1999	
98-421	Topic: Supporting a CP for Climara Transdermal Estradiol Patches.	Docket No. 98P-0434/PSA1	Open	A. Einstein Univ.
99-037	Drug: Estradiol Replacement therapy patch	Concerns with review criteria.	Closed 1/29/1999	Exec Sec/OLA Daschle
99-287	Drug: Estradiol	Requesting guidance	Closed	(b) (4)

	Transdermal	on Labeling of the above drug.	2/11/2000	
99-307	Estradiol Transdermal	Controlled Correspondence; Estradiol Transdermal System Bioequivalence and Irritation Studies	Closed 4/6/2000	(b) (4)

Draft Guidance on Estradiol Transdermal System (RLD 20538), 11/2010, is currently available at the following website:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234963.pdf

The draft guidance general recommendations are attached in Appendix A.

Reviewer's comments: *The studies submitted are consistent with the draft guidance except for the adhesion evaluations performed which will be discussed further in the review.*

II. Description of Clinical Data and Sources

CRO: (b) (4)

Study Center:

Federal State Enterprise "Scientific Research Center for Preventive Medicine of Federal Agency of High Technology Medical Care"
10 Petroverigsky str.,Moscow, 101990, Russian Federation

Study Period: November 8, 2009 to January 15, 2010

Investigator(s): Sergey Martsevich, M.D., Ph.D., D. Sc.

Enrollment: A total of 228 subjects were enrolled into the study.

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

Original Submission: April 26, 2010

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Office of Scientific Investigations Report:

The Federal State Enterprise "Scientific Research Center for Preventive Medicine of Federal Agency of High Technology Medical Care", Moscow, Russia (NAI).

Based on the OSI inspection dated 02/25/2013 to 03/01/2013, no significant objectionable conditions were observed and Form FDA 483 was not issued.

The reviewers recommend that the data for the clinical portion of the study EDOT-0908 be accepted for further agency review.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

According to the sponsor, this study was conducted in accordance with the guidelines set forth by the International Conference on Harmonization (ICH) of Guidelines for Good Clinical Practice (ICH Guideline E6), and the U.S. Code of Federal Regulations Guidelines for Good Clinical Practice (21 CFR Parts 50 and 56) regarding the treatment of human subjects in a study.

D. Evaluation of Financial Disclosure

Form FDA 3454 was submitted by the sponsor, Mylan Pharmaceuticals, Inc., certifying that the sponsor has not entered into any financial arrangements with the investigators of the clinical studies. Each investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor. None disclosed such interest. Finally, the sponsor certified that the investigator(s) were not the recipient of significant payments of any sort.

IV. Review of Skin Irritation, Sensitization, and Adhesion

A. Brief Statement of Conclusions

The data submitted to ANDA 201675 for Mylan's Estradiol Transdermal System show that the **irritation and adhesion performance is worse than that of the RLD**. The sensitization potentials of the generic is no worse than expected with use of the RLD.

B. General Approach to Review of the Comparative Skin Sensitization, Irritation, and Adhesion

The sponsor's data were reviewed to see if their generic patch is no more irritating than the reference patch. In addition, skin sensitization potential and adhesion performance were evaluated to see if they are no worse than those expected with use of the reference patch.

C. Detailed Review of Skin Sensitization, Irritation, and Adhesion Study

Study #EDOT-0908

CLINICAL REVIEW

Title:
Comparative Evaluation of the Adhesion, Cumulative Irritation and Contact Sensitization Potential of Mylan's Estradiol Transdermal System, USP (Twice-Weekly) (0.025 mg/day) to Vivelle-Dot® (Estradiol Transdermal System) (Novartis; 0.025 mg/day) in Healthy Post-Menopausal Women

Objective
to compare the adhesion, cumulative dermal irritation and contact sensitization of Mylan's Estradiol Transdermal System, USP (Twice-Weekly) (0.025 mg/day) to Vivelle-Dot® (Estradiol Transdermal System) (Novartis; 0.025 mg/day) in 200 healthy post-menopausal female volunteers.

Study Design
This was an open-label, multiple-dose, randomized application site, two-treatment, three-phase, one-period, study of the human dermal safety and adhesion of estradiol transdermal systems (TDS) in healthy post-menopausal female volunteers. The dermal safety and adhesion of Mylan's estradiol transdermal system, 0.025 mg/day was compared to that of Novartis' Vivelle-Dot® transdermal system, 0.025 mg/day.

Study Population
Inclusion Criteria
Subjects could participate if they met the following inclusion criteria:
1. Age: 40 to 65 years old
2. Sex: Female.
3. Postmenopausal subjects that had no menses for the past year.
4. Screening FSH levels, determined within 30 days prior to the first patch application, are consistent with postmenopausal status (FSH ≥ 35 mIU/mL).
5. Weight: At least 48 kg (106 lbs) with all subjects having a Body Mass Index (BMI) less than or equal to 37 kg/m2 but greater than or equal to 19 kg/m2. BMI values should be rounded to the nearest integer (ex. 37.4 rounds down to 37, while 18.5 rounds up to 19).
6. Smoking Status: Non-smokers
7. All subjects were judged by the principal or sub-investigator physician as normal and healthy during a pre-study medical evaluation performed at clinic entry which included:
    a. a normal or non-clinically significant physical examination, including vital signs (sitting blood pressure, heart rate, oral temperature, respiratory rate)
    b. a normal pelvic examination that was consistent with hypoestrogenemia (performed within 45 days of first patch application)
    c. mammogram that showed no sign of significant disease (performed within previous 12 months – documentation was available for review)
    d. a negative Papanicolaou ("Pap") smear for subjects with an intact uterus and cervix (performed within previous 6 months – documentation was available for review)
    e. within normal limits or non-clinically significant laboratory evaluation results (unless otherwise noted in the Exclusion Criteria) for the following tests:
        - *Serum Chemistries*
            - Sodium
            - Potassium

- Chloride
- BUN
- Iron
- Albumin
- Total Protein
- AST
- Alk. Phos.
- Calcium
- Creatinine
- ALT
- Total Bilirubin
- Total Cholesterol
- Phosphate
- Uric Acid
- Glucose
- Triglycerides

- *Hematology*
  - Platelet Count,
  - Leukocyte Count w/ Differential
  - Hematocrit
  - Red Blood Cell Count
  - Hemoglobin
- *Coagulogram*
  - APTT (Activated Partial thromboplastin time)
  - Prothrombin time
  - Fibrinogen
  - Prothrombin index
- *Urinalysis*
  - Appearance
  - Specific Gravity
  - Protein
  - pH
  - Microscopic Examination (performed based on clinical judgment)
- Additional tests may be performed, if necessary, based on standard lab panels utilized by the clinical site.

f. negative Hepatitis B and Hepatitis C tests,
g. negative HIV test,
h. normal or non-clinically significant 12-lead ECG
i. negative urine drug screen including amphetamine, barbiturates, benzodiazepines, cannabinoid, cocaine, methadone, opiates, and phencyclidine.
j. if warranted, tests for sexually transmitted diseases (STD) may be performed at the discretion of the Principal Investigator or responsible physician.

Exclusion Criteria

Subjects could not be enrolled if they met any of the following exclusion criteria:

1. Institutionalized subjects.

2. Social Habits:
    a. Any recent, significant change in dietary or exercise habits.
    b. History of drug and/or alcohol abuse within one year of start of study.
    c. Use of any tobacco products within 1 year of start of study.
3. Medications:
    a. Use of any hormone replacement therapy within 3 months prior to study medication dosing.
    b. Use of prescription or over-the-counter (OTC) systemic or topical analgesics or antihistamines within 72 hours of initial patch application or systemic or topical corticosteroids within 3 weeks of initial patch application.
4. Diseases:
    a. History of any significant cardiovascular, hepatic, renal, pulmonary, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, psychological, musculoskeletal disease or malignancies unless deemed not clinically significant by the Principal Investigator or Subinvestigator.
    b. Thrombosis of deep veins and arteries, thromboembolic disorders
    c. Coronary artery or cerebrovascular disease
    d. Liver or kidney dysfunction/disorders
    e. Fibrocystic disease or breast nodules
    f. Family history of breast cancer (direct genetic link, i.e., mother, sister, tc.)
    g. Diabetes or any other endocrinological disease
    h. Estrogen-dependent neoplasia
    i. Postmenopausal uterine bleeding
    j. Endometrial hyperplasia
    k. History of skin diseases (eczema, psoriasis, atopic dermatitis).
    l. Acute illness at the time of either the pre-study medical evaluation or dosing.
    m. History of allergy or hypersensitivity to estradiol or related products or to tapes or adhesives (e.g., Band-aids®, medical tape).
5. Heterogeneity or thickening (> 5 mm) of endometrium determined by ultrasonography.
6. Any reason which, in the opinion of the Principal Investigator or Sub-Investigator, would prevent the subject from safely participating in the study.
7. Subjects who have received an investigational drug within 30 days prior to the initial dose of study medication and/or participated in any transdermal system or patch study for irritation or sensitization within the last 4 weeks.
8. Sunbathing or the use of tanning salons within 7 days prior to initial patch application.
9. Damaged skin in or around test sites that include sunburn, uneven skin tones, tattoos, scars or other disfigurations of the test site.

Reviewer's comments: *The inclusion/exclusion criteria are consistent with the draft guidance.*

Procedures/Observations, and safety measures

The study was conducted at one clinical site and consisted of three phases: an Induction (21 days, 6 applications) phase, a 14-day Rest phase, and a Challenge (5 days, one application) phase. During the induction phase, the transdermal systems were removed at 84 hours ± 2 hours after placement. During the challenge phase, the transdermal systems were removed at 48 hours ± 2 hours after placement.

Study Procedure Schedule

Procedures	Screening (Day 0)	Induction phase (Day 1-22)	Rest phase (14 days)	Challenge phase (Day 38)	Early discontinuation or study exit/discharge
Informed consents	X				
Eligibility (inclusion/exclusion)	X				
Prior medication assessment	X				
Medical history	X				
Vital signs	X	X		X	X
Physical examination	X				X
Clinical laboratory tests	X				X
Urine drug screen	X				
Pelvic exam	X				
Pap smear	X				
Mammography	X				
FSH level	X				
Uterus ultrasound	X				X
Safety 12-lead ECG	X				X
Patch application		X		X	
Patch adhesion evaluation		X		X	
Patch irritation evaluation		X		X	
Skin sensitization evaluation				X	
Adverse events		X	X	X	X
Concomitant medication		X	X	X	X

Patch Application Procedures

Within 60 minutes prior to the first Induction application and the Challenge application and following the 30-minute irritation evaluation for all other applications, each subject's area of skin was wiped gently three times with a warm water washcloth and then lightly patted dry with a soft towel. The skin area was completely dry before the patches were applied. Subjects received a 0.025 mg/day estradiol transdermal system (Mylan) and a 0.025 mg/day Vivelle-Dot® transdermal system simultaneously applied to a clean, dry area of the skin on the abdomen according to the randomization scheme. The application area was not oily, damaged or irritated. Any excess body hair at the system application area was clipped; not shaved. The waistline was avoided, because tight clothing may rub off or loosen the transdermal systems.

Products were opened by hand by a member of the clinical staff. No cutting devices were used. The adhesive surface of the transdermal system was not touched during application and was applied immediately after opening the pouch and removing the protective liner. Each transdermal system was pressed firmly in place with the palm of the hand for about 10 seconds. The patch was in good contact with the application site, especially around the edges. Each patch application site was documented and diagrammed for each subject. Sites of patch placement included the subject's inner and outer areas of the left lower, right lower, left upper and right upper abdomen.

The patches were removed 84 hours ± 2 hours after application. The six induction applications (per transdermal system) were done twice weekly for 21 days. The six applications performed during the three-week phase were designated Applications 1 – 6 respectively. The appropriate transdermal system was re-applied to the identical site until after the sixth patch application, when patch applications were completed. If a subject developed an edematous reaction or a reaction of 3 or greater, according to the Irritation rating scale, the subject did not have any further transdermal systems applied to that same application site during the Induction phase of the study. In this case, any re-applications for Induction were made at a designated alternate site and were appropriately documented and diagrammed. This induction phase was followed by a 14-day rest period and a subsequent 48-hr Challenge phase, which was followed by 3 days of observation and irritation evaluation.

Transdermal Wear Procedures

Subjects were instructed:

- to keep the transdermal systems as dry as possible by keeping showering to a minimum and avoiding baths, soaking or swimming altogether,
- not to use tanning salons or sunbath during the conduct of the study,
- not to apply heat sources of any kind (such as heating pads, electric blankets and tanning beds) to the transdermal system
- to engage in normal activity for the duration of the study, avoiding vigorous exertion due to production of sweat which could decrease patch adherence.

Each subject kept a diary in which they were instructed to record the length and number of baths or showers, any type of physical activity that would induce sweating, and any type of contact with water that may have affected patch adhesion. When reporting to the clinic for the applications and irritation evaluations, subjects were instructed to bring their completed diary for the clinical staff to review. Diaries were dispensed and collected at the end of each study week. In the event that the transdermal system started to lift from the skin at any time, subjects were instructed to apply gentle pressure to smooth out the system, especially around the edges, to ensure adhesion, and to record the date and time at which it occurred in the subject's diary. In the event that a transdermal system fell off, subjects were obligated to return it to a study monitor as soon as possible. If less than 24 hours had elapsed since the patch detachment, the transdermal system was replaced by the clinical site staff. Patch removal and irritation evaluation occurred at the previously scheduled time for the original application. If more than 24 hours had elapsed since the patch detachment, that treatment was discontinued.

Endpoints

Description of scales or instruments used:

IRRITATION:

Dermal Response**:**

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 test site

Other Effects:

A (0)	Slight glazed appearance
B (1)	Marked glazing appearance
C (2)	Glazing with peeling and cracking
F (3)	Glazing with fissures
G (3)	Film of dried serous exudates covering all or part of the patch site
H (3)	Small petechial erosions and/or scabs

ADHERENCE

System Adherence	
Score	**Definitions**
100	Adhesion: 100%
95	Adhesion: >90% to <100%
85	Adhesion: >80% to 90%
75	Adhesion: >70% to 80%
65	Adhesion: >60% to 70%
55	Adhesion: >50% to 60%
45	Adhesion: >40% to 50%
35	Adhesion: >30% to 40%
25	Adhesion: >20% to 30%
15	Adhesion: >10% to 20%
5	Adhesion: >0% to 10%
0	Adhesion: Fall-off

Evaluation:
Adhesion of the estradiol transdermal systems during Induction application 1 was assessed every 24 hours (± 2 hours) and within 1 hour prior to patch removal. Adhesion assessment during Induction applications 2 through 6, and the Challenge application was performed within 1 hour prior to patch removal. Adhesion evaluations were assessed by suitably trained personnel using the adhesion rating scale.

Irritation evaluations were performed 30 to 35 minutes after each Induction application removal. Irritation evaluations during Challenge Phase were performed at 0.5, 24 (±1), 48(±1) and 72(±1) hours after patch removal. Any irritation reaction was graded using the irritation scoring system.

Reviewer's comments*:*

- *The sponsor used a different adhesion scale for assessing adhesion performance than that generally recommended by the OGD*. The sponsor's scale requires a subjective interpretation of a minimum 10% difference in adherence from one score to the next. The study patch is only 2.5 cm^2. Such accuracy is highly related to the skill and experience of the evaluator and there are no provisions in this protocol for evaluation of inter or intra evaluator consistency. Therefore, t*he statistician is asked to evaluate adhesion using the OGD recommended scale:*

System Adherence	
Score	**Definitions**
0	≥90% adhered (essentially no lift off the skin)
1	≥75% to <90% adhered (some edges only lifting off the skin)
2	≥50% to <75% adhered (less than half of the system lifting off the skin)
3	>0% to <50% adhered but not detached (more than half of the system lifting off the skin without falling off)
4	0% adhered-test system detached (test system completely off the skin)

- *According to the draft guidance (comment #19), "After the first application, the adhesion performance of subsequent same site applications could be affected by skin stripping or residual adhesive. Therefore, formally evaluate and compare the adhesion performance of only the first applied test product and RLD for 3.5 days (84 hours) after application. Daily adhesion evaluations are recommended during the first 3.5 day application."*
- *The firm has also evaluated adhesion for induction applications 2 through 6 and the challenge application. This information should not be used in the formal analysis of the adhesion. It may be used as supportive evidence.*

Statistical analysis plan

Irritation
According to the firm the primary statistical parameter is the mean cumulative irritation scores for the Mylan and Vivelle-Dot® transdermal systems. These mean scores were evaluated by Analysis of Variance using Proc GLM of SAS 9.1.3 with a statistical model incorporating terms for Subject and Treatment. Due to the nature of the data, as discussed below, a modification of the statistical plan was made. For a mean cumulative irritation score of the reference found to be less than one, the statistical criteria was modified such that the upper bound of the reference mean was based on reference mean + 0.25, where the absolute value of 0.25 represents 25% of the sensitivity limit of irritation scoring (i.e. a score of one). This approach provides for a fair comparison for reference product with very low irritation (ie. those with mean cumulative irritation scores < 1.00) where the upper bound would be substantially lower than + 0.25. For example, in this study, the upper bound would have been set at the mean cumulative irritation score 0.25*0.142, or + 0.036.

The null hypothesis ($\mu_T - \mu_R + 0.25 > 0$) was tested using the following SAS statement in the Proc GLM analysis:

Estimate 'A – B' TREAT 1 -1

The upper one-sided 95% confidence bound on $\mu_T - \mu_R$ was assessed relative to 0.25 (which equates to an assessment of $\mu_T - \mu_R + 0.25$ relative to zero).

Adhesion
According to the sponsor, the primary assessment parameter for adhesion is the mean adhesion score from Induction application 1. The mean adhesion scores is evaluated by Analysis of Variance using Proc GLM of SAS 9.1 (or higher) incorporating terms for Group, Subject nested-within-group, Treatment, Patch Application Site and Group-by-Treatment interaction. If the Group-by-Treatment interaction term is not detected as significant (i.e. $p \geq 0.01$) then it is removed from the statistical model.
The one-sided hypothesis of interest for comparing adhesion scores for the two transdermal systems (A = Mylan, B = Vivelle-Dot®) is:

H_0: $\mu A - 0.8\mu B < 0$
H_1: $\mu A - 0.8\mu B \geq 0$

The null hypothesis H_0 is rejected when the upper limit of the 90% confidence interval for the quantity $\mu A - 1.25\mu B$ is ≤ 0. If H_0 is rejected, then the Mylan transdermal system will be considered to be non-inferior to the Vivelle-Dot® with regard to adhesion.

The null hypothesis will be tested using the following SAS estimate statement in the Proc GLM analysis of the mean adhesion scores:

Estimate 'A – 0.8B' Intercept 0.2 TREAT 1 -0.8.

A positive value for the Estimate with a p-value ≤ 0.1000 for the t-value constructed as Estimate/SE leads to rejection of H_0. The upper limit of the 90% confidence interval on μA-0.8μB will also be presented.

Sensitization

Observations at a naïve site during the Challenge Phase provide a basis for a dermatologist's interpretation of contact sensitization. Interpretation of a sensitization reaction was based on observation of an edematous reaction score of Grade 3 or greater and characterized by crescendo evolution of the reaction over 72 hours post-removal of the Challenge patch. This reaction is distinguished from an irritation reaction, which would be anticipated to subside after patch removal.

A narrative description of any sensitization reaction was to be documented on the subject's case report form. In the event of an observed sensitization reaction, re-Challenge procedures would have been agreed upon by the clinical site and Sponsor. Sensitization reactions following application of Mylan's estradiol transdermal system will be tabulated and visually compared to those seen with the Vivelle-Dot®. No formal statistical evaluation will be performed on these data.

Study Conduct

Data Sets to be Analyzed:

1) The safety data set consists of all adverse events reported by any subject who was randomized and who had at least one patch of study medication applied.
2) The adhesion data set consists of adhesion scores from any subject who had at least one adhesion score from the Induction Phase patch application 1.
3) The irritation data set consists of irritation scores from subjects who had valid irritation scores for both treatments for all six Induction Phase patch applications.
4) The sensitization data set consists of the sensitization determination from subjects who completed the induction phase, returned after the rest period and had the Challenge Phase patch application.

Discussion of compliance

Patch applications were performed under the direct supervision of the Study coordinators to ensure treatment compliance and proper application at the site location. Labeling of the patches was checked by the clinical personnel for correctness and consistency with the randomization schedule prior to each patch application. In addition, the actual location of the applied patches on the subject's abdomen was checked and documented the next day after first patch application. Subjects were required to have 6 valid cumulative irritation scores for both treatments to qualify for statistical analyses.

Blinding/randomization/retention

Clinic staff, study monitors, and subjects were not blinded to the randomization scheme. The dermatologist or suitably trained personnel who performed the irritation scoring was blinded to the randomization scheme at the time of the evaluations to prevent bias during analysis. The randomization scheme was generated by Mylan Pharmaceuticals Inc., and treatment sequences were randomly assigned to each subject number. The Sponsor supplied sufficient quantities of

the study formulations for the following: (1) completion of this study and (2) retention, as per applicable regulations. All drug supplies provided for this study were stored in a secure area with restricted access, under storage conditions described in the reference drug package labeling.

Prior and Concomitant Medications

Subjects who were taking the following medications were not included in the study:

- Systemic and topical analgesics - within 72 hours prior to the first patch application
- Systemic and topical antihistamines - within 72 hours prior to the first patch application
- Systemic and topical corticosteroids - within 3 weeks prior to the first patch application
- Hormone replacement therapy or hormonal treatments within 3 months prior to the first patch application.

Subjects were not allowed to take any medications listed above or over-the-counter products throughout the entire study, unless such medication was Sponsor approved. Subjects were queried regarding concomitant medications at each study visit.

Study Restrictions:

The following were study prohibitions the subject was instructed to follow when they agreed to participate in this study:

1. Use of any hormone replacement therapy within 3 months prior to study medication dosing, during the study, or during the washout period.
2. Use of any tobacco products within 1 year of start of study, during the study, or during the washout period.
3. Any significant change in dietary or exercise habits throughout the duration of the study (except those imposed by the clinic confinement periods of the study).
4. Subject must restrict from taking any systemic or topical antihistamines, analgesics or corticosteroids throughout the duration of the study.
5. Subject should not use any new over-the-counter product, vitamins, and herbal products during the study. Subject must maintain current drug regimen.
6. Use of perfumes, body lotions or oils prior to transdermal system application or during the wear period.
7. Excessive sweating, long showers, baths, saunas, and soaking in water or swimming will be avoided during each transdermal wear period.
8. Sunbathing or the use of tanning salons during the conduct of the study.

Demographics

Parameters	All Subjects N=228 (all females)
Age	55.1 $\pm$ 3.3
Race	
▪ White	226 (99%)
▪ Black	0
▪ Asian	2 (1%)

▪ Hispanic	0
▪ Other	0
BMI	27.5 ± 4.3

Results

Per the sponsor:

Subject disposition

	Group		Total
	I	II	
Subjects Randomized	135	93	228
Subjects successfully completed	133	88	221
Subjects who withdrew consent	0	2	2
Subjects discontinued by the investigator	2	3	5

Disposition of Enrolled Subjects

Total number of subjects enrolled	228	100.00%
Subjects Included in Safety Analyses	228	100%
Subjects Excluded in Safety Analyses	0	0
Subjects Included in Adhesion Analyses	228	100%
Subjects Excluded in Adhesion Analyses	0	0
Subjects Included in Irritation Analyses	213	93%
Subjects Excluded in Irritation Analyses	15	7%
Subjects Included in Sensitization Analyses	222	97%
Subjects Excluded in Sensitization Analyses	6	3%
Number Completed Study	221	97%
Number of premature discontinuations	7	3%
• Adverse Event	5	2%
• Protocol Violation	1	0.5%
• Lost to Follow-Up	1	0.5%
Safety Population Total	225	100.00%
Evaluable Population	214	95.11%

***Reviewer's comments**: Although it is expected that the "evaluable" irritation population is greater than the "evaluable" sensitization population, those that were excluded from the irritation population were mostly due to not having scores evaluated at the acceptable visit window hours. These subjects still completed the whole induction period, and were thus included in the sensitization population.*

Irritation: (per sponsor):

Number of subjects	Least-Squares Mean		μ_1-μ_2	One-sided 95% Confidence bounds[1]	
	Treatment A (test)	Treatment B (reference)		Lower bound	Upper bound
213	0.165	0.142	0.023	-0.008	0.053

[1] Upper one-sided 95% confidence bound on μ_1-μ_2 is < 0.25, which indicates Mylan estradiol TDS is non-inferior to Vivelle-Dot® TDS

Frequency of Irritation Score Occurrence

	Treatment A, Test patch					*Treatment B, Reference patch*				
Score	*0*	*1*	*2*	*3*	*7*	*0*	*1*	*2*	*3*	*7*
Study Hour										
84	*200*	*8*	*5*	*0*	*0*	*198*	*15*	*0*	*0*	*0*
168	*193*	*18*	*2*	*0*	*0*	*195*	*16*	*2*	*0*	*0*
252	*190*	*16*	*7*	*0*	*0*	*187*	*25*	*1*	*0*	*0*
336	*192*	*12*	*5*	*3*	*1*	*190*	*18*	*5*	*0*	*0*
420	*178*	*21*	*10*	*3*	*1*	*167*	*37*	*9*	*0*	*0*
504	*184*	*21*	*3*	*4*	*1*	*184*	*22*	*6*	*1*	*0*
Total	*1137*	*96*	*32*	*10*	*3*	*1121*	*133*	*23*	*1*	*0*
Total %	*89%*	*7.5%*	*2.5%*	*0.8%*	*0.2%*	*88%*	*10%*	*1.8%*	*0.1%*	*0.0*

Frequency of Mean Cumulative Irritation Scores

Treatment	Frequency of the Mean Irritation Score				
	0	> 0 to ≤ 1	> 1 to ≤ 2	>3	Total
Test	144	61	7	1	213
Reference	130	80	3	0	213

Reviewer's comments:

- *The firm states that a modification of the statistical plan was made due to the nature of the data (both the absolute means, and respective difference between the Test and Reference, are very well below the clinical sensitivity (irritation score of 1) utilized in this study).*
- *Based on this new plan, they state that their patch can be considered no more irritating than Vivelle-Dot® Transdermal System as the upper one-sided 95% confidence bound on μ_T-μ_R was less than 0.25.*
- *Although the firm points out that the majority of scores for both patches were less than or equal to a score of 1 (96.5% for test and 98% for reference), the test patch had a significantly greater number of scores equal to 3 (10 for the test and 1 for the reference) and a greater number of scores equal to 7 (3 for the test and 0 for the reference). In addition, the number of patients with the frequency of mean cumulative irritation score greater than one was 8 for the test and 3 for the reference.*

FDA Statistical Analysis:

Analysis for the mean cumulative irritation scores using mixed model

Test (LS mean μ_T)	Reference (LS mean μ_R)	Upper limit one-sided 95% CB (μ_T-1.25 μ_R)	Pass the non-inferiority test?
0.1925	0.1495	0.047	NO

Frequency of irritation and other effects scores

	Test							Reference						
Visit	Irritation score					Other effect		Irritation score					Other effect	
	0	1	2	3	7	C	H	0	1	2	3	7	C	H
5	200	8	5	0	0	0	0	198	15	0	0	0	0	0
6	193	18	2	0	0	0	0	195	16	2	0	0	0	0
7	190	16	7	0	0	0	0	187	25	1	0	0	0	0
8	192	12	5	3	1	1	3	190	18	5	0	0	2	0
9	178	21	10	3	1	1	3	167	38	8	0	0	2	0
10	184	21	4	3	1	1	4	184	22	6	1	0	1	0

Frequency of the maximum irritation score per subject

Maximum irritation score	0	1	2	3	4	5	6	10
Test	144	42	22	0	0	2	2	1
Reference	130	69	11	1	2	0	0	0

Reviewer's comments: *The one-sided 95% upper CB for the adjusted mean difference (μ_T-1.25μ_R) was greater than zero (0.047) and the non-inferiority test failed for test versus reference patch. In addition, the test patch had a significantly greater number of scores equal to 3 (10 for the test and 1 for the reference) and a greater number of scores equal to 7 (3 for the test and 0 for the reference.*

Sensitization:

The sponsor states that no evidence of sensitization reaction was observed in their study. An edematous reaction score of "3" or greater that was characterized by a crescendo evolution of the reaction over 72-hours post-removal of the Challenge Phase was considered potentially sensitized by the sponsor. This reaction is distinguished from an irritation reaction, which would be anticipated to subside after patch removal. No re-challenge was performed.

Reviewer's comments: *This analysis of sensitization is not consistent with the OGD recommendations. The FDA statistical reviewer is requested to identify subjects with a score of 2 or higher at 48 and/or 72 hours after challenge patch removal and who had higher scores in the challenge period than in the induction period. These subjects are considered potentially sensitized. The test and reference products are to be compared with regard to the sensitization potential based on the proportion of potentially sensitized subjects for each patch type. (If the*

subject had scores in the induction period that were at least as high as the scores in the challenge period, then the reaction should be considered irritation instead of sensitization.)

According to the raw irritation data, no subject was considered potentially sensitized using the OGD's analysis of sensitization also.

FDA Statistical Analysis:
None of the subjects were considered to be potentially sensitized to either product. The test might exceed the reference by at most 1.9 percentage points based on the 95% upper confidence bound for the difference in sensitization rates.

Adhesion:

Per sponsor:

Adhesion Statistical Analysis

Statistical Analysis of Adhesion				
Least-Squares Mean		**μ_1-0.8μ_2**	**Lower bound of 95% confidence region**	**P-value**
Test	Reference			
98.87	98.93	19.73	19.40	<0.0001

According to the firm, their Transdermal System can be considered no less adhesive than Vivelle-Dot® Transdermal System as the lower one-sided 95% confidence bound on μ_T-0.8*μ_R was greater than zero.

Frequency Distribution of Adhesion Scores (per sponsor)

***Test* Patch**	**Study Hour**	**Adhesion Score**								
	Frequency	**0**	**15**	**45**	**55**	**65**	**75**	**85**	**95**	**100**
1	**24hr**	0	0	0	0	0	0	0	0	228
1	**48hr**	0	0	0	0	0	0	1	5	222
1	**72hr**	0	0	0	0	0	1	3	33	191
1	**84hr**	3	1	0	0	0	1	4	57	162
2	**168hr**	1	0	0	0	0	1	15	58	153
3	**252hr**	0	0	0	0	1	2	7	44	174
4	**336hr**	2	0	0	0	0	4	10	70	140
5	**420hr**	1	0	1	0	0	1	7	45	168
6	**504hr**	0	0	0	0	0	0	13	58	152
Total		7	1	1	0	1	10	60	370	1590

Frequency Distribution of Adhesion Scores

***Reference* Patch**	**Study Hour**	**Adhesion Score**								
	Frequency	**0**	**15**	**45**	**55**	**65**	**75**	**85**	**95**	**100**
1	**24hr**	0	0	0	0	0	0	0	1	227

1	**48hr**	0	0	0	0	0	0	0	4	224
1	**72hr**	0	0	0	0	0	0	1	42	185
1	**84hr**	2	0	1	1	0	0	6	67	151
2	**168hr**	2	0	0	0	0	6	20	55	145
3	**252hr**	2	0	0	0	0	2	6	49	169
4	**336hr**	0	0	0	0	0	5	10	79	132
5	**420hr**	0	0	0	0	0	2	13	49	159
6	**504hr**	0	0	0	0	0	4	14	53	152
Total		6	0	1	1	0	19	70	399	1544

Reviewer's comments: *The firm states that the data from the frequency distribution of adhesion scores show that 7 test patches completely fell off vs. 6 patches with the reference. In addition, the total number of patches with adhesion >10% to 70% was 3 for the test vs. 2 for the reference. The total number of patches with adhesion >90% was 1960 for the test vs. 1943 for the reference. As previously mentioned, only the data up to 84hrs should be used for analyzing the adhesion performance per the draft guidance. Accordingly, adhesion scores up to the 84hr mark show that 3 test patches completely fell off vs. 2 patches with the reference. In addition, the total number of patches with adhesion >10% to 70% was 1 for the test vs. 2 for the reference. The total number of patches with adhesion >90% was 803 for the test vs. 787 for the reference*

FDA Statistical Analysis:

Analysis for the mean cumulative adhesion scores using mixed model

Test (Ls mean)	Reference (Ls mean)	Upper limit one-sided 95% CB (test-1.25ref)	Pass the non-inferiority test?
0.027	0.022	0.015	No

Frequency of mean cumulative adhesion scores

Mean	0	0.25	0.5	0.75	1	1.25	1.5
Test	219	4	1	0	2	1	1
Reference	218	6	1	1	1	1	0

Frequency of adhesion scores

Visit	Treatment	Adhesion Score				
		0	1	2	3	4
2	Test	228	0	0	0	0
	Reference	228	0	0	0	0
3	Test	227	1	0	0	0
	Reference	228	0	0	0	0
4	Test	224	4	0	0	0
	Reference	227	1	0	0	0
5	Test	219	5	0	1	3
	Reference	218	6	1	1	2

Reviewer's comments: *From a clinical viewpoint, , the adhesion data does not seem to show a clinically significant difference between the adhesion performance of the test and reference products. There were 3 test patches with a score of 4 vs. 2 reference patches. There was 1 test and 1 reference patch with a score of 3 and 1 reference patch with a score of 2 vs. 0 test patches. The remaining test and reference patches had either a score of 0 or 1. At visit 5, there were 219 test patches vs. 218 reference patches with a score of 0 and 5 test patches vs. 6 reference patches with a score of 1. However, the one-sided 95% upper CB for the adjusted mean difference (μ_T - 1.25μ_R) was greater than zero (0.015) and the non-inferiority test failed for test versus reference patch.*

D. Comparative Skin Sensitization Conclusion

The sponsor states that no evidence of a sensitization reaction was observed in their study. An edematous reaction score of "3" or greater that was characterized by a crescendo evolution of the reaction over 72-hours post-removal of the Challenge Phase was considered potentially sensitized by the sponsor. No re-challenge was performed.

According to the raw irritation data, no subject was considered potentially sensitized using the OGD's analysis of sensitization also.

E. Comparative Irritation Conclusion

Mylan's norelgestromin/ethinyl estradiol transdermal system appears to be **more irritating** than the RLD.

The firm made a modification of the statistical plan due to the nature of the data (both the absolute means, and respective difference between the Test and Reference, are very well below the clinical sensitivity (irritation score of 1) utilized in this study). Based on this new plan, they state that their patch can be considered no more irritating than Vivelle-Dot® Transdermal System as the upper one-sided 95% confidence bound on μ_T-μ_R was less than 0.25.

According to the sponsor, the majority of scores for both patches were less than or equal to a score of 1 (96.5% for test and 98% for reference), the test patch had a significantly greater number of scores equal to 3 (10 for the test and 1 for the reference) and a greater number of scores equal to 7 (3 for the test and 0 for the reference). In addition, the number of patients with the frequency of mean cumulative irritation score greater than one was 8 for the test and 3 for the reference. There were three subjects (Nos. 157, 192 and 203) who had their test sites moved due to irritation for the test patch. Subject 157 had their test sites moved for patches 5 & 6; Subject 192 had their test sites moved for patches 5 & 6; and Subject 203 had their patches moved for patches 5 & 6.

According to the FDA statistical analyses, the 95% upper confidence bounds (CB) for the adjusted mean difference (μ_T -1.25μ_R) was greater than zero (0.047) for irritation. The least mean cumulative score for irritation was 0.1925 for the test and 0.1495 for the reference. In addition, the 95% upper confidence bound for difference in proportions of test versus reference

based on the dichotomized irritation score was at most 4.7% with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1 or to 3.

F. Adhesion Conclusion

According to the FDA statistical analysis, the 95% upper confidence bound (CB) for the adjusted mean difference (μ_T -1.25μ_R) was greater than zero (0.015). **Thus, the test product was found to be inferior to the reference.** Based on the 95% upper confidence bound for the difference in detachment rates of greater than or equal to 10% detached (score≥1), the test might exceed the reference by at most 3.2 percentage points for the mean of the adhesion score.

V. Comparative Review of Safety

A. Brief Statement of Conclusions

No significant safety concerns were identified in this study.

B. Description of Adverse Events

Out of 228 subjects enrolled into the study, 166 (72.8%) subjects experienced a total of 527 adverse events (AEs) over the course of the study. The majority of the adverse events were mild in severity. Most of the adverse events were definitely related to the study medications. There were 2 serious adverse events, which were considered probably related to the study medication.

Serious Adverse Event narratives:
Subject (#120), a 57 year-old white female experienced a serious adverse event, classified as an important medical event. Informed consent was signed on October 16, 2009 and dosing began on November 08, 2009. During the study the subject received two treatments (estradiol TDS and Vivelle-Dot TDS) placed simultaneously (total dose 0.05 mg/day) on the abdomen for a 3.5-day wear cycle per application over a total of 6 applications (21 days), followed by a 14-day Rest phase and 1 application during a subsequent 48-hr Challenge phase, followed by 3 days of observation and irritation evaluations. Signs of multiple uterine myoma in regression stage and focal changes of endometrium was detected during a post-study uterine ultrasound performed on December 18, 2009. A repeat uterine ultrasound examination conducted on January 27, 2010 revealed signs of uterine myoma and possibly endometrial hyperplasia. After uterine ultrasound on March 11, 2010 and consecutive gynecologist consultation on April 01, 2010, the subject was diagnosed with the presence of an endometrial polyp, uterine myoma and involution. The investigator assessed the events as probably related to the study medications. Based on this result, a gynecologist recommended a hysteroscopy and uterine diagnostic scraping.

Subject (#192), a 54 year-old white female has been hospitalized and underwent surgical intervention two month after completion clinical study procedures. Informed consent was signed on (b) (4) During the study the subject received two treatments (estradiol TDS and Vivelle-Dot TDS) placed simultaneously (total dose 0.05 mg/day) on the abdomen for a 3.5-day wear cycle per application over a total of 6 applications (21 days), followed by a 14-day Rest phase and 1 application during a subsequent 48-hr Challenge phase, followed by 3 days of observation and irritation evaluations. Hyperplastic

process of endometrium (9.2 mm) was determined during the study exit uterine ultrasound observation on (b) (4) The uterine ultrasound repeated on (b) (4) showed positive dynamics and absence of endometrial thickening (4.6 mm). Subject was requested to have one more additional uterine ultrasound observation in 1 month however subject was lost to follow-up as she did not answer multiple phone calls. Subject called the clinic on (b) (4) and informed that she visited her gynecologist in the (b) (4) and underwent hysteroscopy with diagnostic scraping due to "Endometrial hyperplasia". As per the subject, results of the histological examinations were good, and she was removed from observation. The investigator assessed the events as probably related to the study medications. Based on this result, a gynecologist recommended a hysteroscopy and uterine diagnostic scraping.

The most common adverse events (experienced by greater than 2% of subjects) were application site erythema (47.8%), abdominal pain lower (13.2%), headache (8.8%), asthenia (7.0%), application site irritation (6.6%), insomnia (6.6%), application site pain (5.3%), nausea (5.3%), application site pruritus (5.3%), blood pressure increased (4.8%), hydrometra (4.8%), ovarian disorder (4.4%), back pain (4.0%), endometrial hyperplasia (3.1%), ovarian cyst (3.1%), hot flush (2.2%).

There were two (2) types of adverse events (application site erythema and application site irritation) that were considered related to the transdermal administration of the Test and Reference products. The most frequently reported adverse event (AE) was application site erythema which was reported for only the Test product in 10 (4.39%) of the subjects, for only the Reference product in 25 (10.96%) of the subjects and for both products by 64 (28.07%) of the subjects.

Application site irritation was reported for only the Test product in 2 (0.88%) of the subjects, for only the Reference product in 0 (0%) of the subjects and for both products by 4 (1.76%) of the subjects.

		Number of (%) of subjects	
Adverse Events	Number of Adverse Events	Test Product	Reference Product
Application site erythema	0	154 (67.54%)	139 (60.96%)
	1	54 (23.68%)	64 (28.07%)
	2	16 (7.02%)	23 (10.09%)
	3	1 (0.44%)	2 (0.88%)
	4	2 (0.88%)	0
	5	1 (0.44%)	0
Application site irritation	0	222 (97.37%)	224 (98.25%)
	1	3 (1.32%)	4 (1.75%)
	2	3 (1.32%)	0

VI. Relevant Findings From Office of Scientific Investigations, Statistics and/or Other Consultant Reviews

Based on the OSI inspection dated 02/25/2013 to 03/01/2013, no significant objectionable conditions were observed and Form FDA 483 was not issued.

Final classification:
NAI: The Federal State Enterprise "Scientific Research Center for Preventive Medicine of Federal Agency of High Technology Medical Care", Moscow, Russia.

The reviewers recommend that the data for the clinical portion of the study EDOT-0908 be accepted for further agency review.

VIII. Conclusion and Recommendation

A. Conclusion

The data submitted to ANDA 201675, for irritation, sensitization and adhesion of Mylan's Estradiol Transdermal System are **not** adequate to demonstrate that it is no more irritating than the RLD system and **does not demonstrate** that it adheres as well as the RLD. The data shows that the test product has no greater potential to cause sensitization than the reference listed drug (RLD), Vivelle Dot®.

B. Recommendation

This application is therefore **not** recommended for approval from a clinical bioequivalence perspective.

CLINICAL REVIEW

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 201675 APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Estradiol Transdermal System, USP 0.025 mg/day; 0.0375 mg/day; 0.05 mg/day; 0.075 mg/day and 0.1 mg/day

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows ___ YES __X__NO

The Division of Clinical Review has completed its review of your skin irritation, sensitization, and adhesion data and has identified the following deficiencies:

1. You have not provided adequate data to ensure that the adhesive performance of your product is at least as good as that of the RLD and that the irritation potential of your product is non-inferior to the RLD.

   In the skin irritation, sensitization and adhesion study (**EDOT-0908)**, your product was statistically significantly less adhesive than the reference product and failed to show that it is no more irritating than the RLD .

2. There are still outstanding issues related to the specification limits of certain excipients that must be resolved. Comments will be forthcoming from the OGD Chemistry Division.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. These comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

{See appended electronic signature page}

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

Appendix A

Active ingredient: Estradiol

Form/Route: Film, Extended Release/Transdermal

Recommended studies: 2 studies

1. Type of study: Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints and Adhesion Study
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.1 mg/24 hr
   Subjects: Healthy, non-smoking, postmenopausal women with no contraindication to estrogen therapy
   Additional comments:
   - The transdermal patch should be applied to clean, dry, intact, healthy skin on the lower abdomen below the waistline, as recommended in the approved reference listed drug (RLD) labeling, and worn for 3.5 days (84 hours).
   - An average baseline correction is obtained by averaging the 3 pre-application sampling times (-48, -24 and 0 hours).
   - A washout period of 7 days after removal of the Estradiol transdermal patch is recommended.
   - Observations and rating of skin adhesion should be documented during this study.

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2. Type of study: Skin Irritation, Sensitization and Adhesion Study
   Design: Randomized, evaluator-blinded, in vivo within-subject repeat test
   Strength: 0.025 mg/24 hr
   Subjects: Healthy, non-smoking, postmenopausal women with no contraindication to estrogen therapy
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the skin irritation, sensitization and adhesion study:

1. The Office of Generic Drugs (OGD) recommends evaluating skin irritation, sensitization and adhesion in a single study. To support approval, the test product must be no more irritating than the RLD, be no more sensitizing than the RLD and adhere at least as well as the RLD. Each parameter is to be evaluated with a separate analysis. The primary endpoints should be considered as co-primary endpoints, e.g., for each of them, the study must demonstrate that the test product is no worse than the RLD. The analysis for each parameter and the primary endpoint(s) and any secondary endpoint(s) for each analysis are to be clearly defined in the protocol prior to the start of the study. A clear, objective definition of a sensitization reaction is also to be prespecified in the protocol.

2. The recommended study consists of two phases, a 21-day Induction Phase, followed by a 14 to 17 day rest period, and a Challenge Phase.

   During the Induction Phase, all test articles (i.e., 0.025 mg/24 hr test product[1], 0.025 mg/24 hr

[1] The test product evaluated should be the actual patches to be marketed.

RLD patch, optional vehicle patch[2] and optional negative control[3]) are to be applied simultaneously to each subject at different sites on the lower abdomen, below the waistline as recommended in the approved reference listed drug (RLD) labeling, with sequential patch applications to the same skin sites every 84 hours for a total of 21 consecutive days. Thus, it is recommended to apply the patches 2 times per week on Monday and Thursday (e.g., Days 1, 4, 8, 11, 15 and 18) to the same sites and to have each of them remain in place for 84 hours (a total of 21 days altogether). The Day 18 patches would be removed on Day 22. The irritation evaluation is to be conducted during the Induction Phase, with assessment of "Dermal Response" and "Other Effects" at the time of each patch change.

The Challenge Phase consists of a single 48-hour application of the 0.025 mg/24 hr test product, 0.025 mg/24 hr RLD patch, optional vehicle patch and optional negative control to a naïve site followed by an assessment of "Dermal Response" and "Other Effects" at 30 minutes and at 24, 48, and 72 hours after challenge patch removal, with a narrative description of any reactions observed, together with the opinion of the investigator as to whether such reactions are felt to be indicative of a contact sensitization. A re-challenge test four to eight weeks following the original challenge, conducted in the same manner, is recommended for all subjects with a potential sensitization reaction.

3. A study on the lowest strength would support each higher strength provided that the concentration of each ingredient per unit area is identical.

4. As a safety precaution, evaluate the subject's seated blood pressure at all visits.

5. An adequate number of subjects should be enrolled to ensure that at least 200 evaluable subjects are included in the PP population.

6. The irritation and adhesive properties may be sensitive to climate conditions. Therefore, the OGD prefers that the study be conducted in multiple centers with different climate conditions.

7. Subjects should not apply make-up, creams, lotions, powders, or other topical products to the skin area where the patch will be placed, as this could affect adhesive performance or irritation potential.

8. Assignment of the test product, RLD, optional vehicle patch, and optional negative control to skin sites should be randomized. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity for each application site on each subject.

9. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, "Handling and Retention of BA and BE Testing Samples", regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, "Good Clinical Practice: Consolidated

[2] The optional vehicle patch should have all of the inactive ingredients and be identical to the test product in every manner except for the absence of estradiol.
[3] An example of the optional negative control is an occlusion type device with normal saline applied on a polyester pad within the device chamber.

Guideline", for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected by each drug site prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

10. Inclusion Criteria (the sponsor may add additional criteria):
    a. Healthy, non-smoking, postmenopausal female subjects with no contraindication to estrogen therapy. "Postmenopausal" is defined as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.
    b. Baseline systolic blood pressure no greater than 150 mm Hg and diastolic blood pressure no greater than 90 mm Hg.
    c. Subjects >40 years have documentation of a negative screening mammogram (obtained at screening or within 9 months of study enrollment) and normal clinical breast examination prior to enrollment in study.
    d. Subjects with intact uterus have baseline vaginal ultrasonography demonstrating inactive endometrial lining with endometrial thickness less than 4 mm.

11. Exclusion Criteria (the sponsor may add additional criteria):
    a. Male subject.
    b. Premenopausal, perimenopausal, pregnant or lactating subject.
    c. Findings indicating any suspicion of breast malignancy.
    d. Subject with tobacco use, obesity, undiagnosed abnormal genital bleeding or a history of significant risk factors for endometrial cancer.
    e. History of venous thromboembolism, pulmonary embolism, stroke, endometrial cancer, breast cancer, cholestatic jaundice, hypertension, serious heart problems, heart failure, myocardial infarction, ventricular arrhythmia, exertional chest pain, insulin dependent diabetes, hypercholesterolemia, hypertriglyceridemia, systemic lupus erythematosus, impaired liver function, or significant renal dysfunction.
    f. History of narcotic abuse, drug abuse or alcoholism.
    g. Medical history of condition that would significantly influence the immune response (e.g., primary or acquired immunodeficiencies such as human immunodeficiency virus (HIV) positive or AIDS, allergic diseases such as anaphylaxis, asthma or generalized drug reaction, neoplasms such as lymphoma or leukemia, rheumatoid arthritis or systemic lupus erythematosus).
    h. Medical history of significant dermatologic diseases or conditions, such as atopy, psoriasis, vitiligo or conditions known to alter skin appearance or physiologic response (e.g. diabetes, porphyria).
    i. History of significant dermatologic cancers (e.g. melanoma, squamous cell carcinoma), except basal cell carcinomas that were superficial and did not involve the application sites.
    j. Within 6 months prior to dosing, estrogen pellet therapy or progestin injectable drug therapy.
    k. Within 3 months prior to dosing, progestin implants and estrogen alone injectable drug therapy.
    l. Within 8 weeks prior to dosing, oral estrogen and/or oral or intrauterine progestin therapy.
    m. Within 4 weeks prior to dosing, transdermal estrogen alone or transdermal estrogen/progestin products.
    n. Within 3 weeks prior to dosing, use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product (e.g. cyclosporine, tacrolimus, systemic or topical corticosteroids, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG),

monoclonal antibodies, radiation therapy).

o. Within 1 week prior to dosing, vaginal hormonal products (rings, creams, gels).
p. Within 72 hours prior to dosing, use of antihistamines or use of topical drugs at patch site.
q. Subject has an obvious difference in skin color between arms or the presence of a skin condition, excessive hair at the application sites, scar tissue, tattoo, or coloration that would interfere with placement of test articles, skin assessment, or reactions to drug.
r. Presence of open sores at the application sites.

12. Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
    a. Antihypertensives and pressor agents.
    b. Estrogens, other than study medication.
    c. Use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product (e.g. antihistamines, systemic or topical corticosteroids, cyclosporine, tacrolimus, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG), monoclonal antibodies, radiation therapy).

13. Subjects should be advised to avoid exposing the patch application site to external sources of direct heat, (e.g., hair dryers, heating pads, electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight) while wearing the patch.

14. During the induction phase, subjects should have the first patch placed on Day 1 and return for adhesion scoring, patch removal, irritation scoring, and patch replacement on Days 4, 8, 11, 15 and 18 and return for adhesion scoring, patch removal and irritation scoring on Day 22. After wearing the challenge patch for 48 hours (or until removal due to intolerable reaction), subjects should return for adhesion scoring, patch removal and irritation scoring at 30 minutes and at 24, 48, and 72 hours after challenge patch removal. Scoring of patch adherence and skin reactions should be performed by a trained and blinded observer at each patch removal. All efforts should be made to ensure that the same scorer is used for most (preferably all) observations. If the same scorer is not used in all cases, inter-scorer variability needs to be addressed in the protocol, specifying the training and standards for each score.

15. Due to likely differences in appearance of the patches, blinding of the observer/evaluator may not be possible, especially for evaluation of patch adhesion, which requires direct observation of the patch itself. However, efforts should be made to blind the evaluation of irritation and sensitization.

16. To ensure adequate adhesion of the test and reference patches in the study, adhesion scores are to be recorded just prior to patch removal. The recommended scoring system for adhesion of transdermal patches is indicated as follows:

    0 = ≥ 90% adhered (essentially no lift off the skin)
    1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin)
    2 = ≥ 50% to < 75% adhered (less than half of the patch lifting off the skin)
    3 = > 0% to < 50% adhered but not detached (more than half of the patch lifting off the skin without falling off)
    4 = 0% adhered - patch detached (patch completely off the skin)

17. During both the Induction Phase and Challenge Phase, the skin reactions are to be evaluated and scored according to the following two scales[4]:

Scale 1: Dermal Response

Skin Appearance	Score
No evidence of irritation	0
Minimal erythema, barely perceptible	1
Definite erythema, readily visible; or minimal edema; or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond test (i.e., application) site	7

Scale 2: Other Effects

Observation	Score (Numeric equivalent)
Slightly glazed appearance	A (0)
Marked glazed appearance	B (1)
Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)
Film of dried serous exudates covering all or part of the patch site	G (3)
Small petechial erosions and/or scabs	H (3)

When an "Other Effects" score is observed, each score should be reported as a number and letter combination score and also as a numerical total (i.e. numerical "Dermal Response" score + numeric equivalent for the "Other Effects" lettered score).

18. For subjects who experience irritation consistent with a combined score of ≥ 3, or who experience symptomatic intolerable irritation, the patch may be moved to a new site in order to complete the 21-day Induction Phase and continue with the sensitization part of the study. In this circumstance the highest score observed (not truncated to 3) prior to discontinuation of a patch site should be carried forward for all remaining observations in the irritation analysis.

19. After the first application, the adhesion performance of subsequent same site applications could be affected by skin stripping or residual adhesive. Therefore, formally evaluate and compare the adhesion performance of only the first applied test product and RLD for 3.5 days (84 hours) after application. Daily adhesion evaluations are recommended during the first 3.5 day application. For patches that completely detach, a score of 4 should be carried forward in the adhesion analysis for all remaining observations in the application period. No patch reinforcement is allowed when the

[4] Berger RS and JP Bowman. A reappraisal of the 21-day cumulative irritation test in man. *J. Toxicol.-Cut. & Ocular Toxicol.* 1982; 1 (2); 109-115.

study is being used to establish adequate adhesion performance to support product approval; thus, no patch reinforcement should be permitted for the first applied test product and RLD patches. Adhesion should also be evaluated prior to patch removal throughout the entire study period to ensure adequate skin contact for maximal induction of irritation and sensitization.

20. Criteria may be established for using tape or an overlay to reinforce any patches (after the first application) that are lifting. This may be preferable to replacing detached patches, because shorter application intervals could give different irritation results. If the patch is reinforced with tape or an overlay, skin irritation associated with the tape or overlay area should be reported separately from that of the patch application area.

21. If a patch completely detaches, it should be replaced within 24 hours and the subject should continue in the study. During the 21-day Induction Phase, if a patch is completely detached for more than 24 hours (unless the patch was removed for an unacceptable degree of irritation), the subject should be excluded from both the irritation and sensitization analyses for that product. During the 48-hr Challenge Phase, if a patch is completely detached for more than 24 hours, the subject should be excluded from the sensitization analysis. The subject should note the date and time of detachment as soon as it occurs.

Safety Data and Analyses

22. All application site reactions are to be reported in the data tables and in the detailed narrative description for each subject's response in both phases of this study in the study report. These would include patient complaints such as dryness, itching, burning, pain, or soreness, etc., identifying to which application site the complaint applies. These reports are to be compared between test articles.

23. The safety analyses should include all patients who received a dose of study medication. Safety analyses should include comparing the test product, RLD, optional vehicle patch, and optional negative control with regard to the occurrence and severity of application site adverse events (AEs). Systemic drug-related AEs and concomitant medications are also to be reported but cannot be distinguished between test articles.

Skin Irritation Data Tables and Analyses

24. For each day during the Induction Phase when the skin is evaluated for irritation, please provide a frequency table showing the number of applications of each test article with each combined "Dermal Response" and "Other Effect" score, using Last Observation Carried Forward for subjects who discontinued a test article because of unacceptable irritation. Please refer to Table 1 as an example.

Table 1: Number (%) of Applications by Induction Phase Day and Test Article with a Specific Combined "Dermal Response" and "Other Effect" Score

Induction Phase Scoring Day; Test Article	**Combined "Dermal Response" and "Other Effect" Score**										
	0	**1**	**2**	**2A**	**2B**	**3**	**3A**	**3B**	**3C**	**3F**	**etc.**
Day 4; Test Product											
Day 4; RLD											
Day 4; Vehicle Patch (optional)											
Day 8; Negative Control (optional)											

Induction Phase Scoring Day; Test Article	Combined "Dermal Response" and "Other Effect" Score										
	0	1	2	2A	2B	3	3A	3B	3C	3F	etc.
Day 8; Test Product											
Day 8; RLD											
etc.											

25. The Analysis Populations should be defined separately for each parameter and should be defined per patch instead of per subject. The Per Protocol (PP) Population for evaluation of skin irritation should be defined as follows:

    Irritation Analysis– the test articles need to be applied sequentially to the same site for the entire 21 day induction phase (without any period of detachment longer than 24 hours) to be evaluated for the cumulative irritation effect OR if a patch is moved or removed due to excessive irritation, it should be included using Last Observation Carried Forward (LOCF).

26. For each test article (test product, RLD, optional vehicle patch and optional negative control), the mean cumulative irritation score is to be calculated as the sum of all combined "Dermal Response" and "Other Effects" scores observed at each observation divided by the total number of observations.

27. In addition to the cumulative irritation scores, the following data should be provided for each test article:
    a. Total number of observations with a combined "Dermal Response" and "Other Effects" irritation score of 3 or more for each test article.
    b. Number of patches that were moved or removed due to an unacceptable degree of irritation.
    c. Number of days until sufficient irritation occurred to preclude repeat application to the same site.

28. To demonstrate non-inferiority of the test product compared to the RLD with regard to the cumulative irritation scores, the upper bound of the one-sided 95% CI of the mean test product score minus 1.25 times the mean RLD score must be less than or equal to 0. For the irritation evaluation, the OGD also considers other clinically relevant data including the number of applications that reach a maximal irritation score and the number of subjects that discontinue the product applications because of unacceptable irritation.

    The same mean cumulative score could be reached with a small number of high scores (e.g., >/= 3) as with a larger number of low scores (e.g., 1, which are of little clinical significance). Thus, it is difficult to determine the clinical meaningfulness of a given cumulative score or a given difference between products with regard to mean cumulative scores. Therefore, in addition to cumulative scores, it is necessary to also evaluate the proportion of subjects with a meaningful degree of irritation for each product. The proportion of subjects with a meaningful degree of irritation should be no higher for the test product than for the RLD, and irritation should not occur earlier in the application period for the test product than for the RLD. To be approved, the test product must be non-inferior with regard to cumulative irritation scores and also show no meaningful difference with regard to degree of irritation.

Sensitization Data Tables and Analyses

29. Please provide a frequency table showing the number of applications of each test article during the Challenge Phase with each specific combined "Dermal Response" numerical score and "Other

Effect" letter score at each evaluation time point.

30. For all subjects with at least one combined score of 2 or more at 48 or 72 hours after patch removal in the Challenge Phase, please provide a table showing the actual scores for each subject at each evaluation time point during the Induction and Challenge Phases.

31. The Analysis Populations should be defined separately for each parameter and should be defined per patch instead of per subject. The PP Population for evaluation of sensitization should be defined as follows:

    Sensitization Analysis – includes all test articles worn (without any period of detachment longer than 24 hours) for the full 21 day induction phase AND the entire 48-hour challenge phase AND the subject must return for at least one of the scheduled evaluations at 48 and 72 hours after removal of the challenge patch. If a test article is removed prior to the end of the 48-hour challenge phase due to an intolerable reaction, the application site should be evaluated at 24, 48, and 72 hours after patch removal and be included in the sensitization analysis using LOCF.

32. For each test article, individually evaluate each PP subject with a combined score of 2 or greater at 48 or 72 hours after patch removal during the Challenge Phase for potential sensitization. A narrative description of each reaction in the challenge phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of a contact sensitization. Consider a subject to be potentially sensitized if all of the following criteria are met:
    a. The subject has at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch.
    b. The subject has a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.
    c. The combined "Dermal Response" and "Other Effects" numeric scores obtained during the Challenge Phase evaluations are generally higher than the combined "Dermal Response" and "Other Effects" numeric scores obtained during the Induction Phase.
    d. If the subject completed a Rechallenge Phase, the above 3 criteria were met during both the Challenge Phase and the Rechallenge Phase.

    Scores that resolve before 48 hours are generally considered to be due to irritation instead of sensitization. Provide the total number of subjects considered sensitized to the test product and RLD.

33. The sponsor should provide descriptive statistics comparing the proportion of subjects sensitized or potentially sensitized to each test article.

Adhesion Data Tables and Analyses

34. Please provide a frequency table showing the number of patches with each adhesion score at each evaluation time point during the first application of the test product and RLD. Also provide the number of patches that are completely detached at each evaluation time point for the test product and RLD. If a patch is completely detached, provide the time from patch application to complete detachment (i.e., duration of patch wear) for the test product and RLD. If a patch is reinforced, provide the time from patch application to reinforcement for the test product and RLD.

35. The Analysis Populations should be defined separately for each parameter and should be defined per patch instead of per subject. The PP Population evaluation for adhesion should be defined as follows:

    Adhesion Analysis – should include all patches except those removed early for unacceptable irritation or those that dropped out of the study before the end of the first 3.5 days (84-hour) application.

36. The adhesion score and the time from application until patch detachment (i.e., duration of patch wear) should be evaluated for the first application of the test product and RLD, and a statistical analysis of the comparative results should be performed.

    The adhesion evaluation of the active test product and RLD must demonstrate that the upper bound of the one-sided 95% CI of the mean adhesion score for the test product minus 1.25 times the mean adhesion score for the RLD must be less than or equal to 0. For the adhesion evaluation, OGD also considers the number of subjects that experience detachment or unacceptable adhesion scores and how early in the application period those unacceptable scores are observed.

    The same mean score could be reached with a small number of high scores (e.g., >/= 3) as with a larger number of low scores (e.g., 1, which are of little clinical significance). Thus, it is difficult to determine the clinical meaningfulness of a given mean score or a given difference between products with regard to mean scores. Therefore, in addition to mean scores, it is necessary to also evaluate the proportion of subjects with a meaningful degree of detachment for each product. The proportion of subjects with a meaningful degree of detachment should be no higher for the test product than for the RLD, and detachment should not occur earlier in the application period for the test than for the RLD. To be approved, the test product must be non-inferior with regard to mean adhesion scores and also show no meaningful difference with regard to degree of detachment.

Data Submission

37. Study data should be submitted to the OGD in electronic format.
    a. A list of file names, with a simple description of the content of each file, should be included.
    b. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
    c. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
    d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
    e. Please provide a separate dataset for each study to include such variables as demographics, baseline admission criteria, baseline vital signs, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.

38. Please provide a summary dataset containing a separate line listing for each test article per subject (if data exist) using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Site identifier: study center
    d. Age

e. Age units (years)
f. Sex
g. Race
h. Name of Actual Treatment (exposure): test article (i.e., test product, RLD, optional vehicle patch and optional negative control)
i. Location of Dose Administration: patch application site
j. Duration of Treatment (total exposure in days) during Induction Phase: time from first application to discontinuation of test article during Induction Phase
k. Duration of Treatment (total exposure in days) during Challenge Phase: time from first application to discontinuation of test article during Challenge Phase
l. PP population inclusion for irritation analysis (yes/no)
m. Reason for exclusion from PP population for irritation analysis
n. PP population inclusion for sensitization analysis (yes/no)
o. Reason for exclusion from PP population for sensitization analysis
p. PP population inclusion for adhesion analysis (yes/no)
q. Reason for exclusion from PP population for adhesion analysis
r. Test article moved (yes/no)
s. Number of times test article moved
t. Test article discontinued (yes/no)
u. Reason for test article discontinuation
v. Adverse event(s) reported for this treatment arm (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of a summary dataset for each individual test article per subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXLOC	EXDURind	EXDURch	ppirr	ppirr_rs
101	1	01	54	YEARS	M	1	A	RLA	21	2	Y	
101	1	01	54	YEARS	M	1	B	LLA	21	2	Y	
101	2	01	45	YEARS	M	2	A	RLA	21	2	Y	
101	2	01	45	YEARS	M	2	B	LLA	21	2	Y	

ppsen	ppsen_ rs	ppadh	ppadh_rs	mv	mv_n	dis	dis_rs	AErpt
Y		Y		Y	1	N		N
Y		Y		Y	1	N		N
N	B	N	B	N		N		N
N	B	N	B	N		N		N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study
SITEID: Study Site Identifier
AGE: Age
AGEU: Age units (years)
SEX: Sex, e.g., M=Male, F=Female, U=Unknown
RACE: Race, e.g. 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
EXTRT: Name of Actual Treatment (exposure), e.g. A=test product, B=RLD, C=optional vehicle patch, D=optional negative control
EXLOC: Location of Dose Administration (exposure): specific anatomical site of patch application, e.g., RLA=right lower abdomen, LLA=left lower abdomen
EXDURind: Duration of Treatment during Induction Phase (exposure in days; 21 days exposure planned during Induction Phase)
EXDURch: Duration of Treatment during Challenge Phase (exposure in days; 2 days exposure planned during Challenge Phase)
ppirr: PP population for irritation analysis, e.g., Y=Yes, N=No
ppirr_rs: Reason for exclusion from PP population for irritation analysis, e.g., A=prematurely discontinued prior to completing irritation phase due to AE that was not intolerable irritation, B=failed to complete irritation phase due to lost to follow-up, C=failed to complete irritation phase due to subject moved out of the area, etc.
ppsen: PP population for sensitization analysis, e.g., Y=Yes, N=No
ppsen_rs: Reason for exclusion from PP population for sensitization analysis, e.g., A=prematurely discontinued prior to completing challenge phase due to AE that was not intolerable irritation, B=failed to return for at least one of the two challenge visits at 48 and 72 hours, etc.
ppadh: PP population for adhesion analysis, e.g., Y=Yes, N=No
ppadh_rs: Reason for exclusion from PP population for adhesion analysis, e.g., A=prematurely discontinued prior to completing Day 1 adhesion scoring due to AE that was not intolerable irritation, B=failed to complete Day 1 adhesion scoring due to lost to follow-up, C=failed to complete Day 1 adhesion scoring due to subject moved out of the area, etc.
mv: Test article moved, e.g., Y=Yes, N=No
mv_n: Number of times test article was moved, e.g., 1, 2, 3, etc.
dis: Discontinuation of the test article, e.g., Y=Yes, N=No
dis_rs: Reason for test article discontinuation, e.g., A=irritation, etc.
AErpt: Adverse event(s) reported for this treatment arm, e.g., Y=Yes, N=No

39. For the Irritation and Sensitization Analyses, please provide a separate line listing for each individual test article per subject, per each visit (if data exist) using the following headers, if applicable:
    a. Subject identifier
    b. Treatment: test article (i.e., test product, RLD, optional vehicle patch and optional negative control)
    c. Application Sequence: number of particular test article application (i.e., 1=first, 2=second, 3=third)
    d. Location of Dose Administration: test article application site

e. Visit number
f. Visit date
g. Number of days since baseline visit
h. Application day of week (i.e., Sunday, Monday, Tuesday, etc.)
i. Application date and time
j. Date and time of removal or complete detachment
k. Duration of Treatment: time (hours) from individual test article application to removal or complete detachment
l. Reason for exclusion of data from this individual test article from analysis
m. Scoring date
n. Adhesion score
o. Induction "Dermal Response" numeric score for each site
p. Induction "Other Effects" letter score for each site
q. Challenge "Dermal Response" numeric score for the site
r. Challenge "Other Effects" letter score for the site
s. Potentially sensitized (yes/no)
t. Identity of the evaluator
u. Was the individual test article reinforced with tape or overlay (yes/no)
v. If individual test article was reinforced, time from individual test article application to reinforcement
w. Individual test article moved (yes/no)
x. Number of times individual test article moved
y. Date of each move of individual test article
z. Individual test article discontinued (yes/no)
aa. Reason for discontinuation
bb. Date individual test article discontinued
cc. Adverse event reported during this visit (yes/no)

Please refer to Table 3 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 3: Example of dataset containing one line listing for each individual test article per visit per subject

SUBJID	EXTRT	EXSEQ	EXLOC	VISITNUM	SVSTDTC	ELTMBS	day_wk	itaSTDTC	itaENDTC	itaDUR	exc_rs	scr_date	adh_2	adh_3	ind_n1	ind_c1
1	A	1	RLA	1	2004-07-01	1	Monday									

ind_n2	ind_c2	ind_n3	ind_c3	ch_n1	ch_c1	potsens	EVAL	reinf	reinf_tm	mv	mv_n	mv_dt1	mv_dt2	mv_dt3	dis	dis_rs	dis_dt	AErpt

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

SUBJID:	Subject Identifier for the Study
EXTRT:	Name of Actual Treatment (exposure), e.g. A=test product, B=RLD, C= optional vehicle patch, D=optional negative control
EXSEQ:	Sequence Number of exposure to particular test article (e.g. application number 1, 2, 3, etc.)
EXLOC:	Location of Dose Administration (exposure): specific anatomical site of patch application, e.g., RLA=right lower abdomen, LLA=left lower abdomen
VISITNUM:	Visit Sequence Number
SVSTDTC:	Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL:	Elapsed Time since Baseline (days)
day_wk:	Day of week of individual test article application (i.e., Sunday, Monday, Tuesday, etc.)
itaSTDTC:	Individual test article application date and time: start date/time of individual test article
itaENDTC:	Individual test article removal date and time: end date/time of individual test article
itaDUR:	Individual test article exposure duration (hours) (i.e., time from individual test article application to removal)
exc_rs:	Reason for exclusion of data from this individual test article from analysis, e.g., A=subject did not show for appointment, B=test article detached for more than 24 hours, C=protocol/exclusion criteria violation, etc.
scr_date:	Scoring date
adh_2:	Adhesion score for Day 2
adh_3:	Adhesion score for Day 3 (etc., for Days 4, 8, 11, 15, 18 and 22)
ind_n1:	Numeric “Dermal Response” score for the first site during Induction
ind_c1:	Character “Other Effects” score for the first site during Induction
ind_n2:	Numeric “Dermal Response” score for the second site (if application site moved due to excessive irritation) during Induction
ind_c2:	Character “Other Effects” score for the second site during Induction
ind_n3:	Numeric “Dermal Response” score for the third site during Induction
ind_c3:	Character “Other Effects” score for the third site during Induction
ch_n1:	Numeric “Dermal Response” score for the Challenge site
ch_c1:	Character “Other Effects” score for the Challenge site
potsens:	Potentially sensitized
EVAL:	Evaluator: identity of the evaluator
reinf	Individual test article reinforced with tape or overlay, e.g., Y=Yes, N=No
reinf_tm	If individual test article was reinforced, time (hours) from individual test article application to reinforcement
mv:	Individual test article moved, e.g., Y=Yes, N=No
mv_n:	Number of times individual test article was moved, e.g., 1, 2, etc.
mv_dt1:	Date of first move of individual test article
mv_dt2:	Date of second move of individual test article
mv_dt3:	Date of third move of individual test article
dis:	Discontinuation of the individual test article, e.g., Y=Yes, N=No
dis_rs:	Reason for individual test article discontinuation, e.g., A=irritation, etc.
dis_dt:	Date individual test article discontinued
AErpt:	Adverse Event reported during this visit, e.g., Y=Yes, N=No

40. Please note that the guidance provided here supersedes information provided in the *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products*, which has been withdrawn. The information given here is general in nature and represents the current thinking of the OGD for this product and may not be appropriate for other transdermal products.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE LEE
05/16/2013

JOHN R PETERS
05/17/2013

DALE P CONNER
05/23/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201675Orig1s000

CHEMISTRY REVIEW(S)

A. Check List

Solid IR/Oral Sol. RPN < 60 or Injection/Ophthalmic Q1/Q2 = RLD – 2 Tier	☐
First Generic – 3 Tier	☐
Other Criteria under "Exceptions List" for Table 1 of SOP – 3 Tier	☒

B. Approvability: – ***Approvable***

ANDA #201675

Estradiol Transdermal System USP (Twice Weekly), 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

Mylan Technologies Inc.

CR #4
Guohua Li, Ph.D.

Chemistry Division V

Table of Contents

Chemistry Review Data Sheet

1. **ANDA: 201675**

2. **REVIEW #: 4**

3. **REVIEW DATE: 09/05/2014, 09/22/2014**

4. **REVIEWER: Guohua Li, Ph.D.**

5. **PREVIOUS DOCUMENTS:**

Submissions	Submission Date
Original Submission (SD #1)	04/26/2010
Quality/Quality Information (SD #4)	01/04/2011
Bioequivalence/Dissolution (SD #8)	07/28/2011
Quality/Response to information request (SD #11)	06/15/2012
Quality/Response to information request (SD #15)	08/15/2013

6. **SUBMISSION(S) BEING REVIEWED:**

Submissions	Submission Date
Amendment (SD #22)	06/23/2014
Response to ECD/quality (SD#26)	09/18/2014

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Mylan Technologies Inc.
Address:	110 Lake St. St. Albans, VT 05478
Telephone:	802-527-7792
Fax:	802-527-8155

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name:	N/A
Non-Proprietary Name (USAN):	Estradiol Transdermal System, USP (Twice-Weekly)

9. **LEGAL BASIS FOR SUBMISSION:**

RLD product:	Vivelle-Dot® (NDA 020538)
RLD dosage form:	Extended release film
Strength of RLD:	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day

10. **PHARMACOL. CATEGORY:**

Treatment of moderate to severe vasomotor symptoms associated with the menopause, moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause, hypoestrogenism due to hypogonadism, castration, or primary ovarian failure, and prevention of postmenopausal osteoporosis.

11. DOSAGE FORM: Extended-release film

12. STRENGTH/POTENCY:
0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
___SPOTS product – Form Completed _X_ Not a SPOTS product

16. CHEMICAL NAME & STRUCTURE, MOLECULAR FORMULA & Wt.:

Chemical Name: Estra-1,3,5(10)-triene-3,17β-diol- (b) (4)
Estra-1,3,5(10)-triene-3,17-diol, (17β) (b) (4)

Empirical Formula: $C_{18}H_{24}O_2$ (b) (4)
Molecular Structure:

(b) (4)

(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				1	Adequate/IR	03/13/2014	Reviewed by Guohua Li
				1	Adequate/IR	03/17/2014	Reviewed by Guohua Li
				3	Adequate	09/06/2013	Reviewed by Caroline

							Strasinger
[redacted] (b) (4)				3	Adequate	04/25/2011	Reviewed by Shahnaz Read
12100	III	Mylan Technologies	Backing Film		Adequate	11/28/2012	By Xihao Li
[redacted] (b) (4)				4			
				4			

1 Action codes for DMF Table:
1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
* New quality-related submissions dated 09/12/2013, 10/22/2013, and 10/25/2013 were reviewed and found no revision since last quality review.
$: IR response dated 05/22/2014 in DARRTs will be reviewed.

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	pending	07/29/2014	
Methods Validation	N/A		
$ Labeling	Pending	08/22/2014	
Bioequivalence	Acceptable	01/20/2012	Dongmei Lu
** Toxicology/Clinical	Pending	08/19/2014	
EA	N/A		
Radiopharmaceutical	N/A		
Samples requested	N/A		
Pharmacology/Toxicology Consult [redacted] (b) (4) (b) (4)	Acceptable	12/10/2012	K.Raheja
Pharmacology/Toxicology Consult for impurities [redacted] (b) (4)	Acceptable	02/25/2014	Lolita Lopez

$: to provide labeling that was revised pursuant to the CDER Internet Posting dated July 31, 2014 for the Reference Listed Drug (RLD), Vivelle-Dot® (estradiol transdermal

system) (NDA 020538/S-032), which contained the most recently approved labeling revisions and updated the labeling to Physicians Labeling Rule (PLR) format. **This amendment is nothing to do with CMC.**

: to provide further cumulative irritation data to demonstrate that the irritation potential of our Estradiol Transdermal System, USP product is non-inferior to that of the Reference Listed Drug, Vivelle-Dot. **This amendment is nothing to do with CMC.

19. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

- Expedited review due to drug shortage

19. EES INFORMATION

Current Overall OC recommendation: pending

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			
Particle Size testing	Mylan Pharmaceuticals Inc.	1110315	AC
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturing, Packaging, Labeling, Quality Control Testing of Components and Finished Dosage Form	Mylan Technologies	1220747	AC
(b) (4)			

Chemistry Review for ANDA 201675

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
CMC is approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
N/A

II. Summary of Chemistry Assessments

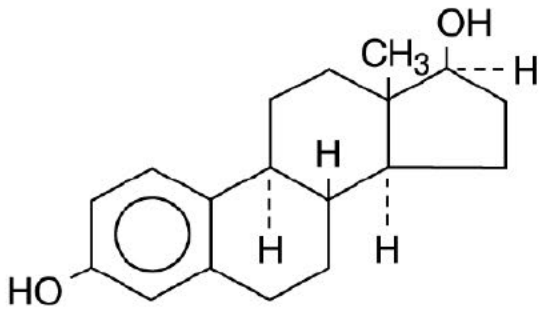
A. Description of the Drug Product(s) and Drug Substance(s)

Estradiol transdermal system (twice-weekly) contains estradiol in a multipolymeric adhesive. The system is designed to release estradiol continuously upon application to intact skin.

Five dosage strengths of estradiol transdermal system (twice-weekly) are available to provide nominal *in vivo* delivery rates of 0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5 cm^2, 3.75 cm^2, 5.0 cm^2, 7.5 cm^2, or 10.0 cm^2 and contains 0.41 mg, 0.62 mg, 0.82 mg, 1.23 mg, or 1.64 mg of estradiol, USP, respectively. The composition of the systems per unit area is identical.

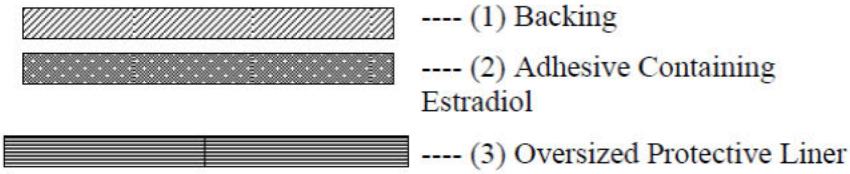
Estradiol, USP is a white, crystalline powder, chemically described as estra-1,3,5 (10)-triene-3,17ß-diol.

The structural formula is



The molecular formula of estradiol is $C_{18}H_{24}O_2$. The molecular weight is 272.39.

Estradiol transdermal system (twice-weekly) is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin backing film printed with brown ink, (2) an adhesive formulation containing estradiol, USP, silicone adhesive, acrylic adhesive, dipropylene glycol, povidone and oleyl alcohol, and (3) an oversized slit polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.



---- (1) Backing

---- (2) Adhesive Containing Estradiol

---- (3) Oversized Protective Liner

The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive.

B. Description of How the Drug Product is Intended to be Used

INDICATIONS AND USAGE

Estradiol transdermal system, USP (twice-weekly) is indicated in:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

DOSAGE AND ADMINISTRATION

The adhesive side of estradiol transdermal system (twice-weekly) should be placed on a clean, dry area of the abdomen. *Estradiol transdermal system (twice-weekly) should not be applied to the breasts.* Estradiol transdermal system (twice-weekly) should be replaced twice-weekly. The sites of application must be rotated, with an interval of at least one week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the oversized protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. In the event that a system should fall off, the same system may be reapplied. If the same system cannot be reapplied, a new system should be applied to another location. In either case, the original treatment schedule should be continued. If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. The new patch should be applied on the original treatment schedule. The interruption of treatment in women taking estradiol transdermal system (twice-weekly) might increase the likelihood of breakthrough bleeding, spotting and recurrence of symptoms.

HOW SUPPLIED

Estradiol Transdermal System USP, 0.025 mg/day (Twice-Weekly) - each 2.5 cm^2 system contains 0.41 mg of estradiol, USP for nominal* delivery of 0.025 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0378-4644-26

Estradiol Transdermal System USP, 0.0375 mg/day (Twice-Weekly) - each 3.75 cm^2 system contains 0.62 mg of estradiol, USP for nominal* delivery of 0.0375 mg of estradiol per day.

Patient Calendar Pack of 8 Systems .....NDC 0378-4643-26

Estradiol Transdermal System USP, 0.05 mg/day (Twice-Weekly) - each 5.0 cm^2 system contains 0.82 mg of estradiol, USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 Systems .....NDC 0378-4642-26

Estradiol Transdermal System USP, 0.075 mg/day (Twice-Weekly) - each 7.5 cm^2 system contains 1.23 mg of estradiol, USP for nominal* delivery of 0.075 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0378-4641-26

Estradiol Transdermal System USP, 0.1 mg/day (Twice-Weekly) - each 10.0 cm^2 system contains 1.64 mg of estradiol, USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0378-4640-26

*See DESCRIPTION.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Do not store unpouched. Apply immediately upon removal from the protective pouch.

Basis for Approvability or Not-Approval Recommendation

From CMC perspective, this ANDA is recommended for approval.

48 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

List of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 201675

APPLICANT: Mylan Technologies Inc.

DRUG PRODUCT: Estradiol Transdermal System USP (Twice Weekly), 0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.075mg/day, and 0.1mg/day

cc: ANDA
ANDA DUP
DIV FILE
Field Copy

Endorsements Block:
Reviewer: Guohua Li, 09/09/2014, 09/22/2014
Team Leader: Dhaval K. Gaglani, 09/12/2014, 09/16/14, 09/23/14
Supervisor: Bhagwant Rege, 09/23/2014
Project Manager: Brijet Burton Coachman, 9-16-2014, 9-23-2014

F/T by/
File Name and Path:

TYPE OF LETTER: Approval (pending adequacy of other disciplines)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GUOHUA LI
09/24/2014

BRIJET N BURTON COACHMAN
09/24/2014

DHAVAL GAGLANI
09/24/2014

BHAGWANT D REGE
09/24/2014

ANDA #201675

Estradiol Transdermal System USP (Twice Weekly), 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

Mylan Technologies Inc

CR #3
Guohua Li

Chemistry Division I
OGD

Table of Contents

Chemistry Review Data Sheet

1. **ANDA: 201675**

2. **REVIEW #: 3**

3. **REVIEW DATE: October 29, 2013**

4. **REVIEWER: Guohua Li, Ph.D.**

5. **PREVIOUS DOCUMENTS:**

Submissions	Submission Date
Original Submission (SD #1)	04/26/2010
Quality/Quality Information (SD #4)	01/04/2011
Bioequivalence/Dissolution (SD #8)	07/28/2011
Quality/Response to information request (SD #11)	06/15/2012

6. **SUBMISSION(S) BEING REVIEWED:**

Submissions	Submission Date
Amendment (SD #15)	08/15/2013

7. **NAME & ADDRESS OF APPLICANT:**

Name: Mylan Technologies Inc.
Address: 110 Lake St.
St. Albans, VT 05478
Telephone: 802-527-7792
Fax: 802-527-8155

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name: N/A
Non-Proprietary Name (USAN): Estradiol Transdermal System, USP (Twice-Weekly)

9. **LEGAL BASIS FOR SUBMISSION:**
RLD product: Vivelle-Dot® (NDA 020538)
RLD dosage form: Extended release film

Strength of RLD: 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day

10. PHARMACOL. CATEGORY:
Treatment of moderate to severe vasomotor symptoms associated with the menopause, moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause, hypoestrogenism due to hypogonadism, castration, or primary ovarian failure, and prevention of postmenopausal osteoporosis.

11. DOSAGE FORM: Extended-release film

12. STRENGTH/POTENCY:
0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day

13. ROUTE OF ADMINISTRATION: Transdermal

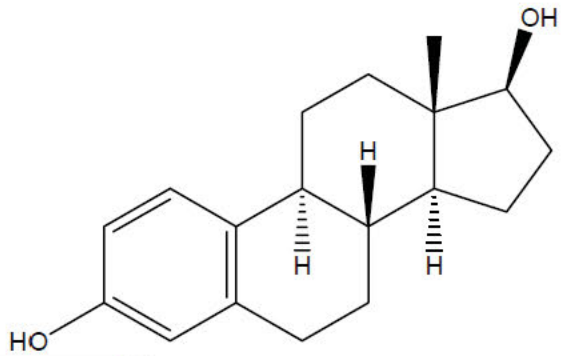
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
___SPOTS product – Form Completed __X__Not a SPOTS product

16. CHEMICAL NAME & STRUCTURE, MOLECULAR FORMULA & Wt.:

Chemical Name: Estra-1,3,5(10)-triene-3,17β-diol (b) (4)
Estra-1,3,5(10)-triene-3,17-diol, (17β) (b) (4)

Empirical Formula: C18H24O2 (b) (4)
Molecular Structure:



(b) (4)

(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				1	Adequate/IR	03/13/2014	Reviewed by Guohua Li
				1	Adequate/IR	03/17/2014	Reviewed by

(b) (4)						Guohua Li (b) (4)
					3	Adequate 09/06/2013 Reviewed by Caroline Strasinger
					3	Adequate 04/25/2011 Reviewed by Shahnaz Read
12100	III	Mylan Technologies	Backing Film		Adequate	11/28/2012 By Xihao Li
(b) (4)					4	
					4	

1 Action codes for DMF Table:
1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

* New quality-related submissions dated 09/12/2013, 10/22/2013, and 10/25/2013 were reviewed and found no revision since last quality review.

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	08/08/2013	
Methods Validation	N/A		
Labeling	Acceptable	10/31/2013	Malik Imam
Bioequivalence	Acceptable	01/20/2012	Dongmei Lu
Toxicology/Clinical	Adequate		Huaixiang Li
EA	N/A		
Radiopharmaceutical	N/A		
Samples requested	N/A		
Pharmacology/Toxicology Consult (b) (4)	Acceptable	12/10/2012	K.Raheja

(b) (4)			
Pharmacology/Toxicology Consult for impurities (b) (4)	Acceptable	02/25/2014	Lolita Lopez

19. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

Expedited review due to drug shortage

20. EES INFORMATION

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			AC
			AC
Particle Size testing	Mylan Pharmaceuticals Inc.	1110315	AC
Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
Manufacturing, Packaging, Labeling, Quality Control Testing of Components and Finished Dosage Form	Mylan Technologies	1220747	AC
(b) (4)			AC

Chemistry Review for ANDA 201675

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to minor deficiencies for CMC.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

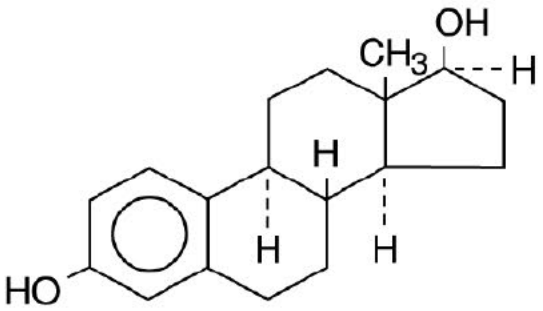
A. Description of the Drug Product(s) and Drug Substance(s)

Estradiol transdermal system (twice-weekly) contains estradiol in a multipolymeric adhesive. The system is designed to release estradiol continuously upon application to intact skin.

Five dosage strengths of estradiol transdermal system (twice-weekly) are available to provide nominal *in vivo* delivery rates of 0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5 cm^2, 3.75 cm^2, 5.0 cm^2, 7.5 cm^2, or 10.0 cm^2 and contains 0.41 mg, 0.62 mg, 0.82 mg, 1.23 mg, or 1.64 mg of estradiol, USP, respectively. The composition of the systems per unit area is identical.

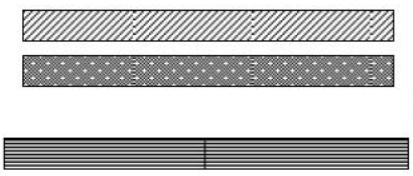
Estradiol, USP is a white, crystalline powder, chemically described as estra-1,3,5 (10)-triene-3,17ß-diol.

The structural formula is



The molecular formula of estradiol is $C_{18}H_{24}O_2$. The molecular weight is 272.39.

Estradiol transdermal system (twice-weekly) is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin backing film printed with brown ink, (2) an adhesive formulation containing estradiol, USP, silicone adhesive, acrylic adhesive, dipropylene glycol, povidone and oleyl alcohol, and (3) an oversized slit polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.



---- (1) Backing

---- (2) Adhesive Containing Estradiol

---- (3) Oversized Protective Liner

The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive.

B. Description of How the Drug Product is Intended to be Used

INDICATIONS AND USAGE

Estradiol transdermal system, USP (twice-weekly) is indicated in:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

DOSAGE AND ADMINISTRATION

The adhesive side of estradiol transdermal system (twice-weekly) should be placed on a clean, dry area of the abdomen. *Estradiol transdermal system (twice-weekly) should not be applied to the breasts.* Estradiol transdermal system (twice-weekly) should be replaced twice-weekly. The sites of application must be rotated, with an interval of at least one week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the oversized protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. In the event that a system should fall off, the same system may be reapplied. If the same system cannot be reapplied, a new system should be applied to another location. In either case, the original treatment schedule should be continued. If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. The new patch should be applied on the original treatment schedule. The interruption of treatment in women taking estradiol transdermal system (twice-weekly) might increase the likelihood of breakthrough bleeding, spotting and recurrence of symptoms.

HOW SUPPLIED

Estradiol Transdermal System USP, 0.025 mg/day (Twice-Weekly) - each 2.5 cm^2 system contains 0.41 mg of estradiol, USP for nominal* delivery of 0.025 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0378-4644-26

Estradiol Transdermal System USP, 0.0375 mg/day (Twice-Weekly) - each 3.75 cm^2 system contains 0.62 mg of estradiol, USP for nominal* delivery of 0.0375 mg of estradiol per day.

Patient Calendar Pack of 8 Systems .....NDC 0378-4643-26

Estradiol Transdermal System USP, 0.05 mg/day (Twice-Weekly) - each 5.0 cm^2 system contains 0.82 mg of estradiol, USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 Systems .....NDC 0378-4642-26

Estradiol Transdermal System USP, 0.075 mg/day (Twice-Weekly) - each 7.5 cm^2 system contains 1.23 mg of estradiol, USP for nominal* delivery of 0.075 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0378-4641-26

Estradiol Transdermal System USP, 0.1 mg/day (Twice-Weekly) - each 10.0 cm^2 system contains 1.64 mg of estradiol, USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0378-4640-26

*See DESCRIPTION.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Do not store unpouched. Apply immediately upon removal from the protective pouch.

Basis for Approvability or Not-Approval Recommendation

CMC is not approvable due to ECDs.

49 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

III. List of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 201675

APPLICANT: Mylan Technologies Inc.

DRUG PRODUCT: Estradiol Transdermal System USP 0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.075mg/day, 0.1mg/day

The deficiencies presented below are minors:

A. Deficiencies

1. In your response to Comment 3, a limit of [redacted] (b) (4) in the finished product was proposed, but the limit is found to be [redacted] (b) (4) Finished Product Specifications. Please revise.

2. Please analyze release and stability samples of your products for shear against RLD to assure your estradiol product is comparable to RLD with respect to this property.

3. Please tighten the release and stability specifications for known related substances namely 17 alpha-Estradiol and 1-methylestradiol.

4. Oleyl alcohol is used as [redacted] (b) (4). We note that oleyl alcohol decreases by ~10% at 24 month time point in long term stability studies. Please provide in vitro skin permeation data on drug product containing oleyl alcohol near the lower specification limit. Using appropriate statistical analysis, please demonstrate equivalence to the drug product lot containing the target amount.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GUOHUA LI
04/01/2014

HANY S EDWARD
04/02/2014

BHAGWANT D REGE
04/02/2014

Final version for DARRTS 2/22/13
CMC is deficient. Pending Clinical Bio and EES. All others are acceptable.

Reviewer /Xihao Li 02/12/2013
Team Leader/Bhagwant Rege/ 11/21/2012, 2/18/2013
DDD/Bing Cai/2/20/2013
Project Manager/TT/2/22/2013

ANDA 201675

Estradiol Transdermal System USP 0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.075mg/day, 0.10mg/day

Mylan Technologies Inc

Xihao Li, Ph.D.
Division of Chemistry I
Office of Generic Drugs

Review #2

Table of Contents

Chemistry Review Data Sheet

1. ANDA 201675

2. REVIEW # 2

3. REVIEW DATE: 08/08/2012

4. REVIEWER: Xihao Li

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
New/ANDA (SD#1)	04/26/2010
Quality/Quality Information (SD#4)	01/04/2011
Bioequivalence/Dissolution (SD#8)	07/28/2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Quality/Response To Information Request (SD #11)	06/15/2012

7. NAME & ADDRESS OF APPLICANT:

125Name:	Mylan Technologies Inc.
Address:	110 Lake St. St. Albans, VT 05478
Representative:	Joseph J. Sobecki Vice President, Regulatory Affairs
Telephone:	304-599-2595
Fax:	802-527-8155

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: NA
Non-Proprietary Name (USAN): Estradiol transdermal system
Code Name/# (ONDC only):
Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

Mylan provides the following with regard to the basis for this amended Abbreviated New Drug Application:
1) The name of the reference listed drug is Vivelle-Dot® (NDA 020538);
2) The dosage form of the reference listed drug is an extended release film;
3) The strengths of the reference listed drug are 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day.

10. PHARMACOL. CATEGORY:

Treatment of moderate to severe vasomotor symptoms associated with the menopause, moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause, hypoestrogenism due to hypogonadism, castration, or primary ovarian failure, and prevention of postmenopausal osteoporosis.

11. DOSAGE FORM: Extended-release film

12. STRENGTH/POTENCY:

0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _xx__Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__xx___Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

__xx__Not a NANO product

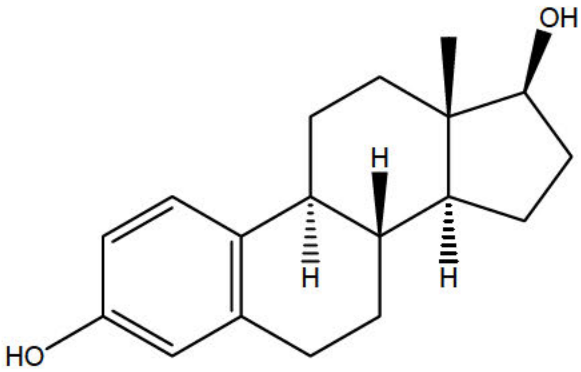
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Estra-1,3,5(10)-triene-3,17β-diol (b) (4)

Estra-1,3,5(10)-triene-3,17-diol, (17β) (b) (4)

Empirical Formula: $C_{18}H_{24}O_2$ (b) (4)

Molecular Structure:



(b) (4)

(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)					Adequate*	07/11/11	J. Liang
				1	Adequate/IR**	11/1/2011	By Xihao Li
				3			(b) (4)
				3		04/07/2011	
				3		04/25/2011	
12100	III	Mylan Technologies	Backing Material	1	Adequate	10/19/2012	By Xihao Li
(b) (4)				4			
				4			

[1] Action codes for DMF Table:

1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

*New submissions dated 10/13/11, 5/04/12, 10/12/12, and 11/6/12 will be reviewed at the next review cycle.
**New submissions dated 1/24/12, 6/26/12, and 12/10/12 will be reviewed at the next review cycle.

Deficiency: It appears that [redacted] is not used in the drug product. Please clarify why DMF [redacted] is referenced.

B. Other Documents: NA

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending		
Methods Validation	NA		
Labeling	Acceptable	1/23/2013	M.Imam
Bioequivalence	Acceptable	1/20/2012	D. Lu
Clinical Bio	Pending		
EA	NA		
Radiopharmaceutical	NA		
Pharmacology/Toxicology Consult [redacted]	Acceptable	12/10/2012	K.Raheja
Pharmacology/Toxicology Consult for impurities [redacted]	Deficient	12/10/2012	K.Raheja

Chemistry Review Data Sheet

Name of Facility	**Functions of the Facility** (manufacturer, testing lab, etc.)	**EES Status** (adequate, pending, to be entered into EES, etc)
Drug Substance		
(b) (4)		Acceptable
		Acceptable
Mylan Pharmaceuticals Inc.	Particle Size testing	Acceptable
Drug Product		
Mylan Technologies	Manufacturing, Packaging, Labeling, Quality Control Testing of Components and Finished Dosage Form	Acceptable
(b) (4)		Acceptable

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:
Minor deficiencies

Chemistry Review for ANDA 201-675

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to minor deficiencies. Pending Clincal Bio and EES. All others are acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

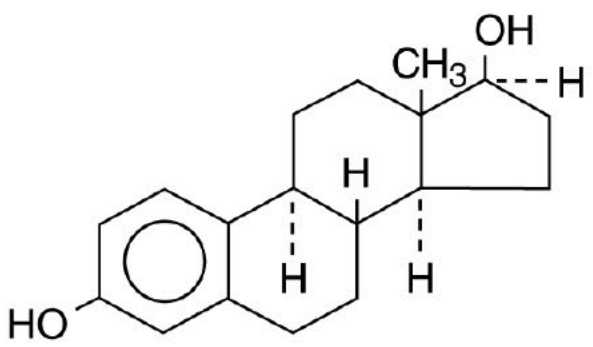
A. Description of the Drug Product(s) and Drug Substance(s)

Estradiol transdermal system (twice-weekly) contains estradiol in a multipolymeric adhesive. The system is designed to release estradiol continuously upon application to intact skin.

Five dosage strengths of estradiol transdermal system (twice-weekly) are available to provide nominal *in vivo* delivery rates of 0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5 cm^2, 3.75 cm^2, 5.0 cm^2, 7.5 cm^2, or 10.0 cm^2 and contains 0.41 mg, 0.62 mg, 0.82 mg, 1.23 mg, or 1.64 mg of estradiol, USP, respectively. The composition of the systems per unit area is identical.

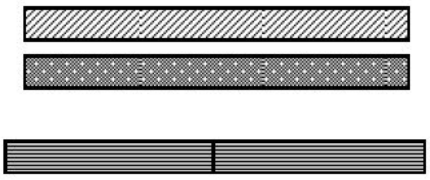
Estradiol, USP is a white, crystalline powder, chemically described as estra-1,3,5 (10)-triene-3,17ß-diol.

The structural formula is



The molecular formula of estradiol is $C_{18}H_{24}O_2$. The molecular weight is 272.39.

Estradiol transdermal system (twice-weekly) is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin backing film printed with brown ink, (2) an adhesive formulation containing estradiol, USP, silicone adhesive, acrylic adhesive, dipropylene glycol, povidone and oleyl alcohol, and (3) an oversized slit polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.



---- (1) Backing

---- (2) Adhesive Containing Estradiol

---- (3) Oversized Protective Liner

The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive.

B. Description of How the Drug Product is Intended to be Used

INDICATIONS AND USAGE

Estradiol transdermal system, USP (twice-weekly) is indicated in:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

DOSAGE AND ADMINISTRATION

The adhesive side of estradiol transdermal system (twice-weekly) should be placed on a clean, dry area of the abdomen. *Estradiol transdermal system (twice-weekly) should not be applied to the breasts.* Estradiol transdermal system (twice-weekly) should be replaced twice-weekly. The sites of application must be rotated, with an interval of at least one week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the oversized protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. In the event that a system should fall off, the same system may be reapplied. If the same system cannot be reapplied, a new system should be applied to another location. In either case, the original treatment schedule should be continued. If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. The new patch should be applied on the original treatment schedule. The interruption of treatment in women taking estradiol transdermal system (twice-weekly) might increase the likelihood of breakthrough bleeding, spotting and recurrence of symptoms.

HOW SUPPLIED

Estradiol Transdermal System USP, 0.025 mg/day (Twice-Weekly) - each 2.5 cm^2 system contains 0.41 mg of estradiol, USP for nominal* delivery of 0.025 mg of estradiol per day.
Patient Calendar Pack of 8 Systems.....NDC 0378-4644-26

Estradiol Transdermal System USP, 0.0375 mg/day (Twice-Weekly) - each 3.75 cm^2 system contains 0.62 mg of estradiol, USP for nominal* delivery of 0.0375 mg of estradiol per day.
Patient Calendar Pack of 8 Systems .....NDC 0378-4643-26

Estradiol Transdermal System USP, 0.05 mg/day (Twice-Weekly) - each 5.0 cm^2 system contains 0.82 mg of estradiol, USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 Systems .....NDC 0378-4642-26

Estradiol Transdermal System USP, 0.075 mg/day (Twice-Weekly) - each 7.5 cm^2 system contains 1.23 mg of estradiol, USP for nominal* delivery of 0.075 mg of estradiol per day.

Patient Calendar Pack of 8 Systems…….....NDC 0378-4641-26

Estradiol Transdermal System USP, 0.1 mg/day (Twice-Weekly) - each 10.0 cm^2 system contains 1.64 mg of estradiol, USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0378-4640-26

*See DESCRIPTION.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Do not store unpouched. Apply immediately upon removal from the protective pouch.

C. Basis for Approvability or Not-Approval Recommendation

CMC minor deficiencies. Pending Clincal Bio and EES. All others are acceptable.

69 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

cc: ANDA
ANDA DUP
DIV FILE
Field Copy

Endorsements Block:

Reviewer /Xihao Li 02/12/2013
Team Leader/Bhagwant Rege/ 11/21/2012, 2/18/2013
DDD/Bing Cai/2/20/2013
Project Manager/TT/2/22/2013

F/T by/
File Name and Path:

TYPE OF LETTER: CMC is deficient. Pending Clinical Bio and EES. All others are acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIHAO LI
02/25/2013

TRANG Q TRAN
02/25/2013

BHAGWANT D REGE
02/25/2013

BING CAI
02/25/2013

ANDA 201675

Estradiol Transdermal System USP 0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.075mg/day, 0.10mg/day

Mylan Technologies Inc

Xihao Li, Ph.D.
Division of Chemistry I
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA 201675

2. REVIEW #: 1

3. REVIEW DATE: 08-16-2011

4. REVIEWER: Xihao Li

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
New/ANDA (SD#1)	04/26/2010
Quality/Quality Information (SD#4)	01/04/2011
Bioequivalence/Dissolution (SD#8)	07/28/2011

7. NAME & ADDRESS OF APPLICANT:

125Name:	Mylan Technologies Inc.
Address:	110 Lake St. St. Albans, VT 05478
Representative:	S. Wayne Talton Vice President, Regulatory Affairs
Telephone:	802-527-7792
Fax:	802-527-8155

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: NA
Non-Proprietary Name (USAN): Estradiol transdermal system
Code Name/# (ONDC only):
Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:

Mylan provides the following with regard to the basis for this amended Abbreviated New Drug Application:
1) The name of the reference listed drug is Vivelle-Dot® (NDA 020538);
2) The dosage form of the reference listed drug is an extended release film;
3) The strengths of the reference listed drug are 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day.

10. PHARMACOL. CATEGORY:

Treatment of moderate to severe vasomotor symptoms associated with the menopause, moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause, hypoestrogenism due to hypogonadism, castration, or primary ovarian failure, and prevention of postmenopausal osteoporosis.

11. DOSAGE FORM: Extended-release film

12. STRENGTH/POTENCY:

0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _xx__Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__xx___Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

__xx__Not a NANO product

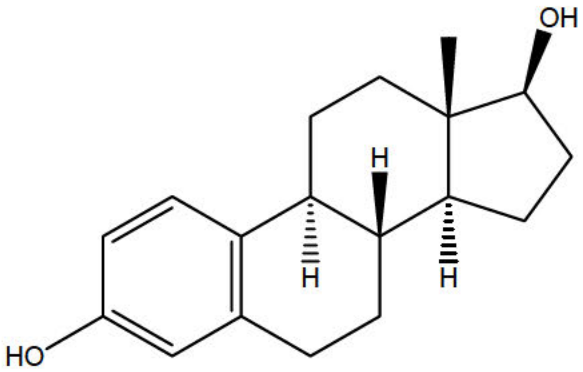
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Estra-1,3,5(10)-triene-3,17β-diol (b) (4)

Estra-1,3,5(10)-triene-3,17-diol, (17β) (b) (4)

Empirical Formula: $C_{18}H_{24}O_2$ (b) (4)

Molecular Structure:



(b) (4)

(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
			(b) (4)	3	Adequate*	07/11/2011	*AR dated 10/13/11 will be reviewed at next cycle.
				1	Adequate/IR	11/1/2011	By Xihao Li
				3			Last found adequate 11/15/04 New information will be reviewed at next review cycle.
				3			Last found adequate 4/7/11. New information will be reviewed at next review cycle.
				3			Last found adequate 04/25/2011
12100	III	Mylan Technologies	Backing Material	4			
			(b) (4)	4			
				4			

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: NA

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	11/2/2011	M. Stock
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Deficient	10/31/2011	D. Lu
EA	NA		
Radiopharmaceutical	NA		

Name of Facility	**Functions of the Facility** (manufacturer, testing lab, etc.)	**EES Status** (adequate, pending, to be entered into EES, etc)
Drug Substance		

[redacted]	(b) (4)	Acceptable
		Acceptable
Mylan Pharmaceuticals Inc.	Particle Size testing	Acceptable
Drug Product		
Mylan Technologies	Manufacturing, Packaging, Labeling, Quality Control Testing of Components and Finished Dosage Form	Acceptable
[redacted]	(b) (4)	Acceptable

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __xx__ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 201-675

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to minor deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

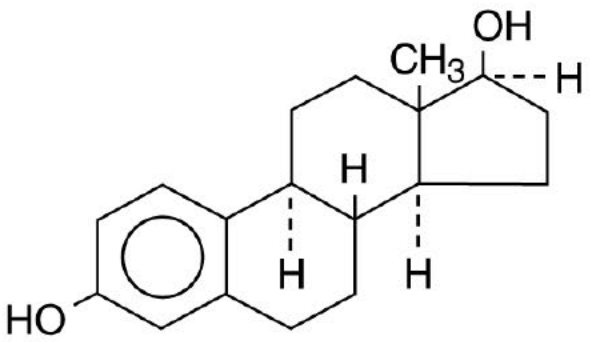
A. Description of the Drug Product(s) and Drug Substance(s)

Estradiol transdermal system (twice-weekly) contains estradiol in a multipolymeric adhesive. The system is designed to release estradiol continuously upon application to intact skin.

Five dosage strengths of estradiol transdermal system (twice-weekly) are available to provide nominal *in vivo* delivery rates of 0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5 cm^2, 3.75 cm^2, 5.0 cm^2, 7.5 cm^2, or 10.0 cm^2 and contains 0.41 mg, 0.62 mg, 0.82 mg, 1.23 mg, or 1.64 mg of estradiol, USP, respectively. The composition of the systems per unit area is identical.

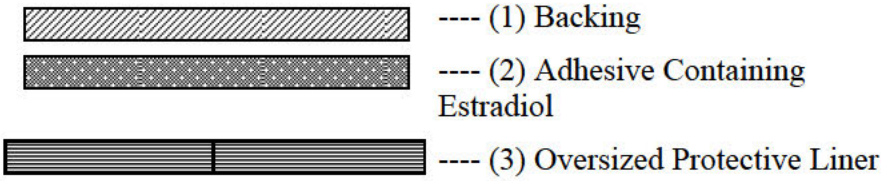
Estradiol, USP is a white, crystalline powder, chemically described as estra-1,3,5 (10)-triene-3,17ß-diol.

The structural formula is



The molecular formula of estradiol is $C_{18}H_{24}O_2$. The molecular weight is 272.39.

Estradiol transdermal system (twice-weekly) is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin backing film printed with brown ink, (2) an adhesive formulation containing estradiol, USP, silicone adhesive, acrylic adhesive, dipropylene glycol, povidone and oleyl alcohol, and (3) an oversized slit polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.



The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive.

B. Description of How the Drug Product is Intended to be Used

INDICATIONS AND USAGE

Estradiol transdermal system, USP (twice-weekly) is indicated in:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

DOSAGE AND ADMINISTRATION

The adhesive side of estradiol transdermal system (twice-weekly) should be placed on a clean, dry area of the abdomen. *Estradiol transdermal system (twice-weekly) should not be applied to the breasts.* Estradiol transdermal system (twice-weekly) should be replaced twice-weekly. The sites of application must be rotated, with an interval of at least one week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the oversized protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. In the event that a system should fall off, the same system may be reapplied. If the same system cannot be reapplied, a new system should be applied to another location. In either case, the original treatment schedule should be continued. If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. The new patch should be applied on the original treatment schedule. The interruption of treatment in women taking estradiol transdermal system (twice-weekly) might increase the likelihood of breakthrough bleeding, spotting and recurrence of symptoms.

HOW SUPPLIED

Estradiol Transdermal System USP, 0.025 mg/day (Twice-Weekly) - each 2.5 cm^2 system contains 0.41 mg of estradiol, USP for nominal* delivery of 0.025 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0378-4644-26

Estradiol Transdermal System USP, 0.0375 mg/day (Twice-Weekly) - each 3.75 cm^2 system contains 0.62 mg of estradiol, USP for nominal* delivery of 0.0375 mg of estradiol per day.

Patient Calendar Pack of 8 Systems .....NDC 0378-4643-26

Estradiol Transdermal System USP, 0.05 mg/day (Twice-Weekly) - each 5.0 cm^2 system contains 0.82 mg of estradiol, USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 Systems .....NDC 0378-4642-26

Estradiol Transdermal System USP, 0.075 mg/day (Twice-Weekly) - each 7.5 cm^2 system contains 1.23 mg of estradiol, USP for nominal* delivery of 0.075 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0378-4641-26

Estradiol Transdermal System USP, 0.1 mg/day (Twice-Weekly) - each 10.0 cm^2 system contains 1.64 mg of estradiol, USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 Systems.....NDC 0378-4640-26

*See DESCRIPTION.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Do not store unpouched. Apply immediately upon removal from the protective pouch.

C. Basis for Approvability or Not-Approval Recommendation

Not approvable due to minor deficiencies.

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cc: ANDA
ANDA DUP
DIV FILE
Field Copy

Endorsements Block:

Reviewer /Xihao Li
Team Leader/Bing Cai
Project Manager/Esther Chuh

F/T by/
File Name and Path:

TYPE OF LETTER:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIHAO LI
12/16/2011

EUNJUNG E CHUH
12/20/2011

BING CAI
12/20/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201675Orig1s000

PHARMACOLOGY REVIEW(S)

OGD P/T Consult Request Memo to the file

Date: 11-19-2012

ANDA #: 201675 Amendment

Sequence Number: 0010

Date of submission: 6/15/2012

Date received by the Division: 10/18/2012

Desired completion date: 12/16/2012

Sponsor: Mylan Technologies Inc.

Drug Product: Estradiol Transdermal System (Twice Weekly)

Dosage Form: Transdermal

Strength: 0.1, 0.075, 0.05, 0.0375, and 0.025 mg/day

Route of Administration: Transdermal

Classification of Drug: Estrogen derivative

Indication: Treatment of moderate to severe vasomotor symptoms and treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. Treatment of hypoestrogenism and for prevention of postmenopausal osteoporosis.

Subject: Response to Agency correspondence dated 12/20/2012

Consult No. 2012-0724

Consult Tracking No.: 374

Consult description: OGD has requested a P/T review of information provided by Mylan Technologies Inc. regarding the limits of (b) (4) impurities found in the (b) (4) (b) (4). Sponsor has proposed limits of (b) (4) in the finished drug product of Estradiol Transdermal System. P/T was asked to review the information and determine if these levels can be considered safe for human use.

From: Krishan L. Raheja, D.V.M., Ph.D.

Through: Alex Jordan, Ph.D. Expert Reviewer

To: Trang Q Tran

Review Subject: The P/T reviewer was asked to provide comments on the sponsor's proposed limits of the (b) (4) impurities found in the (b) (4) with regards to their safety for human use.

Sponsor's justification for the proposed limits for the (b) (4) impurities in the excipient is provided in response to FDA comment 7, which is stated as follows:

FDA Comment 7: Please contact the supplier of (b) (4) regarding the (b) (4) impurities of the (b) (4) Please establish suitable acceptance criteria for (b) (4) in the final drug product specification.

Mylan Response 7: "Mylan contacted the supplier of (b) (4) and has added (b) (4) impurities, (b) (4) to our Finished Product specifications"

Sponsor arrived at the specifications as follows:

(b) (4)

(b) (4)

The toxicity of (b) (4) was reviewed in detail by this reviewer (b) (4) (b) (4). In a 90-day repeated dose inhalation study in rats, a NOAEL of 400 ppm was determined. An in vitro dermal absorption study using human cadaver skin suggested that less than 0.5% of the applied dose would be considered bioavailable, suggesting no significant safety risk for its human use.

Reviewer comments and conclusion: Mylan proposed specifications of (b) (4) (b) (4) in the Estradiol Transdermal System (Twice Weekly). No toxicity data for these impurities has been provided. Toxicity data needs to be submitted and reviewed before the proposed limits can be assessed.

Reviewer' recommendations:

Specification limits for (b) (4) (b) (4) have been proposed. No toxicology data were submitted with the application. Please submit toxicity data or a justification as to why these limits should be considered acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISHAN L RAHEJA
12/03/2012

ALEXANDER W JORDAN
12/10/2012

OGD P/T Consult Request Memo to the file

Date: 11-19-2012

ANDA #: 201675 Amendment

Sequence Number: 0010

Date of document: 6/15/2012

Date received by the Division: 10-18-2012

Desired completion date: 12-16-2012

Sponsor: Mylan Technologies Inc.

Drug Product: Estradiol Transdermal System (twice weekly)

Dosage Form: Transdermal

Strength: 0.1, 0.075, 0.05, 0.0375 and 0.025 mg/day

Route of Administration: Transdermal

Classification of Drug: Estrogen derivative

Indication: Treatment of moderate to severe vasomotor symptoms and treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. Also for the treatment of hypoestrogenism and for prevention of postmenopausal osteoporosis.

Subject: Response to Agency correspondence dated 12-20-2011

Consult No.: 2012-0723

Consult Tracking No.: 374

Consult description: OGD has requested a P/T review of one of the excipients (b) (4) (b) (4) used in the drug product. The 0.1 mg/day strength has a (b) (4) concentration of (b) (4) than the IID list of 57.1 mg. The sponsor has provided a safety assessment in a Quality Amendment submitted on 6/15/2012.

Review from: Krishan L. Raheja, D.V.M., Ph.D.

Through: Alex Jordan, Ph.D. Expert Reviewer

To: Trang Q Tran

Review Subject: P/T reviewer to provide comments if the proposed level of [redacted] in 0.1 mg/day system of excipient [redacted] is safe for human use.

The present Mylan Technologies Inc. submission is in response to OGD correspondence dated 12-20-2011 to sponsor regarding product quality questions. OGD requested response to 10 questions. However, question 2 for Consult No. 2012-0723 and question 7 for Consult No. 2012-0724 are submitted for P/T review.

FDA comment Question 2 entitled "The amount of [redacted] used in 0.1 mg/day drug product is [redacted] than the IID limit of 57.14 mg. Please provide justifications.

Mylan Response: Mylan stated that Mylan's Estradiol Transdermal System, USP (Twice Weekly) 0.1 mg/day contains [redacted] and defended the [redacted] than the IID (it was IIG earlier) limit of 57.14 mg as follows:

The version of the Inactive Ingredients Database (Jannuary 13, 2010) that was available at the time when Mylan submitted its original ANDA on 4/26/2010 contained 2 listings for [redacted] using different descriptions. The maximum use levels were all substantially higher than Mylan's proposed drug product and none of the listings available at that time were identified as [redacted]

The Inactive Ingredients Database Listing for [redacted] available on 1/13/2010 is summarized in table below:

Description	Route of administration	Maximum use
[redacted]		

Since none of the listings available identified as [redacted], Mylan contacted the manufacturer, [redacted] for guidance on the appropriate IID listing to reference. [redacted] due to confidentiality did not provide definitive answer and just stated that "We believe this product is listed on the US FDA IID list as "Transdermal;film, controlled release". [redacted] also indicated that a list of US FDA approved products containing a [redacted] is included in DMF [redacted] and DMF [redacted] are, therefore, are quite similar. Based on this information Mylan submitted their original application.

This reviewer checked DMF [redacted] for products which contain [redacted] have

been used widely in approved NDAs and ANDAs for transdermal drug delivery systems. The following are a few approved NDAs and NDAs that have used the (b) (4) (b) (4) (b) (4) :

Subsequent to Mylan's application, the Inactive Ingredients Database was upgraded on 4/22/2010, and listing was included for (b) (4), with a maximum use level of (b) (4)

The DMF also provided summary of Health Data which included acute toxicity studies including eye irritation, skin irritation, and skin sensitization on rabbits, guinea pigs and human skin. Genetic toxicity studies included bacterial reverse mutation assay and cell culture. Other tests included pyrogen, UPS Class V Extractables, and 90 day implant in rabbits. In general, these tests showed minimal or no toxicity .Based on the preclinical data and the fact that the (b) (4) have been widely used in approved products, sponsor concluded that (b) (4) is safe to use in transdermal drug delivery systems.

Reviewer comments and conclusion: This reviewer considers that the information provided and reviewed suggests that Mylan's Estradiol Transdrmal System, USP (Twice Weekly) 0.1 mg/day that contains (b) (4) is safe for human use.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISHAN L RAHEJA
12/03/2012

ALEXANDER W JORDAN
12/10/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201675Orig1s000

BIOEQUIVALENCE

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	201675		
Drug Product Name	Estradiol Transdermal System, USP (Twice-weekly)		
Strength(s)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day		
Applicant Name	Mylan Technologies, Inc		
Address	110 Lake St St Albans, VT 05478		
Applicant's Point of Contact	S. Wayne Talton		
Contact's Telephone Number	304-599-2595		
Contact's Fax Number	802-527-8155		
Original Submission Date(s)	4/26/2010 refuse to receive; 9/10/2010 Accepted for filing		
Submission Date(s) of Amendment(s) Under Review	12/2/2011		
Reviewer	Dongmei Lu, Ph.D.		
Study Number (s)	EDOT-0922	EDOT-0908 (to be reviewed by Division of Clinical Review)	
Study Type (s)	Fasting PK study	Adhesion, irritation and sensitization study	
Strength (s)	1 x 0.1 mg/day	1 x 0.025 mg/day	
Clinical Site & Address	Cetero Research 1405 NW 167 Street Miami Gardens, FL33169	Scientific Research Center for Preventive Medicine of Federal Agency of High Technology Medical Care 10 Petroverigsky str., Moscow, 101990, Russian Federation	
Analytical Site Address	(b) (4)		
OUTCOME DECISION	**ADEQUATE**		
OSI INSPECTION RESULTS	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 2, 9	**FASTING**	**0.1 mg/day**	**ADEQUATE**
1, 3, 8, 9	**DISSOLUTION**	**0.1 mg/day**	**ADEQUATE**
1, 3, 8, 9	**DISSOLUTION**	**0.075 mg/day**	**ADEQUATE**
1, 3, 8, 9	**DISSOLUTION**	**0.05 mg/day**	**ADEQUATE**
1, 3, 8, 9	**DISSOLUTION**	**0.0375 mg/day**	**ADEQUATE**
1, 3, 8, 9	**DISSOLUTION**	**0.025 mg/day**	**ADEQUATE**

1 Executive Summary

On December 2nd, 2011, Mylan Technologies, Inc submitted its responses to the deficiency letter issued from the Division of Bioequivalence I (DB I) on 11/9/2011[1]. The firm was asked to provide information on deficiencies identified by the DB I. In the current amendment, the firm provided acceptable point-point responses to the deficiencies. The firm's responses to these clinical and drug release testing deficiencies are acceptable. Thus, the fasting study and the drug release testing are now **adequate.**

Given the acceptable fasting study, drug release testing, and formulation proportionality among all strengths, the DB I deems the lower test strengths of test product (0.025 mg/day, 0.0375 mg/day, 0.05 mg/day and 0.075 mg/day) to be bioequivalent to the corresponding strengths of the Reference product under *Title 21 Code of Federal Regulations (CFR) § 320.24 (b) (6).*

No Office of Scientific Investigations (OSI) inspection is pending or necessary for the clinical and analytical site. [2, 3]

The application is **acceptable** with no deficiencies.

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[1] DARRTS, ANDA201675, COR-ANDADE-01(Bio Incomplete Deficiencies), submission date 11/9/2011. Last accessed 1-5-2012.

[2] The clinical site was recently inspected on 10/19-22/10, 10/25-29/10, 11/1-4/10, 11/24/10) for ANDA091694. It resulted as Voluntary Action Indicated (VAI). The OSI finding was on clinical study exclusion criteria on Estradiol level. It does have relevance to the current application. Please see Section 4.4 in the original review (DARRTS, ANDA201675, REV-BIOEQ-01(General Review) submitted 10/31/2011) for additional details.

[3] The analytical site recently inspected on (b) (4) and resulted as Voluntary Action Indicated (VAI) for (b) (4) The OSI findings were concerning long-term stability studies (LTSS), documentation failure, drug adsorption on collection tubes, and security issues. The reviewer deems that these finding should have no impact on the current application. Please see details in Section 4.4 in the original review (DARRTS, ANDA201675, REV-BIOEQ-01(General Review) submitted 10/31/2011).

2 Table of Contents

3 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	-	-
Single-dose fed	-	-
Steady-state	-	-
In vitro dissolution	-	-
Waiver requests	-	-
BCS Waivers	-	-
Clinical Endpoints	-	-
Failed Studies	-	-
Amendments	Yes	1

4 Background

On April 26, 2010 (refused to receive) and September 10, 2010 (accepted for filing), the firm, Mylan Technologies, Inc, submitted one fasting bioequivalence (BE) study comparing a test product, Mylan Technologies, Inc's Estradiol Transdermal System, USP (Twice-weekly), 0.1 mg/day, to the corresponding reference product, Novartis's Vivelle-Dot® (estradiol transdermal system) continuous delivery for twice-weekly application, 0.1mg/24hr.

The Division of Bioequivalence (DB I) in the Office of Generic Drugs performed the review of the original application. At that time, the firm's fasting BE study was incomplete due to clinical and dissolution deficiencies. The results are summarized in the tables below:

Baseline-adjusted, CONTINU2.SAS:

In the previous review [DARRTS, ANDA201675, REV-BIOEQ-01(General Review), submitted 10/31/2011], for this study analysis, the reviewer found that subject 14 had low AUCt/AUCi (0.03) in reference treatment and much higher last time-point concentration than the prior time points. The reviewer did the analysis in the original review by removing the AUCi in the reference treatment of subject 14 since this parameter is undeterminable. In addition, in the current review, the reviewer did another analysis by removing AUCi of subject 14 in both periods to compare the initial analysis results. Again, two kinds of analysis indicated that the PK parameters are within the acceptable range of 80.00-125.00%.

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 for lnAUCt and lnCmax(female 47, male 0)- exclusion of subject 14 reference treatment AUCi Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Corrected Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	7804.99	7293.88	1.07	100.97	113.40
AUC∞ (hr *pg/ml)	8026.19	7398.48	1.08	102.45	114.88
Cmax (pg/ml)	134.05	116.95	1.15	107.29	122.45

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 for lnAUCt and lnCmax(female 47, male 0)- exclusion of subject 14 reference and test treatment AUCi Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Corrected Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	7804.99	7293.88	1.07	100.97	113.40
AUC∞ (hr *pg/ml)	8113.30	7478.78	1.08	102.51	114.81
Cmax (pg/ml)	134.05	116.95	1.15	107.29	122.45

Baseline-unadjusted, CONTINU2.SAS:

In the previous review [DARRTS, ANDA201675, REV-BIOEQ-01(General Review), submitted 10/31/2011], for this study analysis, the reviewer found that subject 14 had low AUCt/AUCi (0.00) in reference treatment and much higher last time-point concentration than the prior time points; subject 25 had low AUCt/AUCi (0.25) in the test treatment and much higher last time-point concentration than the prior time points. The reviewer did the analysis in the original review by removing the AUCi in the reference treatment of subject 14 and AUCi in the test treatment of subject 25 since this parameter is undeterminable. In addition, in the current review, the reviewer did another analysis by

removing AUCi of subject 14 and subject 25 in both periods to compare with the initial analysis results. Again, two kinds of analysis indicated that the PK parameters are within the acceptable range of 80.00-125.00%.

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 for lnAUCt and lnCmax (female 47, male 0)-exclude AUCi of subject 14 reference treatment and subject 25 test treatment Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Uncorrected Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	8364.33	7616.83	1.10	104.04	115.91
AUC∞ (hr *pg/ml)	8468.48	7746.11	1.09	103.53	115.44
Cmax (pg/ml)	137.77	119.10	1.16	108.31	123.55

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 for lnAUCt and lnCmax (female 47, male 0)-exclude AUCi of subject 14 and subject 25 in both R and T treatments Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Uncorrected Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	8364.33	7616.83	1.10	104.04	115.91
AUC∞ (hr *pg/ml)	8404.54	7687.62	1.09	103.54	115.44
Cmax (pg/ml)	137.77	119.10	1.16	108.31	123.55

The firm was requested to provide the information on the deficiencies identified by the DB I.

In this current amendment, the firm submitted its point-to-point responses to each deficiency issued by the DB I (dated 11/9/2011).

5 Review of Current Amendment

Deficiencies Related to the Fasting BE Study:

Deficiency 1:
In the protocol deviation table for the fasting BE study (Report # EDOT-0922 (M1GJ09001), Table 10.3), you stated that *"there were pharmacokinetic (PK) sample processing errors: Period II, 12 hour B samples tubes were out of order at dispensing. It is unknown which subject's samples were in which tube."* This statement was applied to

the Period II, 12-hour samples of subjects Nos. 9, 10, 12, 13, 16 (test treatment) and subjects 11, 14 and 15 (reference treatment). Please clarify how the issue was resolved and how you were able to confirm the sample identities.

Firm's Response:
The above referenced samples were not analyzed as they were from the back-up aliquot ("B" samples). Upon discovery of the error and the Sponsor's direction, the clinical CRO (Cetero) labeled the samples "Do Not Analyze". Email correspondence identifying the deviation and instructing that the samples be labeled as "Do not Analyze" is provided. Notification provided by Cetero to the bioanalytical CRO (b) (4) instructing them not to analyze the samples is also provided. The primary aliquot ("A" samples) was assayed for these samples, and thus there was no impact of the deviation. An e-mail from (b) (4) confirming that the affected "B" samples were not analyzed is provided in Section 3.3.

Reviewer's Comment:
The firm provided the documentation evidence on this protocol violation. All these related B samples were labeled as "Do not analyze" and only A samples (which were correctly labeled) were analyzed and the data of A samples were incorporated in the study results.

The reviewer checked the documentation dates, which were accordingly consistent with the study dates.

The firm's response to this deficiency is acceptable.

Deficiency 2:
In the protocol deviation table for the fasting BE study (Report # EDOT-0922 (M1GJ09001), Table 10.3), you indicated that there was a deviation in the "*transdermal sample handling: the Period 1 Control Sample 1A was found under the freezer*". Please explain how the issue was resolved and whether the found sample was used during the study.

Firm's Response:
At the time of the Estradiol Transdermal System removals for Period 1 of EDOT-0922 on October 9, 2009, three (3) control systems for both the test and reference products were processed (ie. removed from their original packaging with subsequent removal from their original release liners, applied to the same release liners as that used to collect Estradiol Transdermal Systems being removed in Period 1. These samples were then placed in individual pouches, heat sealed, and placed in a -20°C or colder freezer until shipment to Mylan Technologies Inc.). On October 27, 2009, all of the used and control sample Estradiol Transdermal Systems (test and reference) were inventoried from the freezer and boxed for shipment to Mylan Technologies for residual/depletion analysis. It was discovered at this time, that the Period 1 Control Sample 1A (Test product) was missing from the samples removed from the freezer. The missing sample was subsequently located under the freezer in an unfrozen condition; however, the length of time the

sample was outside of the defined storage conditions of the protocol is unknown. Proper documentation of this deviation was noted in the source documents at that time as well as being reported in Appendix 16.2.2.3 of the submitted EDOT-0922 Clinical Report in Module 5. Control Sample 1A from Period 1 was then included in the sample shipment box with the rest of the samples. A copy of the Shipping Inventory Form documenting the storage deviation was included in the box as well as being faxed to [redacted] (b) (6) at Mylan Technologies Inc.

Control Sample 1A in Period 1 was never applied to a subject in EDOT-0922, however it was analyzed as a control sample for residual analysis along with the used Estradiol Transdermal Systems and other control samples. The results of the residual analysis were included in Section 16.1.9 of the EDOT-0922 Pharmacokinetics Study Report in the original submission. The results of the residual analysis demonstrated that the deviation in storage conditions for Control Sample 1A in Period 1 had no apparent affect on the estradiol content of the transdermal system (Please see except from the depletion report below, reporting assay results of all three control patches).

Treatment A Estradiol Assay of Control Patches

Date	Patch Assay (mg)
10/06/09 #1	[redacted] (b) (4)
10/06/09 #2	
10/06/09 #3	
avg	1.620
RSD %	0.4

Therefore, there was no apparent impact on the conclusions of the study due to the storage deviation for Control Sample #1 of Treatment A.

Reviewer's Comment:
This sample was never applied on the patients and only used in the residual assay study. The control sample 1A has similar assay results as other control patches. It does not have any significant impact on the BE study outcome.

The firm's response to this deficiency is acceptable.

Deficiency Related to Dissolution Testing:

Deficiency 3:

You have conducted comparative dissolution testing using the FDA-recommended method. Based on the data you submitted, the DB recommends the specification below. Please acknowledge your acceptance of the FDA recommended dissolution method and specifications as follows:

Apparatus: USP VI (cylinder, modified)
Speed: 50 rpm

Medium: Water
Volume: 500 mL for 0.025 mg/day and 0.0375 mg/day; 900 mL for 0.05 mg/day, 0.075 mg/day and 0.1 mg/day
Temperature: 32º C ± 0.5ºC

The test product should meet the following specifications:
2 hr: (b) (4)
6 hr:
12 hr: 70-90%

Firm's Response:
As requested by the Agency, Mylan has updated our drug release method to be consistent with the drug release method proposed by the Agency.

Apparatus: USP VI (cylinder, modified)
Speed: 50 rpm
Medium: Water
Volume: 500 mL for 0.025 mg/day and 0.375 mg/day;
900 mL for 0.05 mg/day, 0.075 mg/day and 0.1 mg/day
Temperature: 32º C ± 0.5ºC

Mylan proposes the following modifications to the Agency recommended specifications:

Agency's recommended specifications	Mylan's proposed specifications
2 hr: (b) (4) 6 hr: 12 hr: 70-90%	2 hr: 20-40%; 6 hr: 48-68%; 12 hr: 70-90%

Mylan has adopted the Agency's recommended 12 hour limit of 70 – 90%. For the 6 hour limit, Mylan is proposing to maintain the Agency's proposed ±10% range, but is proposing to center the limits about the data provided in our July 28, 2011 comment letter response (Refer to Sequence 0007). As for the 2 hour time point, Mylan is proposing limits of 20 – 40%. This adjusts the limit to the standard ±10% window that is frequently assigned for drug release limits and centers the limit about the data.

Please note that since this is not the method originally submitted in the ANDA, we have generated very limited data with this method. As additional batches are manufactured, Mylan commits to further evaluate this drug release specification to ensure it is suitable for our product. If adjustments are warranted, Mylan commits to contacting the Agency with proposed changes and appropriate justification.

The drug release method and specifications above have been incorporated into Mylan's release and stability quality control programs. Revised finished product specifications for ETS USP, 0.025 mg/day, ETS USP, 0.0375 mg/day, ETS USP, 0.05 mg/day, ETS USP, 0.075 mg/day and ETS, USP 0.1 mg/day are provided in Section 3.2.P.5.1. A revised

drug release test method, STM-0762, and associated method validation report addendum are provided in Section 3.2.P.5.2 and 3.2.P.5.3., respectively. In addition to the changes already described for STM-0762, the following changes have been made: 1) revised the appropriate sections throughout the test method to be in alignment with the Agency's recommended dissolution method; 2) the specific reference to the [redacted] has been removed in Section 1.12; 3) added a note in Section 4.3; 4) changed runtime from [redacted] in Section 8 [redacted] 5) changed [redacted] to [redacted] 5) updated SOP reference in Section 12.0 to reflect the current naming convention. In addition, a revised Post-Approval Stability Protocol is provided in Section 3.2.P.8.2. It is important to note that a Post-Approval Stability Protocol for each strength was provided in the original ANDA; however, per current practice, Mylan has consolidated these protocols into a single protocol. These revised finished product specifications, test method, method validation report addendum and Post-Approval Stability Protocol will be submitted in a chemistry amendment in response to CMC comments once received.

Reviewer's Comment:

- The firm proposed different specifications from the Agency's recommendation at 2 hr and 6 hr time points. The reviewer checked the dissolution data for different strengths for these two time points and listed as below:

Specifications		
Agency's recommendation	Firm's new proposal	RLD's specifications[4]
2 hr: [redacted] 6 hr: 12 hr: 70-90%	2 hr: 20-40%; 6 hr: 48-68%; 12 hr: 70-90%	2 hr: [redacted] 4 hr: 6 hr:
N=12 for each strength dissolution testing	Dissolution drug release Mean % (range)	
Strength (mg/day, mfg date-testing date)	2 hr	6 hr
0.025 (8/2009-6/2011)	31 [redacted]	59 [redacted]
0.0375 (9/2009-6/2011)	30	58
0.05 (9/2009- 5/2011)	30	58
0.075 (9/2009-5/2011)	30	58
0.1 (8/2009- 5/2011)	30	56

These data are from the dissolution testing submitted in the amendment dated 7/28/2011 (the data reviewed in the original ANDA review to set up the specifications). The 2 hr mean values for all the strengths are around 30% with small ranges, 6 hr mean values are around 58% with small ranges as well. The firm's newly proposed specifications tried to center around the mean values with [redacted] The

[4] EDR, NDA020538, Module 3.2.P.8.1 Stability-summary. Submitted 9/27/2008. Last accessed 1-4-2012.

firm's dissolution data all met the newly proposed specifications at L1 level. In addition, the reviewer checked the BE study outcome, the 3 primary PK parameters are within the acceptable range of 80.00-125.00%. Other PK parameters- Tmax, Kel and half-life all have mean ratios around 1.00. Therefore, the reviewer deems the firm's newly proposed specifications are adequate.

- The firm performed the dissolution testing using the test products of [redacted] (b) (4). At this time, the DB I tentatively accepts the firm proposed specifications. However, the firm will be requested to submit data from three [redacted] (b) (4) to confirm and verify the tentative dissolution method and specification that the DB I is recommending.

The firm's response to this deficiency is acceptable.

6 Deficiency Comments

None.

7 Recommendations

1. The Division of Bioequivalence **accepts** the single-dose fasting bioequivalence (BE) study (EDOT-0922) conducted by Mylan Technologies, Inc., comparing its test product, Estradiol Transdermal System, USP (Twice-weekly), 0.1 mg/day (Lot # R6A0030), to the corresponding reference product, Novartis's Vivelle-Dot® (estradiol transdermal system) continuous delivery for twice-weekly application, 0.1mg/24hr (Lot # 51508).

2. The dissolution testing conducted by the firm, Mylan Technologies, Inc, on its test products, Estradiol Transdermal System, USP (Twice-weekly), 0.025 mg/day (Lot R6A0028), 0.0375 mg/day (Lot R6A0036), 0.05 mg/day (Lot R6A0037), 0.075 mg/day (Lot R6A0038) and 0.1 mg/day (Lot R6A0030) is **adequate**. The dissolution method is: 500 mL of Water for 0.025 mg/day and 0.0375 mg/ day; or 900 mL of Water for 0.05 mg/ day, 0.075 mg/ day and 0.1 mg/ 24hr, at 32ºC ± 0.5ºC, using USP apparatus VI (Cylinder, modified- Attach the patch on the cylinder using double-sided tape, release side facing away from the cylinder. The release side should not be covered by a membrane) at 50 rpm.

   The test product should meet the following specifications:

   2 hr: 20-40%
   6 hr: 48-68%
   12 hr: 70-90%

   The firm performed the dissolution testing using the test products of [redacted] (b) (4). At this time, the DB I tentatively accepts the firm proposed specifications. However, the firm will be requested to submit data from

three (b) (4) to confirm and verify the tentative dissolution method and specification that the DB I is recommending.

The firm conducted **adequate** in vivo bioequivalence study (submitted 4/26/2010 (refuse to receive); 9/10/2010 (Accepted for filing)) comparing with the corresponding reference product, Novartis's Vivelle-Dot® (estradiol transdermal system) continuous delivery for twice-weekly application, 0.025 mg/24hr (Lot 49382), 0.0375 mg/24hr (Lot 50548), 0.05 mg/24hr (Lot 51510) 0.075 mg/24hr (Lot 51509) and 0.1mg/24hr (Lot 51508). The drug release profiles are similar among the various strengths when using the FDA-recommended dissolution method. The firm's dissolution testing is **acceptable** (please see original review (DARRTS, ANDA201675, REV-BIOEQ-01(General Review) submitted 10/31/2011) p49-98 for details). The formulations for the strengths are proportionally similar to strength of 0.1 mg/ day which underwent bioequivalence testing.

3. The Division of Bioequivalence deems the test products, Estradiol Transdermal System, USP (Twice-weekly), 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day, manufactured by Mylan Technologies, Inc, to be bioequivalent to the reference product, Vivelle-Dot® (estradiol transdermal system) continuous delivery for twice-weekly application, 0.025 mg/24hr, 0.0375 mg/24hr, 0.05 mg/24hr, 0.075 mg/24hr and 0.1mg/24hr, manufactured by Novartis, under 21 CFR 320.24 (b)(6),

The firm should be informed of the above recommendations.

8 Comments for Other OGD Disciplines

None.

9 Additional Attachment

From: Munshi, Utpal
Sent: Tuesday, June 07, 2011 9:20 AM
To: Zhang, Hongling
Cc: Anand, Om*; Li, Bing; Nguyen, Hoainhon T
Subject: RE: Clarification Needed on Bioequivalence Correspondence Received for ANDA 201675

Hi Hongling:

Based on the file that you have attached, it would appear that the information on our website is incorrect. The description of the apparatus in the method should read as follows on the External Database Website:

Apparatus: VI (cylinder, modified). Attach the patch on the cylinder using double-sided tape, release side facing away from the cylinder. The release side should not be covered by a membrane.

This interpretation of the modified USP VI apparatus is also consistent with the description found in DARRTS, NDA 020538, REV-QUALITY-03, Final Date: 6/16/2004.

The above reference, the file that you have attached, and information-to-date in DARRTS indicate that the method description as stated in the External database with the modified apparatus description above, is the current and correct RLD method.

So, I would clarify the method to the ANDA applicant as I have described above. However, we will also need to modify the external database accordingly. Given that Om (who modifies the database) is out of town for the next few days, I am not sure if we can inform the firm of the modified method immediately, or if we have to wait for the External Database to be updated first. I would consult with Hoai and Bing before communicating with the firm on this issue any further.

Please let me know if there are any additional questions.

Thanks,
Utpal

P.S.: I do note that the specifications for the RLD product that you have given in your 3/29/2011 review are different than those stated in the 9/2010 Annual Report for the RLD product (2 h, (b) (4); 4h: (b) (4); 6 h: (b) (4)).

From: Zhang, Hongling
Sent: Monday, June 06, 2011 3:05 PM
To: Munshi, Utpal
Subject: RE: Clarification Needed on Bioequivalence Correspondence Received for ANDA 201675

Hi Utpal,

Please see attached file for the detail information of the RLD's dissolution method. I have scanned the relevant pages. Looks like the innovator's method is straightforward. Please let me know if you have any questions. I have the Jacket.

Thank you,

Hongling

From: Munshi, Utpal
Sent: Monday, May 23, 2011 5:22 PM
To: Zhang, Hongling
Subject: RE: Clarification Needed on Bioequivalence Correspondence Received for ANDA 201675

Before we can answer this question, I think we should identify exactly the type of modification the innovator has used on Apparatus VI. Unfortunately, the OCBP review does not provide a clear picture of what the modified apparatus actually entails. Taking Mylan's statement at face value, it would seem to me that the description that we have of the Apparatus on our website is inaccurate or incomplete in some way, and therefore we should make sure that we are correctly stating the method. As a result, I would recommend that you order the NDA jacket(s) with the pertinent information, and then we can proceed from there.

Thanks,
Utpal

From: Zhang, Hongling
Sent: Friday, May 20, 2011 2:52 PM
To: Munshi, Utpal
Subject: FW: Clarification Needed on Bioequivalence Correspondence Received for ANDA 201675

Hi Utpal,

Please see the following question by the firm. The firm was asked to conduct the dissolution testing using the current FDA-recommended method listed in the external dissolution database (updated 10/28/2010). Apparently, the method listed in the database is the same as the RLD product (NDA 020538). According to the OCPB review of NDA 020538 dated 7/9/2004, the innovator used the modified Apparatus VI (involving use of a

double sided tape to attach the patch to a disk at the bottom of the cylinder, thereby removing all barriers between the surface of the patch and the release medium and paddle). Do you think we should recommend the firm to do the same?

Thank you,

Hongling

From: Solana-Sodeinde, Diana A
Sent: Friday, May 20, 2011 1:48 PM
To: Zhang, Hongling
Subject: FW: Clarification Needed on Bioequivalence Correspondence Received for ANDA 201675

Hello Hongling

Can you please help respond to the firm's inquiry so that I can call them back?

Thank you,

Diana (Lola) Solana-Sodeinde, Pharm. D.

LT, USPHS, Regulatory Health Project Manager,
Division of BioEquivalence I, Branch IV and X,
Office of Generic Drugs
Center for Drugs, Evaluation and Research
Food & Drug Administration
7520 Standish Place,
Rockville, MD 20855
work: (240) 276-8782
fax: (240) 276-8766

From: Wayne.Talton@mylanlabs.com [mailto:Wayne.Talton@mylanlabs.com]
Sent: Friday, May 20, 2011 11:45 AM
To: Solana-Sodeinde, Diana A
Subject: Clarification Needed on Bioequivalence Correspondence Received for ANDA 201675

Good morning Diana

We received correspondence from the DBE dated April 15, 2011 regarding our pending ANDA for Estradiol Transdermal System (ANDA 201675). Our R&D Chemistry team would like to get some clarification regarding the apparatus requested in the April 15, 2011 letter as stated below:

The USP Apparatus as listed in the FDA letter, "VI (Cylinder) attach the patch to a disk at the bottom of the cylinder", appears to be asking us to adhere a stainless steel disk to the bottom of the apparatus VI rotating cylinder and then adhere a patch to the disk. We are not sure how this can be done and also note that the cylinder flow dynamic would be disturbed by attaching a disk to the bottom of a cylinder.

It is not clear, but possible that the intention of the request is for us to place the patch on a disk that sits in the bottom of the vessel and to use the cylinder like a paddle above the patch on disk.

We also note that 500mL of medium is not enough to cover the top of the cylinder and therefore would prevent the intended apparatus VI flow dynamic.

Can the Agency please provide some clarification so that we can ensure we perform the test as requested? Thanks for your time.

Wayne
Mylan
304.554.6551

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 201675

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Estradiol Transdermal System, USP (Twice-weekly), 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day

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

It was noticed that you performed the drug release testing using the test lots of [redacted] (b) (4). As a result, the DB I **tentatively** accepts the drug release method and specifications below. Please submit drug release data from 12 units from each of at least three [redacted] (b) (4) production size lots for each strength of the test product, when available, to confirm and verify the tentative dissolution method and specifications that the DB I is recommending. These lots should be manufactured using the FDA-approved manufacturing site, process, equipment, formulation, and specifications.

Apparatus:	USP VI (cylinder, modified- Attach the patch on the cylinder using double-sided tape, release side facing away from the cylinder. The release side should not be covered by a membrane)
Speed:	50 rpm
Medium:	Water
Volume:	500 mL for 0.025 mg/day and 0.0375 mg/day; 900 mL for 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day
Temperature:	32°C ± 0.5°C

The test product should meet the following specifications:

2 hr: 20-40%;
6 hr: 48-68%;
12 hr: 70-90%

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may

result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

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

10 OUTCOME PAGE

ANDA: 201675

Enter Review Productivity and Generate Report

COMPLETED ASSIGNMENT FOR 201675 ID: 15771

Reviewer: Lu, Dongmei **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Estradiol transdermal patch- amendment

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
15771	12/2/2011	Other	Study Amendment	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONGMEI LU
01/19/2012

UTPAL M MUNSHI
01/20/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
01/20/2012

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	201675		
Drug Product Name	Estradiol Transdermal System, USP (Twice-weekly)		
Strength(s)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day		
Applicant Name	Mylan Technologies, Inc		
Address	110 Lake St St Albans, VT 05478		
Applicant's Point of Contact	S. Wayne Talton		
Contact's Telephone Number	304-599-2595		
Contact's Fax Number	802-527-8155		
Original Submission Date(s)	4/26/2010 refuse to receive; 9/10/2010 Accepted for filing		
Submission Date(s) of Amendment(s) Under Review	5/25/2010 (LTSS data), 9/10/2010 (resubmission), and 7/28/2011 (dissolution)		
Reviewer	Dongmei Lu, Ph.D.		
Study Number (s)	EDOT-0922	EDOT-0908 (to be reviewed by Division of Clinical Review)	
Study Type (s)	Fasting PK study	Adhesion, irritation and sensitization study	
Strength (s)	1 x 0.1 mg/day	1 x 0.025 mg/day	
Clinical Site & Address	Cetero Research 1405 NW 167 Street Miami Gardens, FL33169	Scientific Research Center for Preventive Medicine of Federal Agency of High Technology Medical Care 10 Petroverigsky str., Moscow, 101990, Russian Federation	
Analytical Site Address	(b) (4)		
OUTCOME DECISION	**INADEQUATE**		
OSI INSPECTION RESULTS	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 2	**FASTING**	**0.1 mg/day**	**INADEQUATE**
1, 3, 8	**DISSOLUTION**	**0.1 mg/day**	**INADEQUATE**
1, 3, 8	**DISSOLUTION**	**0.075 mg/day**	**INADEQUATE**
1, 3, 8	**DISSOLUTION**	**0.05 mg/day**	**INADEQUATE**
1, 3, 8	**DISSOLUTION**	**0.0375 mg/day**	**INADEQUATE**
1, 3, 8	**DISSOLUTION**	**0.025 mg/day**	**INADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of one fasting bioequivalence (BE) study comparing a test product, Mylan Technologies, Inc's Estradiol Transdermal System, USP (Twice-weekly), 0.1 mg/day, to the corresponding reference product, Novartis's Vivelle-Dot® (estradiol transdermal system) continuous delivery for twice-weekly application, 0.1mg/24hr. This BE study was designed as a single-dose, two-way crossover study in healthy female subjects. The firm's fasting BE study is **inadequate** due to clinical,and dissolution deficiencies. The results are summarized in the tables below.

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 (female 47, male 0)- exclusion of subject 14 AUCi Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Corrected Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	7804.99	7293.88	1.07	100.97	113.40
AUC∞ (hr *pg/ml)	8026.19	7398.48	1.08	102.45	114.88
Cmax (pg/ml)	134.05	116.95	1.15	107.29	122.45

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 (female 47, male 0)-exclude subject 14 and subject 25 for analysis of AUCi Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Uncorrected Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	8364.33	7616.83	1.10	104.04	115.91
AUC∞ (hr *pg/ml)	8468.48	7746.11	1.09	103.53	115.44
Cmax (pg/ml)	137.77	119.10	1.16	108.31	123.55

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 (female 47, male 0)-exclude subject 14 AUCi and subject 25 AUCi, AUCt and Cmax * Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline Uncorrected Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	7952.04	8061.48	0.99	89.85	108.30
AUC∞ (hr *pg/ml)	8107.01	8205.71	0.99	89.88	108.60
Cmax (pg/ml)	126.25	130.57	0.97	85.06	109.91

* Subject 25 had an abnormal high pre-dose estradiol value in Period II (test treatment). The reviewer did this calculation in order to investigate whether this abnormal value has significant impact on the bioequivalence outcome. It does have significant impact on 90%CIs of PK parameters to shift the PK 90%CIs, However, this does not have significant impact on the bioequivalence outcome.

The firm has conducted comparative dissolution testing on all strengths using the FDA-recommended dissolution method. The dissolution testing is pending upon the firm's acceptance and acknowledgement of the FDA recommended specifications.

The DBE **denies** the waiver requests for in vivo BE study requirements for the following strengths: 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, and 0.075 mg/day pending on the completeness of the BE study submission.

No Office of Scientific Investigations (OSI) inspection is pending or necessary.[1, 2]

The application is **inadequate** with deficiencies.

[1] The analytical site was recently inspected on [redacted] (b) (4) for [redacted] (b) (4) It resulted as Voluntary Action Indicated (VAI). The OSI finding was on clinical study exclusion criteria on Estradiol level. It does have relevance to the current application. Please see Section 4.4 for additional details.

[2] The analytical site recently inspected on [redacted] (b) (4) and resulted as Voluntary Action Indicated (VAI) for [redacted] (b) (4). The OSI findings were concerning long-term stability studies (LTSS), documentation failure, drug adsorption on collection tubes, and security issues. The reviewer deems that these finding should have no impact on the current application. Please see details in Section 4.4

2 TABLE OF CONTENTS

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[3]

Test Product	Estradiol Transdermal System, USP (Twice-weekly) 0.025mg, 0.0375 mg, 0.05mg, 0.075mg and 0.1 mg/day
Reference Product *	Vivelle-Dot® (estradiol transdermal system) Continuous delivery for twice-weekly application, 0.025mg/24hr (BX), 0.0375mg/24hr (BX), 0.05mg/24hr (AB1), 0.075mg/24hr (BX), 0.1mg/24hr (AB1)
RLD Manufacturer	NOVARTIS
NDA No.	020538
RLD Approval Date	5/3/2002- 0.025mg/24hr, 1/8/1999 - other strengths
Indication[4]	Vivelle-Dot® (estradiol transdermal system) is indicated in: 1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Prevention of postmenopausal osteoporosis. *Special Populations* Vivelle-Dot was only investigated in postmenopausal women.

* AB1: actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence. Since there are multiple RLDs at the same strength, the number 1 represents one of the specific RLD.
BX: drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence. Often the problem is with specific dosage forms rather than with the active ingredients.[5]

3.2 PK/PD Information [6]

Bioavailability	In a multiple-dose study consisting of three consecutive system applications of the original formulation [Vivelle® (estradiol transdermal system)] which was conducted in 17 healthy, postmenopausal women, blood levels of estradiol and estrone were compared following application of these units to sites on the abdomen and buttocks in a crossover fashion. Systems that deliver nominal estradiol doses of approximately 0.0375 mg/day and 0.1 mg/day were applied to abdominal application sites while the 0.1 mg/day doses were also applied to sites on the buttocks. These systems increased estradiol levels above baseline within 4 hours and maintained respective mean levels of 25 and 79 pg/mL above baseline following application to the abdomen;

[3] Electronic Orange Book, search Estradiol. Last accessed 6-17-2011
[4] DRUGS@FDA. search Estradiol. Last accessed 6-17-2011
[5] Electronic Orange Book Annual Edition. Last accessed 9-9-201
[6] DRUGS@FDA. search Estradiol. Last accessed 7-27-2011

	slightly higher mean levels of 88 pg/mL above baseline were observed following application to the buttocks. At the same time, increases in estrone plasma concentrations averaged about 12 and 50 pg/mL, respectively, following application to the abdomen and 61 pg/mL for the buttocks. While plasma concentrations of estradiol and estrone remained slightly above baseline at 12 hours following removal of the systems in this study, results from another study show these levels to return to baseline values within 24 hours following removal of the systems.
Food Effect	N/A
Tmax	28.5-38.0 hour [7]
Metabolism	The skin metabolizes estradiol only to a small extent. Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.
Excretion	Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. After removal of the transdermal systems, serum concentrations of estradiol and estrone returned to baseline levels within 24 hours.
Half-life	5.9-7.7 hours
Drug Specific Issues (if any)	**BLACK BOX WARNING** **ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER** Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See **WARNINGS, Malignant neoplasms, *Endometrial cancer*.**) **CARDIOVASCULAR AND OTHER RISKS** Estrogens with or without progestins should not be used for the prevention of cardiovascular disease. (See **WARNINGS, Cardiovascular disorders**.) The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with

[7] DARRTS, NDA020538, REV-CLINPHARM-01(General Review), submitted 11/7/2001. Last accessed 8-1-2011

	medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (see **CLINICAL PHARMACOLOGY, Clinical Studies.**) The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.) Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Adhesion[8]	Based on combined data from three short-term clinical trials consisting of 471 observations, 85% of Vivelle-Dot adhered completely to the skin over the 3.5-day wear period. Three (3%) of the systems detached and were reapplied or replaced during the 3.5- day wear period. Approximately 80% of the transdermal systems evaluated in these studies were Vivelle-Dot 0.05 mg/day.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2

1.	**Type of study:**	Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints and Adhesion Study
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	0.1 mg/day
	Subjects:	Healthy, non-smoking, postmenopausal women with no contraindication to estrogen therapy
	Additional Comments:	• The transdermal patch should be applied to clean, dry, intact, healthy skin on the lower abdomen below the waistline, as recommended in the approved reference listed drug (RLD) labeling, and worn for 3.5 days (84 hours). • An average baseline correction is obtained by averaging the 3 pre-application sampling times (-48, -24 and 0 hours). • A washout period of 7 days after removal of the Estradiol transdermal patch is recommended. • Observations and rating of skin adhesion should be documented during this study.

2.	**Type of study:**	Skin Irritation, Sensitization and Adhesion Study
	Design:	Randomized, evaluator-blinded, in vivo within-subject repeat test
	Strength:	0.025 mg/day

[8] DRUGS@FDA, search Vivelle-dot. Last accessed 9-9-2011

Subjects:	Healthy, non-smoking, postmenopausal women with no contraindication to estrogen therapy
Additional Comments:	Specific recommendations are provided on the guidance page.

Analytes to measure (in plasma/serum/blood):	Estradiol in plasma (PK study only)
Bioequivalence based on:	(90% CI) Estradiol, using both baseline corrected and uncorrected data (PK study only)
Waiver request of in-vivo testing:	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day and 0.075 mg/day
Source of most recent recommendations:	Bioequivalence recommendation. It is also available via FDA public internet webpage: http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234963.pdf (draft, 11/2010)
Summary of OGD or DBE History	There are two approved ANDAs on this product (ANDA075233 and 075182 both by Mylan Technologies Inc.). [9]

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	-	-
Steady-state	-	-
In vitro dissolution	Yes	5
Waiver requests	Yes	4
BCS Waivers	-	-
Clinical Endpoints	Yes	1
Failed Studies	-	-
Amendment	Yes	1 (5/25/2010 LTSS data)
Amendment	Yes	1 (9/10/2010, resubmission)
Amendment	Yes	1 (7/28/2011, dissolution)
OSI Report - Analytical Site	Yes	1
OSI Report – Clinical Site	Yes	1

[9] DARRTS, search Estradiol. Last accessed 7-26-2011

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Estradiol Bioanalytical Method Validation Report, and Estradiol Partial Validation 3
Analyte	Estradiol
Internal Standard (IS)	(b) (4)
Method Description	Liquid/Liquid Extraction, HPLC/MS/MS
Limit of Quantitation (pg/mL)	5.04
Anticoagulant used	K_2EDTA (di-potassium Ethylenediaminetetraacetate).
Recovery of Drug (%)	QC means (CV%): 86.88 (0.75%), 85.61(1.02%), and 86.59%(1.83%), (Stripped) [b] QC means (CV%): 82.36 (4.93%), 82.61(1.51%), and 83.85% (1.36%) (Unstripped) [b]
Recovery of IS (%)	93.18% (CV 1.85%) (Stripped) [b] 90.55% (CV 1.23%) (Unstripped) [b]
Standard Curve Concentrations (pg/mL)	5.04, 10.07, 12.59, 25.18, 50.36, 100.72, 201.44, 251.80 [b]
QC Concentrations (pg/mL)	5.00, 15.00, 87.50, 187.50 [b]
LLOQ Intraday precision (%)	coefficients of variation: 1.67% (unstrapped) coefficients of variation: 3.76% (strapped)
LLOQ Intraday accuracy (%)	Bias: 0.09% (unstrapped) Bias: 1.37% (strapped)
LLOQ Interday precision (%)	coefficients of variation: 1.74% (unstrapped) coefficients of variation: 3.76% (strapped)
LLOQ Interday accuracy (%)	Bias: -1.02% (unstrapped) Bias: 1.37% (strapped)
QC Intraday Precision Range (%)	QC coefficients of variation: 1.34 to 3.76% (Stripped) [b] QC coefficients of variation: 1.16 to 2.02% (Unstripped) [b]
QC Intraday Accuracy Range (%)	QC bias: -1.37 to 1.67% (Stripped) [b] QC bias: -0.88 to 3.18% (Unstripped) [b]
QC Interday Precision Range (%)	QC coefficients of variation: 1.74 to 4.63% (Stripped) [b] QC coefficients of variation: 1.74 to 2.80% (Unstripped) [b]
QC Interday Accuracy Range (%)	QC bias: -0.10 to 2.67% (Stripped) [b] QC bias: -1.02 to 1.01% (Unstripped) [b]
Bench-Top Stability (hrs)	27 hours @ room temperature [a] Stripped-QC1:-3.39%; QC3: -2.24% Unstripped-QC1: -4.43%; -2.27%
Stock Stability (days)	Estradiol 250 days @ -20°C [a] change: 5.22% (CV 1.02%) Estradiol-D_5 250 days @ -20°C [a] change: -6.85% (CV 1.01%)
Processed Stability (hrs)	312 hours @ room temperature [a] Stripped: QC1: -0.07%; QC3:-0.49% Unstripped: QC1: -8.32%; QC3:-0.88%
Freeze-Thaw Stability (cycles)	-20 Stripped = 4 cycles [a] Stripped: QC1: 98.35% (CV 5.24%); QC3:102.96% (CV 1.27%) -80 Stripped = 4 cycles [a] Stripped: QC1: 105.16% (CV 5.61%); QC3:103.12% (CV 1.54%) -20 Unstripped = 6 cycles [a] Unstripped: QC1: 94.43% (CV 2.43%); QC3:93.80%(CV 2.31%) -80 Unstripped = 6 cycles [a] Unstripped: QC1: 95.59% (CV 0.75%); QC3:93.91% (CV 0.92%)
Long-Term Storage Stability (days)	50 days @ -80°C (K_2EDTA Stripped) [c] QC1: -8.60% (CV

	5.44%) and QC3:-6.73% (CV 2.50%) 50 days @ -80°C (K_2EDTA Unstripped) [c] QC1: -5.60% (CV 2.66%) and QC3:-7.38% (CV 1.12%) 327 days @ -20°C (K_3EDTA Stripped) [a] QC1: -2.85% (CV 2.65%) and QC3:-0.79% (CV 0.45%) 447 days @ -20°C (K_3EDTA Unstripped) [a] QC1: 4.73% (CV 1.89%) and QC3:-2.28% (CV 2.15%)
Dilution Integrity Accuracy	QC bias: -4.12 (2 fold dilution of QC3-207.17pg.mL) and -0.87% (20 fold dilution of DQC-2519.67pg/mL)(Unstripped) [b]
Dilution Integrity Precision	QC coefficients of variation: 1.66% (2 fold dilution of QC3-207.17pg.mL) and 3.02% (20 fold dilution of DQC-2519.67pg/mL)((Unstripped) [b]
Selectivity	No significant interference observed in 10 of 10 tested matrices for internal standard (Unstripped) [a]

[a] Generated in Estradiol Validation
[b] Generated in Estradiol Partial Validation 1
[c] Generated in Estradiol Partial Validation 3

Note:
Unstripped refers to regular postmenopausal human EDTA K_2 or K_3 plasma
Stripped refers to plasma which was treated with activated charcoal to remove endogenous levels of estrone and Estradiol prior to use.

SOPs submitted		
SOP number (b) (4)	Title	Effective date
	Sample Reassays and Reporting of Final Concentrations	7/10/2009
	Preparation, Identification, Acceptance Criteria of Stock Solutions, Calibration Standards, Quality Controls and Reference Solutions	7/6/2009
	Application of Bioanalytical Methods to Routine Drug Analysis	8/31/2009
	Chromatographic Acceptance Criteria and Verification of Chromatograms	4/6/2009
Bioanalytical method is Acceptable		
Was the % recovery consistent across QC concentrations?		Yes
Is the same anticoagulant used in the pre-method validation study used in the sample assay?		Yes
If not, was cross validation study conducted?		N/A
Was the dilution factor adequate for the current study sample analysis?		Yes
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?		Yes
Does the duration of the each of the stability parameters support the sample preparation and assay dates		Yes
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?		Acceptable

Comments on the Pre-Study Method Validation:

1. The firm submitted the pre-study bioanalytical validation for estradiol as well as estrone. Since the Agency only recommends Estradiol in the bioequivalence criteria, the reviewer only reviewed the application contents on Estradiol currently.

2. The method used by the firm for the analysis of estradiol in human plasma was automated sample liquid extraction, derivatization and high performance liquid chromatography with tandem mass spectroscopy (HPLC/MS/MS).

3. [redacted] (b) (4)

4. The anticoagulant used in the method validation is K_2EDTA (di-potassium Ethylenediaminetetraacetate). The diluent used in the dilution integrity was K_2EDTA plasma.

5. The study samples were stored at -80ºC freezer for 48 days. The long term storage stability periods (50 days at -80ºC stripped and unstripped) exceed the actual sample storage period.

6. The blood samples analyzed were in unstripped conditions.

The pre-study method validation is acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route), [Product ID]	Subjects Number (M/F), Type, Age (yrs), Mean (Range)	Mean Parameters (± SD)						Study Report Location
					C_{max} (pg/mL)	T_{max} (hr)	AUC0-t (pg/mL•hr)	AUC∞ (pg/mL•hr)	$T_{1/2}$ (hr)	Kel (hr^{-1})	
EDOT-0922	Single-Dose Fasting Bioequivalence Study of Estradiol Transdermal System, USP (Twice Weekly) (0.1 mg/day; Mylan) and Vivelle-Dot® (0.1 mg/day; Novartis) in Healthy Post-Menopausal Women	Open-label, Single-dose, Randomized, Two-period, Two- treatment Crossover	A= Estradiol Transdermal System, 0.1 mg/day worn for 3.5 days, transdermal route, Lot# R6A0030	47 Dosed 47 Completed 47 Analyzed Healthy Subjects Mean Age: 56 (Range: 46 to 65)	Baseline-corrected estradiol						Section 5.3.1.2
					144.9 ± 60.24	24.00 (8-48)	8264 ± 2757	8420 ± 2787	14.61 ± 9.334	0.0681 ± 0.0555	
			B= Vivelle-Dot®, 0.1 mg/day worn for 3.5 days, transdermal route, Lot #38967 exp. 02/2011		126.2 ± 51.32	24.00 (18-72)	7742 ± 2768	7913 ± 2777	13.18 ± 6.543	0.0702 ± 0.0408	
			A= Estradiol Transdermal System, 0.1 mg/day worn for 3.5 days, transdermal route, Lot# R6A0030		Baseline-uncorrected estradiol						
					148.7 ± 60.85	24.00 (8-48)	8722 ± 3023	8726 ± 2742	18 22 ± 10 57	0.0527 ± 0.0351	
			B= Vivelle-Dot®, 0.1 mg/day worn for 3.5 days, transdermal route, Lot #38967 exp. 02/2011		128.4 ± 51.48	24.00 (18-72)	7998 ± 2868	8243 ± 2973	16.33 ± 9.856	0.0618 ± 0.0421	

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 (female 47, male 0)- exclusion of subject 14 AUCi Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Corrected Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	7804.99	7293.88	1.07	100.97	113.40
AUC∞ (hr *pg/ml)	8026.19	7398.48	1.08	102.45	114.88
Cmax (pg/ml)	134.05	116.95	1.15	107.29	122.45

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 (female 47, male 0)-exclude subject 14 and subject 25 for analysis of AUCi Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Uncorrected Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	8364.33	7616.83	1.10	104.04	115.91
AUC∞ (hr *pg/ml)	8468.48	7746.11	1.09	103.53	115.44
Cmax (pg/ml)	137.77	119.10	1.16	108.31	123.55

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 (female 47, male 0)-exclude subject 14 AUCi and subject 25 AUCi, AUCt and Cmax * Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Unadjusted Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	7952.04	8061.48	0.99	89.85	108.30
AUC∞ (hr *pg/ml)	8107.01	8205.71	0.99	89.88	108.60
Cmax (pg/ml)	126.25	130.57	0.97	85.06	109.91

* Subject 25 had an abnormal high pre-dose estradiol value in Period II (test treatment). The reviewer did this calculation in order to investigate whether this abnormal value has significant impact on the bioequivalence outcome. It does have significant impact on 90%CIs of PK parameters to shift the PK 90%CIs, However, this does not have significant impact on the bioequivalence outcome.

Table 3. Reanalysis of Study Samples

EDOT-0922 – BE Study Repeat Analysis Results for Estradiol Additional Information in Table 4B of the EDOT-0922 Bioanalytical Study Report								
Reason why assay was repeated[1]	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual Number		**% of total assays**		**Actual Number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0%	0%	0	0	0%	0%
Reason A	2	1	0.10%	0.05%	2	1	0.10%	0.05%
Reason B	0	3	0%	0.15%	0	3	0%	0.15%
Reason C	4	3	0.19%	0.15%	4	3	0.19%	0.15%
Total	6	7	0.29%	0.34%	6	7	0.29%	0.34%

[1]Reason A = Unacceptable Internal Standard Response
Reason B = Loss of Sample During Processing
Reason C = Sample Concentration Above Limits of Quantitation

Table 4. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	7/10/2010	Sample Reassays and Reporting of Final Concentrations

Reanalysis SOPs submitted?	Yes
Do you agree that the reassay criteria: **analytical and pharmacokinetic**	Yes
If not, list the criteria that you don't agree and provide additional comment below	N/A
Are the data in the summary table consistent with the data in the full analytical report?	Yes
If not, provide comment below	N/A
Did reviewer reanalyze study results?	No. The reviewer checked all the original and repeated values for these reassayed samples and there were no significant difference between the values before and after repeats
Was the study outcome changed based on reviewer reanalysis?	No
Did the firm provide a comprehensive table of repeat samples in the format recommended by the DBE?	Yes
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log)?	Yes

Did use of recalculated plasma concentration data change study outcome?

No.

Comments from the Reviewer:

Note: In this section that Reason as labeled/specified in the Table 3 are consistent with the Codes as specified in the SOP for repeat analysis, although the alphabetical identification may differ. Please see details in the following comments 1 and 2.

1. In the standard operating procedure (SOP) of Repeat Analysis # (b) (4) (effective date: 7/10/2010) stated the repeat analysis reasons and reporting final values.
   Code A- Poor chromatography
   Code B- Unacceptable internal standard response
   Code C- Incomplete analysis
   Code D-Sample concentration above the upper limit of quantitation
   Code E- Sample Concentration Below or Above the Modified Calibration Curve
   Code F- Pharmacokinetic Repeats

Code G- Samples Reanalyzed to Obtain Confirming Value
Code H- Rejected Sample Dilution
Code I- Reassays Requested by the Client
Code M- Disregarded Value
Code O-Value Outside Acceptance Range
Code P- Sample Stability Exceeding Validation Data
Code Q- Determination of Bioanalytical Method Reproducibility
Code R- High Coefficient of Variation (%CV) between Readings (ELISA) or Difference between Concentrations of Duplicates (RIA) - Immunoassays

2. In the bioanalytical report EDOT-0922 (submitted 4/26/2010), the repeats fir this study are as follows:
    - There are 3 samples repeated for reason 4 (Code B - Unacceptable internal standard response)
    - There are 7 sample repeated for reason 5 (Code D- Sample concentration above the upper limit of quantitation);
    - There are 3 samples repeated for reason 6 (Code C1- Sample loss during a processing step, such as during extraction, filtration or protein precipitation.)

3. The reviewer checked the repeats and there is no significant difference in the values before and after repeats. The reviewer deems that the repeats for reasons for code 4, 5 and 6 would not have significant impact on the BE outcome.

3.7 Formulation

Location in appendix	Section 4.2
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**FORMULATION ACCPETABLE**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS, ANDA 201675, REV-BIOEQ-02 (Dissolution Review), submitted 3/29/2011 and current review for amendment dated 7/28/2011
Source of Method (USP, FDA or Firm)	FDA
Medium	Water
Volume (mL)	500 mL: 0.025 mg/day and 0.0375 mg/day; 900 mL: 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day
USP Apparatus type	VI (cylinder, modified).
Rotation (rpm)	50
DBE-recommended specifications	2 hr: (b) (4) 6 hr: 12 hr: 70-90%
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	**METHOD INCOMPLETE**
If not then why?	The firm is requested to acknowledge the FDA-recommended method and specifications for its test product.

3.9 Waiver Request(s)

Strengths for which waivers are requested	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day and 0.075 mg/ day
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	No
Waivers granted?	**WAIVERS DENIED**
If not then why?	Incomplete due to clinical and dissolution deficiencies.

3.10 Deficiency Comments

Deficiencies Related to the Fasting BE Study:

1. In the protocol deviation table for the fasting BE study (Report # EDOT-0922 (M1GJ09001), Table 10.3), the firm stated that "*there were pharmacokinetic (PK) sample processing errors- Period II, 12 hour B samples tubes were out of order at dispensing. It is unknown which subject's samples were in which tube*". This applied to subject Nos. 9, 10, 12, 13, 16 (test treatment) and subjects 11, 14 and 15 (reference treatment). The firm did not indicate how this issue was resolved. The firm will be asked to clarify how the issue was resolved and whether there is any consequence related to this issue in the BE study sample analysis.

2. In the protocol deviation table for the fasting BE study (Report # EDOT-0922 (M1GJ09001), Table 10.3), the firm indicated that *"there was a deviation in the Transdermal Sample Handling. Period 1 Control Sample 1A was found under the freezer".* The firm did not provide the information on how this issue was resolved and whether the found sample was used during the study. The firm will be asked to explain how the issue was resolved and whether the found sample was used during the study.

Deficiency Related to Dissolution Testing:

3. The firm has conducted comparable dissolution testing using the FDA-recommended method. The firm will be asked to accept and acknowledge the FDA recommended dissolution method and specifications as follows:

   Apparatus: USP VI (cylinder, modified)
   Speed: 50 rpm
   Medium: Water
   Volume: 500 mL for 0.025 mg/day and 0.0375 mg/day;
   900 mL for 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day
   Temperature: 32ºC ± 0.5ºC

   The test product should meet the following specifications:

   2 hr: (b) (4)
   6 hr:
   12 hr: 70-90%

   The dissolution testing is inadequate *pending* the firm's acceptance and acknowledgement of the FDA-recommended method and specification.

3.11 Recommendations

1. The Division of Bioequivalence finds the single-dose fasting bioequivalence (BE) study (EDOT-0922) **incomplete** due to deficiency comments 1-3. The firm, Mylan Technologies, Inc, conducted the fasting study by comparing its test product, Estradiol Transdermal System, USP (Twice-weekly), 0.1 mg/day (Lot # R6A0030), to the corresponding reference product, Novartis's Vivelle-Dot® (estradiol transdermal system) continuous delivery for twice-weekly application, 0.1mg/24hr (Lot # 51508).

2. The dissolution testing was conducted by the firm, Mylan Technologies, Inc, on its test products, Estradiol Transdermal System, USP (Twice-weekly), 0.025 mg/day (Lot R6A0028), 0.0375 mg/day (Lot R6A0036), 0.05 mg/day (Lot R6A0037), 0.075 mg/day (Lot R6A0038) and 0.1 mg/day (Lot R6A0030) is inadequate pending its acceptance and acknowledgement of the FDA method and specifications.

   The dissolution testing should be conducted in 500 mL of Water for 0.025 mg/day and 0.0375 mg/ day; or 900 mL of Water for 0.05 mg/ day, 0.075 mg/ day and 0.1 mg/ 24hr at 32ºC ± 0.5ºC, using USP apparatus VI (Cylinder, modified) at 50 rpm.

   The test product should meet the following specifications:

   2 hr: (b) (4)
   6 hr:
   12 hr: 70-90%

3. The firm conducted inadequate in vivo bioequivalence study (submitted 4/26/2010 (refuse to receive); 9/10/2010 (Accepted for filing)) comparing with the corresponding reference product, Novartis's Vivelle-Dot® (estradiol transdermal system) continuous delivery for twice-weekly application, 0.025 mg/24hr (Lot 49382), 0.0375 mg/24hr (Lot 50548), 0.05 mg/24hr (Lot 51510) 0.075 mg/24hr 9Lot 51509) and 0.1mg/24hr (Lot 51508). The firm's dissolution testing is incomplete pending on the acknowledgement of the FDA-recommended dissolution method and specifications as in recommendation 2. The formulations for the strengths are proportionally similar to strength of 0.1 mg/ day which underwent bioequivalence testing. However, the DBE denied waivers of in vivo bioequivalence study requirements for 0.025, 0.0375, 0.05 and 0.075 mg/day of the test product at this time due to inadequate BE study.

The firm should be informed of the above deficiency comments and recommendations.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
Division of Chemistry	(b) (4) The RLD has the API of estradiol (molecular weight 272.39) (b) (4)

	(b) (4)

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 5 Study Information

Study Number	EDOT-0922
Study Title	Single-Dose Fasting Bioequivalence Study of Estradiol Transdermal System, USP (Twice Weekly) (0.1 mg/day; Mylan) and Vivelle-Dot® (0.1 mg/day; Novartis) in Healthy Post-Menopausal Women
Clinical Site (Name, Address, Phone #)	Cetero Research – Miami 1405 NW 167 Street Miami Gardens, FL 33169 305-624-9191
Principal Investigator	Lawrence A. Galitz, M.D.
Dosing Dates	Period I: 06-Oct-2009 Period II: 17-Oct-2009
Analytical Sites (Name, Address, Phone #)	(b) (4)
Analysis Dates	04-Nov-2009 – 21-Nov-2009
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	48 days at a minimum of -70ºC ± 15ºC [Date of 1st sample collection – 04-Oct-2009; Date of last sample extraction – 21-Nov-2009]

Table 6. Product information

Product	Test	Reference
Treatment ID	Treatment A	Treatment B
Product Name	Estradiol Transdermal System (Twice Weekly)	Vivelle-Dot®
Manufacturer	Mylan Technologies Inc.	Noven Pharmaceuticals, Inc.
Batch/Lot No.	R6A0030	38967
Manufacture Date	08/2009	N/A
Expiration Date	N/A	02/2011
Strength	0.1 mg/day	0.1 mg/day
Dosage Form	Transdermal System	Transdermal System
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	101.7%	101.1%
Content Uniformity (range, %CV)	(b) (4) (2.2%)	No t available
Dose Administered	1 x 0.1 mg/day worn for 3.5 days	1 x 0.1 mg/day worn for 3.5 days
Route of Administration	Transdermal	Transdermal

Table 7. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 47 Dosed: 47 Completed: 47 Analyzed: 47 (firm); 46 (reviewer, for baseline-corrected); 45 (reviewer, for baseline-uncorrected)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	6 days
Randomization Scheme	AB: 1, 2, 6, 7, 8, 11, 14, 15, 17, 19, 20, 21, 28, 29, 30, 31, 32, 33, 37, 38, 39, 46, 47, and 48 BA: 3, 4, 5, 9, 10, 12, 13, 16, 18, 22, 22, 23, 24, 25, 26, 27, 34, 35, 36, 40, 41, 42, 43, 44, and 45
Blood Sampling Times	Blood samples were collected at the following times relative to dosing: -48, -24, 0, 2, 4, 8, 12, 18, 24, 30, 36, 48, 60, 72, 84, 86, 88, 92, 96, 100, 108, and 120 hours
Blood Volume Collected/Sample	During each study period, 22 blood samples were collected (10 mL each) from each subject by direct venipuncture using tubes containing K2 EDTA.
Blood Sample Processing/Storage	Samples were collected by direct venipuncture, inverted 5-10 times immediately after collection, and immediately placed in an ice bath. The samples were then centrifuged at 3000 rpm for 10 minutes under refrigeration (4°C). Each plasma sample was divided equally into two (2) aliquots and frozen in an upright position within 90 minutes of sample collection in a -70°C ± 15°C freezer
IRB Approval	Yes. 10/1/2009
Informed Consent	Yes. 10/1/2009
Length of Fasting	An overnight fast of at least 10 hours. A fast was maintained for at least 4 hours after dosing
Length of Confinement	All subjects checked into the clinical facility on the day prior to dosing. Check-in occurred at least 12 hours prior to patch application for each study period. The subjects were allowed to leave the clinical facility after the 120 hour blood sample collection.
Safety Monitoring	During each period admission, vital signs were obtained from all subjects (systolic and diastolic blood pressures, pulse rate, temperature and respiration). On the morning of dosing, subjects were examined to confirm normal vital signs prior to patch application (within 120 minutes prior to dosing). Vital signs were taken at other times if deemed necessary, during the study. A 12-lead ECG was recorded during the screening visit and at study exit. Electrocardiography equipment was available for cardiac monitoring, if judged necessary, during the study.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 8. Demographics Profile of Subjects Completing the Bioequivalence Study

FASTING BIOEQUIVALENCE STUDY MYLAN STUDY NUMBER – EDOT-0922			
		TREATMENT GROUPS	
		Test Product N=47 [1]	Reference Product N=47 [1]
Age (years)	Mean ± SD Range	56 ± 5 40 – 65	56 ± 5 40 – 65
Age Groups	<18 18-40 41-64 65-75 >75	0 (0%) 0 (0%) 46 (97.9%) 1 (2.1%) 0 (0%)	0 (0%) 0 (0%) 46 (97.9%) 1 (2.1%) 0 (0%)
Sex	Male Female	0 (%) 47 (100%)>	0 (%) 47 (100%)>
Race	Asian Black Caucasian Hispanic Other	0 (%) 2 (4.2%) 45 (95.7%) 46 (97.9%) 0 (%)	0 (%) 2 (4.2%) 45 (95.7%) 46 (97.9%) 0 (%)
BMI	Mean ± SD Range	27.9 ± 2.9 22 – 33	27.9 ± 2.9 22 – 33
Other Factors		n/a	n/a

Table 9. Dropout Information, Fasting Bioequivalence Study

Mylan FASTING Study Number – EDOT-0922				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
n/a	n/a	n/a	n/a	n/a

Table 10. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study Mylan Study Number – EDOT-0922	
	Test N=47[2]	Reference N=47[2]
	n (%)[3]	n (%)[3]
Cardiovascular		
Hypertension	1 (2.1%)	
Gastrointestinal		
Abdominal Discomfort	2 (4.3%)	
Abdominal Distension	1 (2.1%)	
Abdominal Pain Lower	1 (2.1%)	1 (2.1%)
Constipation	3 (6.4%)	2 (4.3%)
Diarrhoea		1 (2.1%)
Dyspepsia		1 (2.1%)
Nausea		2 (4.3%)
Throat Irritation		1 (2.1%)
Nervous System		
Dizzyness		2 (4.3%)
Headache	1 (2.1%)	2 (4.3%)
Psychiatric Disorders		
Insomnia		1 (2.1%)
Musculoskeletal and Connective Tissue		
Arthralgia		2 (4.3%)
Back Pain	3 (6.4%)	3 (6.4%)
Pain in Extremity	3 (6.4%)	
Reproductive System and Breast		
Breast Discomfort	1 (2.1%)	
Genital Rash		1 (2.1%)
Vulvovaginal Discomfort	2 (4.3%)	
Respiratory, thoracic and Mediastinal Disorders		
Nasal Congestion	1 (2.1%)	
Nasal Discomfort		1 (2.1%)
Skin and Subcutaneous Tissue		
Erythema	10 (21.3%)	16 (34.0%)
General Disorders and Administration Site Conditions		
Application Site Pruritis	1 (2.1%)	
Total Subjects Reporting at Least One Adverse Event	**21 (44.7%)**	**23 (48.9%)**

Table 11. Protocol Deviations, Fasting Bioequivalence Study

Mylan FASTING Study Number – EDOT-0922		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Concomitant medication	08, 21, 30, 31, 32, 46 – glycerin suppository 47 – ibuprofen	09, 10, 23, 43 – glycerin suppository
Blood sample collection time deviations.	03, 06, 08, 19(4), 27, 28(2), 31, 34, 36, 41, 42(2), 44(2), 45	04(2), 05, 09, 12, 19(2), 23, 25, 27, 30, 32, 38, 45, 46, 48
Period I and II - Pre-dose procedures. Clean, disposable cotton pads were used to wash and dry the application sites as opposed to washcloth/soft towel, as stated in the protocol.	01-28, 30-48	01-28, 30-48
Period I and II - Patch application procedure. Second overlay placed over transdermal system and first overlay.	02	02
Study population. 47 of 48 subjects dosed.	N/A	N/A
Period I - Meal deviations. On 06-Oct-09 subject declined to eat snack.	48	N/A
Period I - Meal deviation. On 08-Oct-09 subjects only completed 50% of snack,.	01, 07, 15, 19, 20, 21, 32, 37, 48	09, 16, 18, 25, 26, 36
Period I - Meal deviation. On 09-Oct-09 & 10-Oct-09 subject 44 declined to eat snack. On 09-Oct-09 subject 01 declined to eat snack.	01	44 (x 2)
Period I - Meal deviation. On 10-Oct-09 subject only completed 50% of Lunch.	N/A	25
Period II - PK sample processing. - 12 hour B samples, tubes were out of order at dispensing. Since tubes were out of order it is unknown which subject's samples were in which tube.	09, 10, 12, 13, 16	11, 14, 15
Transdermal Sample Handling. Period 1 Control Sample 1A (test product) found under freezer.	Control Patch A, Period 1	N/A
Period II - Irritation Evaluation. Evaluation performed at 29 minutes after removal.	N/A	37
End of Study Hematology not performed	23	N/A

Comments on Dropouts/Adverse Events/Protocol Deviations:

1. No SAEs (severe adverse events) were reported in this BE study.

2. There were seventy (70) adverse events (AEs) reported at least once by thirty-four (34) subjects over the course of the study. AEs were mild in intensity. Thirty-three (33) mild AEs were related to the test drug and 37 mild AEs were related to the reference drug.

3. The most frequently reported adverse event (AE) following patch application of Treatment A were Minimal Erythema (10) which was reported by 10/47 (21.3%) subjects. Minimal Erythema was the most frequent AE experienced by subjects following patch application of Treatment B and was reported by 12/47 (25.5%) of the subjects.

4. There was no emesis adverse event during the study.

5. There were concomitant medications during the study. The subject and medication information are listed as follows:

Subject	Period	Medication	Strength	Unit	Route	Frequency	Start Date	Stop Date	Reason
08	1	Glycerin Suppository	2.1	g	Per anal	QD	09 Oct 09	09 Oct 09	Pre-Study Condition – Constipation
09	1	Glycerin Suppository	2.1	g	Per anal	QD	09 Oct 09	09 Oct 09	Pre-Study Condition – Constipation
10	1	Glycerin Suppository	2.1	g	Per anal	QD	09 Oct 09	09 Oct 09	Adverse Event – Constipation
21	1	Glycerin Suppository	2.1	g	Per anal	QD	09 Oct 09	09 Oct 09	Pre-Study Condition – Constipation
23	2	Glycerin Suppository	2.1	g	Per anal	QD	21 Oct 09	21 Oct 09	Adverse Event – Constipation
30	1	Glycerin Suppository	2.1	g	Per anal	QD	09 Oct 09	09 Oct 09	Pre-Study Condition – Constipation
31	1	Glycerin Suppository	2.1	g	Per anal	QD	09 Oct 09	09 Oct 09	Adverse Event – Constipation
32	1	Glycerin Suppository	2.1	g	Per anal	QD	09 Oct 09	09 Oct 09	Adverse Event – Constipation
43	1	Glycerin Suppository	2.1	g	Per anal	QD	09 Oct 09	09 Oct 09	Adverse Event – Constipation
46	1	Glycerin Suppository	2.1	g	Per anal	QD	09 Oct 09	09 Oct 09	Pre-Study Condition – Constipation
47	1	Ibuprofen	800	mg	Per oral	QD	12 Oct 09	16 Oct 09	Adverse Event – Bloating

The reviewer checked the RLD labeling and did a scientific literature searching (via PubMed) and found that there is no report on the possible drug interaction of Estradiol with glycerin suppository or ibuprofen.

There were 34 blood sampling time deviations. Among these deviations, only two deviated by more than 5% from the scheduled time point. The firm and the reviewer used the actual time points in the PK data analysis. Therefore, the blood sampling deviations would not have significant impact on the PK parameters.

7. The firm stated that there were PK sample processing errors- Period II, 12 hour B samples (one of the two aliquots samples at each time points), tubes were out of order at dispensing. It is unknown which subject's sample were in which tube. This applied to subject 9, 10, 12, 13, 16 (test treatment) and subjects 11, 14 and 15 (reference treatment). The firm did not indicate how it resolved this issue or if it relied on the other aliquot of the sample. The firm will be asked to clarify how the issue was resolved.

8. In the protocol deviation table, the firm indicated that there was a deviation in the Transdermal Sample Handling. Period 1 Control Sample 1A was found under freezer. The firm did not provide the information on how it resolved this issue. The firm will be asked to explain how the issue was resolved and whether the found sample was used in the study.

The clinical results are incomplete with deficiencies.

4.1.1.3 Bioanalytical Results

Table 12. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study EDOT-0922 ESTRADIOL								
Parameter	**Standard Curve Samples**							
Concentration (pg/mL)	5.04	10.07	12.59	25.18	50.36	100.72	201.44	251.80
Inter day Precision (%CV)	4.38	3.35	2.22	2.41	2.83	2.33	1.92	2.45
Inter day Accuracy (%Actual)	99.6	100.70	100	100.56	100.18	100.24	99.41	99.38
Linearity	0.9931-0.9997							
Linearity Range (pg/mL)	5.04-251.80							
Sensitivity/LOQ (pg/mL)	5.04							

Bioequivalence Study EDOT-0922 ESTRADIOL					
Parameter	**Quality Control Samples**				
Concentration (pg/mL)	15.00	45.00	87.50	187.50	187.50 (Dilution = 2)
Inter day Precision (%CV)	3.46	2.28	6.54	3.77	1.37
Inter day Accuracy (%Actual)	104.07	104.47	104.56	101.59	100.03

Number of Acceptable Runs for Estradiol	50 runs
Number of Rejected Runs for Estradiol (Run ID, volume/page location)	3 Rejected runs, Run ID # 1,2 and 29 (Module 5.3.1.4.3 Bioanalytical report, Table 7B)
If sample and QC diluted during study, specify all dilution factors	2 folds and 20 folds dilution
Was 100% of raw numerical data submitted?	Yes

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Do you agree with the firm's accepted and rejected runs?	Yes

Comments on Study Assay Validation:

Acceptable.

1. The total number of incurred sample reanalysis (ISR) for estradiol was 108 (5.22% of the total samples of 2067 for this fasting study). 107 samples (99.07% of total ISR samples) were within the acceptance range specified by the firm's

SOP. Currently the Agency does not have any guidance or recommendation on the incurred sample reanalysis for ANDA submissions.

2. The effective dates of all SOPs on the bioanalytical method are prior to the analytical dates of this fasting study. It is acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes, 10 subjects
Were chromatograms serially or randomly selected?	Serially, subject 1-10

Comments on Chromatograms:

Acceptable

Table 13. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	2009-07-10	Sample Reassays and Reporting of Final Concentrations

Table 14. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Agree. Please refer to Section 3.6.
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

Acceptable.

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Baseline Adjusted Results

Table 15. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 19 and Figure 1

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Corrected Analysis N =47 (female 47, male 0)									
Parameter (units)	**Test (n =47)**				**Reference (n =47)**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *pg/ml)	8264.286	33.36	3328.34	15767.44	7741.854	35.75	3407.72	15234.13	1.07
AUC∞ (hr *pg/ml)	8400.325	32.75	3329.45	15871.18	11461.29	212.09	3512.96	173514.4	0.73
Cmax (pg/ml)	144.857	41.58	56.68	374.69	126.238	40.65	48.73	284.46	1.15
Tmax* (hr)	24.000	.	8.00	48.00	24.000	.	18.00	72.00	1.00
Kel (hr^{-1})	0.062	73.72	0.02	0.25	0.062	63.88	0.00	0.17	0.99
T1/2 (hr)	15.018	47.17	2.72	37.67	122.285	599.32	4.00	5039.29	0.12

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Corrected Analysis N =47 (female 47, male 0)- exclude subject 14 AUCi									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *pg/ml)	8264.185	33.36	3328.34	15767.44	7741.939	35.75	3407.72	15234.13	1.07
AUC∞ (hr *pg/ml)	8420.330	33.10	3329.13	15895.01	7913.085	35.09	3535.90	15289.99	1.06
Cmax (pg/ml)	144.857	41.58	56.68	374.69	126.238	40.65	48.73	284.46	1.15
Tmax* (hr)	24.000	.	8.00	48.00	24.000	.	18.00	72.00	1.00
Kel (hr^{-1})	0.068	81.52	0.01	0.36	0.070	58.06	0.03	0.17	0.97
T1/2 (hr)	14.607	63.90	1.93	55.30	13.184	49.62	4.11	25.37	1.11

* Tmax values are presented as median, range

Table 16. Geometric Means and 90% Confidence Intervals - Firm Calculated

ESTRADIOL TRANSDERMAL SYSTEM, 0.1 MG/DAY Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
EDOT-0922 Baseline-corrected estradiol				
Parameter	**Test**	**Reference**	**Ratio***	**90% C.I.****
AUC0-t	7805	7294	1.07	101% – 113%
AUC∞	8026	7398	1.08	102% – 115%
C_{max}	134.0	116.9	1.15	107% – 122%
EDOT-0922 Baseline-uncorrected estradiol				
Parameter	**Test**	**Reference**	**Ratio***	**90% C.I.****
AUC0-t	8228	7529	1.09	104% – 115%
AUC∞	8422	7711	1.09	103% – 115%
C_{max}	137.8	119.1	1.16	108% – 124%

Table 17. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 (female 47, male 0) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Corrected Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	7805.18	7293.83	1.07	100.98	113.40
AUC∞ (hr *pg/ml)	7947.25	8024.44	0.99	86.09	113.93
Cmax (pg/ml)	134.05	116.95	1.15	107.29	122.45

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 (female 47, male 0)- exclusion of subject 14 AUCi Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Corrected Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	7804.99	7293.88	1.07	100.97	113.40
AUC∞ (hr *pg/ml)	8026.19	7398.48	1.08	102.45	114.88
Cmax (pg/ml)	134.05	116.95	1.15	107.29	122.45

Table 18. Additional Study Information, Fasting Study No. EDOT-0922

DBE SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALCKE for initial analysis CONTINU2 for recalculation	
Reason(s) for Selecting Above SAS Program Macro	T o calculate the PK parameters independently and not replying on the firm's PK data	
Root mean square error, AUC0-t	0.1675 (n=47 excluding subject 14 AUCi)	
Root mean square error, AUC∞	0.1614 (n=47 excluding subject 14 AUCi)	
Root mean square error, Cmax	0.1907 (n=47 excluding subject 14 AUCi)	
	Test	**Reference**
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞	47	47
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC∞	Disagree since firm excluded both subject 14 and 25 AUCi	Disagree since firm excluded both subject 14 and 25 AUCi
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞ (n =47)				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	47	0.98	0.89	1.00
Reference	47	0.96	0.03	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	Subject 14 has the reference treatment, AUCt/AUCi=0.03. Please see comment 3 for more details.			
Ratio of AUC0-t/AUC∞ (n =47)- exclude subject 14 AUCi				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	46	0.98	0.94	1.00
Reference	46	0.98	0.93	1.00

Comments on Pharmacokinetic and Statistical Analysis:

1. The subjects were dosed in one group. The firm and the reviewer's calculations both are based on one group.

2. The reviewer used the SAS code, CALCKE, for statistical analysis of the data. This particular SAS code allows the reviewer to select the values which are used as the time points to calculate the elimination rate constant, Kel (Note: AUCI and THALF are dependent variables), along with other PK parameters. The elimination rate constant (Kel) was calculated by using the last three or four non-zero data. The selection of the time points for calculating the Kel was based on the terminal log-linear phase of the parent drug for the subjects. The firm and the reviewer used the actual sampling times to calculate the 90% CIs.

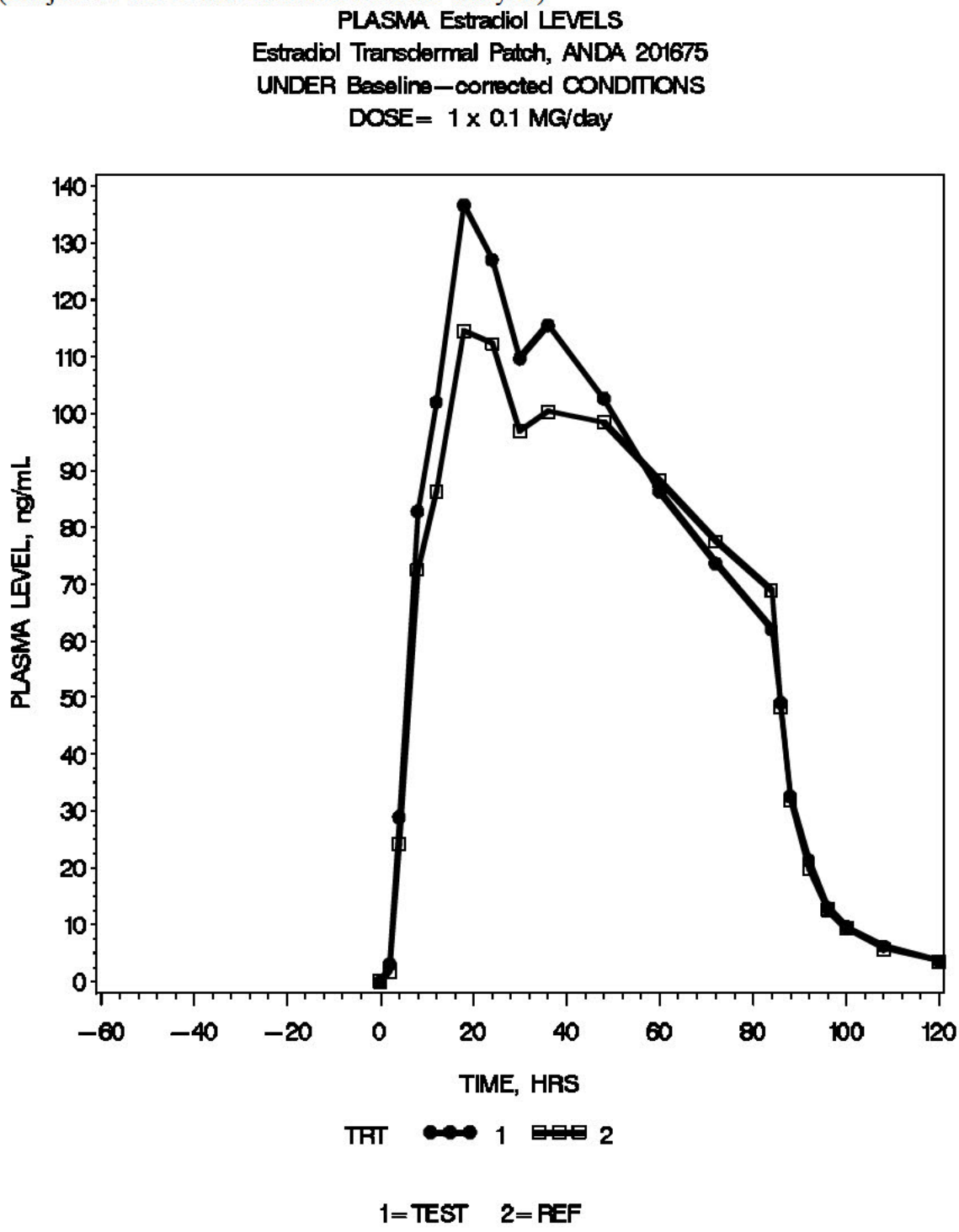
3. The reviewer originally included all 47 subjects in the SAS analysis and obtained the pharmacokinetic (PK) parameters for these 47 subjects. The 90% CIs are in the acceptable range. However, the arithmetic ratio of AUCi of test and reference is 0.73, which is more than 20% difference. In addition, the reviewer found that subject 14 (Period II, reference treatment) has an AUCt/AUCi value of 0.03. It has a higher concentration in the last time point- 120 hours than that at 108 hours. Therefore, it is appropriate to exclude subject 14 –AUCi parameter from the statistic analysis. The reviewer redid the SAS calculation and found that the subject 14 does not have significant impact on the bioequivalence outcome. The 90% CIs of AUCi, AUCt and Cmax are all within acceptable range of 80-125%. The arithmetic ratio of AUCi of test and reference is 1.06 when subject 14 AUCi was excluded from the analysis.

Table 19. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Estradiol Baseline-Corrected N =47 (female 47, male 0)- exclusion of subject 14 AUCi					
Time (hr)	Test		Reference		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
-48.00	.	.	.	.	.
-24.00	.	.	.	.	.
0.00	0.00	.	0.00	.	.
2.00	3.05	191.20	1.89	163.32	1.62
4.00	28.97	117.20	24.19	132.04	1.20
8.00	82.79	68.29	72.48	69.72	1.14
12.00	102.01	53.01	86.37	56.69	1.18
18.00	136.69	45.69	114.57	46.17	1.19
24.00	127.09	35.33	112.31	39.76	1.13
30.00	109.69	32.82	96.92	38.99	1.13
36.00	115.56	35.47	100.32	34.22	1.15
48.00	102.69	29.96	98.49	41.08	1.04
60.00	86.31	35.83	88.31	35.98	0.98
72.00	73.63	34.45	77.47	34.66	0.95
84.00	61.99	39.47	68.82	35.07	0.90
86.00	49.10	37.05	48.38	30.48	1.01
88.00	32.64	33.66	31.93	29.45	1.02
92.00	21.35	63.51	19.85	32.77	1.08
96.00	13.06	36.96	12.62	43.76	1.03
100.00	9.64	43.39	9.47	52.52	1.02
108.00	6.25	52.18	5.80	67.79	1.08
120.00	3.64	104.25	3.63	140.56	1.01

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

(Subject 14 AUCi was excluded from the analysis)



4.1.1.4.2 Baseline-Unadjusted Results

Table 20. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 24 and Figure 2

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-uncorrected analysis N =47 (female 47, male 0)									
Parameter (units)	**Test (n =47)**				**Reference (n =47)**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *pg/ml)	8907.718	37.81	4073.84	22456.46	8099.439	36.17	3407.72	15234.13	1.10
AUC∞ (hr *pg/ml)	10585.28	115.09	4291.85	90310.20	78317.92	611.94	3535.90	3293962	0.14
Cmax (pg/ml)	148.744	40.91	56.68	374.69	128.373	40.10	48.73	284.46	1.16
Tmax* (hr)	24.000	.	8.00	48.00	24.000	.	18.00	72.00	1.00
Kel (hr^{-1})	0.043	71.56	0.00	0.19	0.045	71.62	0.00	0.16	0.94
T1/2 (hr)	29.348	196.73	3.73	410.34	1517.828	676.03	4.46	70366.50	0.02

- Tmax values are presented as median, range

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-uncorrected analysis N =47 (female 47, male 0)-exclude subject 14 and subject 25 for analysis of AUCi									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *pg/ml)	8907.614	37.81	4073.84	22456.46	8099.443	36.17	3407.72	15234.13	1.10
AUC∞ (hr *pg/ml)	8763.682	31.21	4216.33	15895.01	8282.557	36.25	3535.90	15289.99	1.06
Cmax (pg/ml)	148.744	40.91	56.68	374.69	128.373	40.10	48.73	284.46	1.16
Tmax* (hr)	24.000	.	8.00	48.00	24.000	.	18.00	72.00	1.00
Kel (hr^{-1})	0.068	81.52	0.01	0.36	0.070	58.06	0.03	0.17	0.97
T1/2 (hr)	14.607	63.90	1.93	55.30	13.184	49.62	4.11	25.37	1.11

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-uncorrected analysis N =47 (female 47, male 0)-exclude subject 14 AUCi and subject 25 AUCi, AUCt and Cmax									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *pg/ml)	8569.354	41.10	3407.72	22456.46	8427.924	33.59	3846.14	15767.44	1.02
AUC∞ (hr *pg/ml)	8718.297	40.45	3542.35	22513.77	8614.839	33.46	3950.63	15826.34	1.01
Cmax (pg/ml)	137.339	40.37	48.73	284.46	139.801	42.71	56.09	374.69	0.98
Tmax* (hr)	24.000	.	18.00	72.00	24.000	.	8.00	60.00	1.00
Kel (hr^{-1})	0.109	262.89	0.01	2.00	0.071	57.38	0.03	0.17	1.54
T1/2 (hr)	14.304	66.16	0.35	55.30	12.979	49.81	4.11	25.37	1.10

Table 21. Geometric Means and 90% Confidence Intervals - Firm Calculated

ESTRADIOL TRANSDERMAL SYSTEM, 0.1 MG/DAY Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
EDOT-0922 Baseline-corrected estradiol				
Parameter	**Test**	**Reference**	**Ratio***	**90% C.I.****
AUC0-t	7805	7294	1.07	101% – 113%
AUC∞	8026	7398	1.08	102% – 115%
C_{max}	134.0	116.9	1.15	107% – 122%
EDOT-0922 **Baseline-uncorrected estradiol**				
Parameter	**Test**	**Reference**	**Ratio***	**90% C.I.****
AUC0-t	8228	7529	1.09	104% – 115%
AUC∞	8422	7711	1.09	103% – 115%
C_{max}	137.8	119.1	1.16	108% – 124%

Table 22. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 (female 47, male 0) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Unadjusted Analysis					
Parameter (units)	**Test (n = 47)**	**Reference (n = 47)**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	8364.48	7616.84	1.10	104.04	115.91
AUC∞ (hr *pg/ml)	8872.16	9007.53	0.98	77.81	124.69

Cmax (pg/ml)	137.77	119.10	1.16	108.31	123.55

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 (female 47, male 0)-exclude subject 14 and subject 25 for analysis of AUCi Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Unadjusted Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	8364.33	7616.83	1.10	104.04	115.91
AUC∞ (hr *pg/ml)	8468.48	7746.11	1.09	103.53	115.44
Cmax (pg/ml)	137.77	119.10	1.16	108.31	123.55

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 (female 47, male 0)-exclude subject 14 AUCi and subject 25 AUCi, AUCt and Cmax Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Unadjusted Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	7952.04	8061.48	0.99	89.85	108.30
AUC∞ (hr *pg/ml)	8107.01	8205.71	0.99	89.88	108.60
Cmax (pg/ml)	126.25	130.57	0.97	85.06	109.91

Table 23. Additional Study Information, Fasting Study No. EDOT-0922

DBE SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALCKE (initial) CONTINU2 (recalculation)	
Reason(s) for Selecting Above SAS Program Macro	T o calculate the PK parameters independently and not replying on the firm's PK data	
Root mean square error, AUC0-t	0.1558 (excluding subject 14 and 25 AUCi)	
Root mean square error, AUC∞	0.1534 (excluding subject 14 and 25 AUCi)	
Root mean square error, Cmax	0.1900 (excluding subject 14 and 25 AUCi)	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	47	47
Do you agree or disagree with firm's decision?	agree	agree
Indicate the number of subjects with the following:		

measurable drug concentrations at 0 hr	11 *	11*
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?		

* This analysis is baseline-unadjusted. It is normal to have measurable concentration at 0 hour.

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	47	0.95	0.25	1.00
Reference	47	0.95	0.00	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	Subject 14 - reference treatment, AUCt/AUCi=0.00. Subject 25 - test treatment AUCt/AUCi=0.25. Please see comment 2 for more details.			

Ratio of AUC0-t/AUC∞ N =47 (female 47, male 0)-exclude subject 14 and subject 25 for analysis of AUCi				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	46	0.98	0.94	1.00
Reference	46	0.98	0.91	1.00

Ratio of AUC0-t/AUC∞ N =47 (female 47, male 0)-exclude subject 14 AUCi and subject 25 AUCi, AUCt and Cmax				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	47	0.98	0.94	1.00
Reference	45	0.98	0.91	1.00

Comments on Pharmacokinetic and Statistical Analysis:

1. The subjects were dosed in one group. The firm and the reviewer's calculations both are based on one group.

2. Initially the reviewer included all 47 subjects in the SAS analysis and obtained the pharmacokinetic (PK) parameters for these 47 subjects. For the test product, when included all 47 subjects, the 90% CIs of AUCt and Cmax are within the acceptable range of 80-125%. However, the 90% CI of AUCi is 77.81% to 124.69% which is out of the acceptable range of 80-125%. The baseline-uncorrected analysis does not meet the acceptable BE criteria with all 47 subjects. The reviewer investigated the failure source and found that:

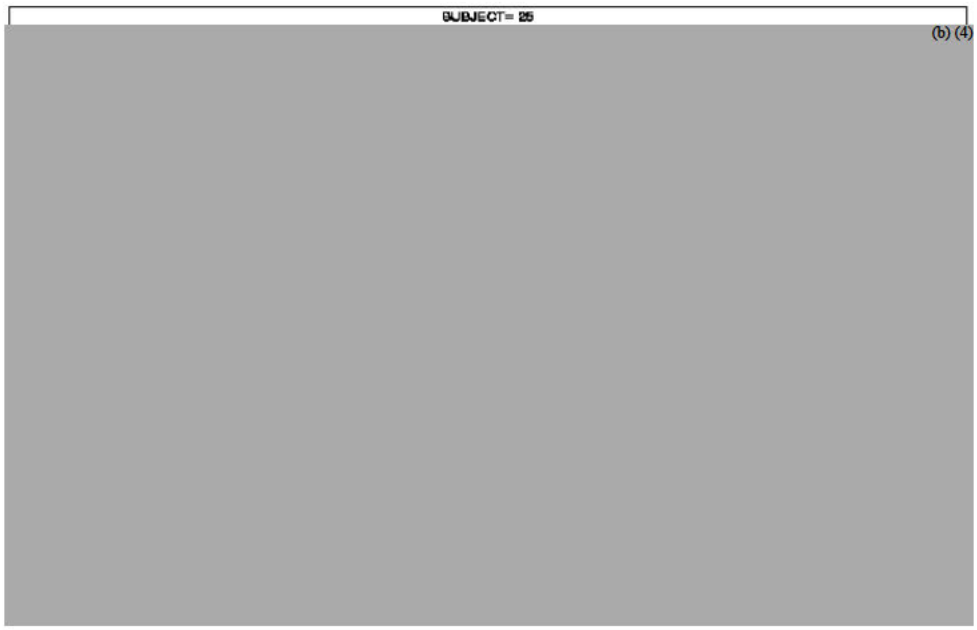
   Although the mean values of AUCt/AUCi for reference and test products are more than 0.90, there is a minimum value of 0-subject 14 (Period 2) in reference treatment and a minimum value of 0.25 – subject 25 (Period 2) and in test treatment. The

reviewer checked the individual plasma concentration – time profile and PK parameters, found that, for subject 14 (reference treatment, Period II) and subject 25 (test treatment, Period II), the elimination phase has not been confirmed as the last measurable concentrations at 120 hours were higher than the preceding values. Therefore, Kel cannot be determined for these subjects. Consequently, AUCi values for these subjects are also undeterminable. Therefore, Subjects 14 and 25 were excluded from the AUCi analysis.

The PK profiles of subject 14 (Period 2, reference treatment) and subject 25 (Period 1, test treatment) are as follows:

Subject 14:

Subject 25:



It should be noted that the plasma concentrations at time 0 hour for subject 25 (test treatment, Period II) is 88.97. The normal endogenous Estradiol level in the post-menopausal females is 0-36 pg/mL.[10] Therefore, subject 25 in the test treatment appeared to have the abnormal level of Estradiol. In order to investigate whether this abnormal high level of pre-dose estradiol in subject 25 has any impact on the bioequivalence outcome, the reviewer removed AUCt, AUCi, Cmax of subject 25 (besides removal of subject 14 AUCi) and redid the statistical analysis. It was found that the 90% CIs of three PK parameters are still within the acceptable range of 80-125%. However, the 90%CI of AUCt shift from 104-116% to 90-108%, AUCi from 103-115% to 90-109% and Cmax from 108-124% to 85-110%. The abnormal high pre-dose value of subject 25 does have significant impact on the 90% CIs, but not significantly impact the bioequivalence outcome.

3. The 90% CIs of PK parameters are all within acceptable range of 80-125% under two calculation conditions: removal of AUCi of subject 14 and 25, and removal of subject 14 AUCI and subject 15 AUCi, AUCt and Cmax.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The fasting study is incomplete with deficiencies.

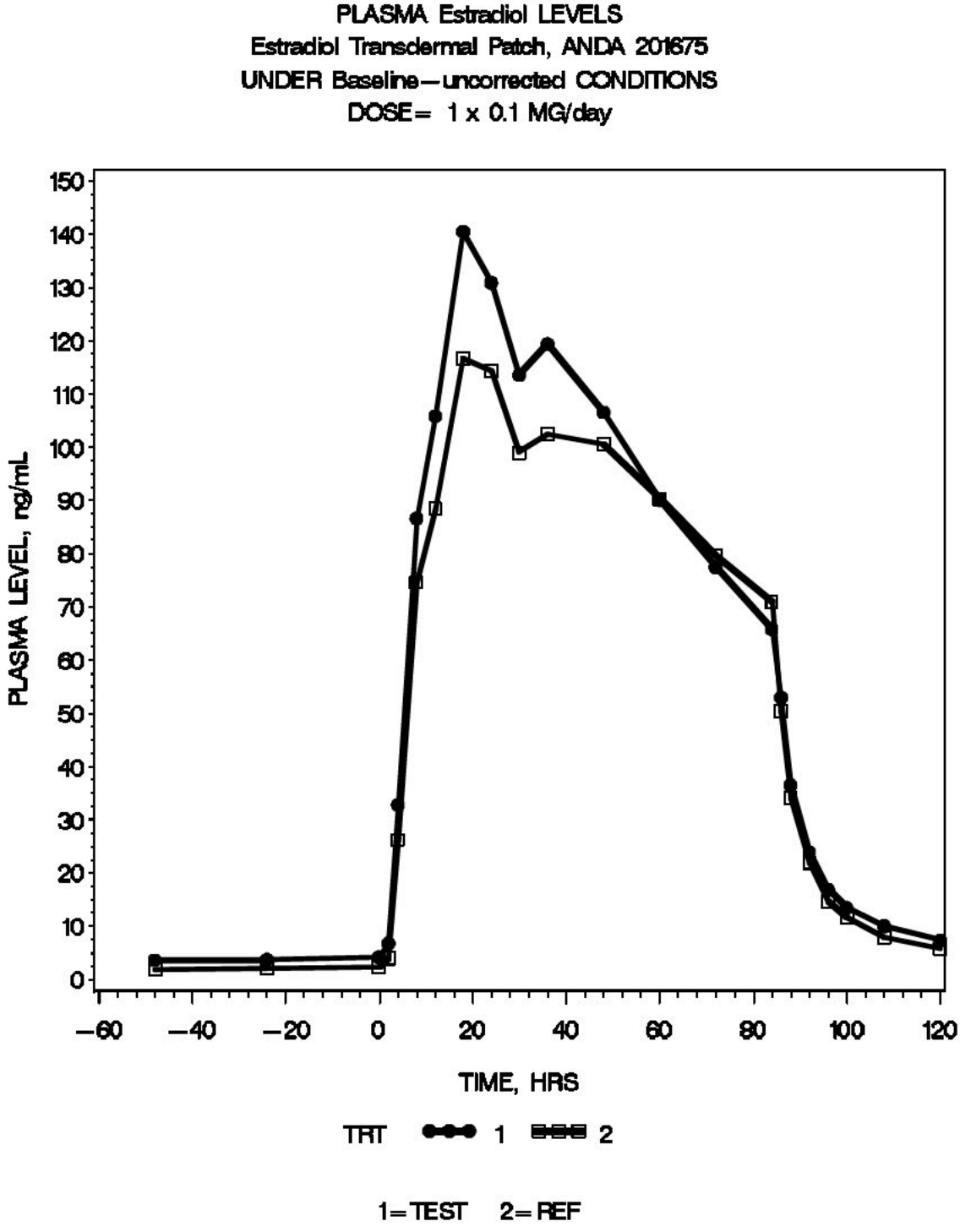
[10] Internet, http://webcache.googleusercontent.com/search?hl=en&safe=active&q=cache:v9sW5-DbjU4J:http://www.earlymenopause.com/tests.htm+estradiol+levels+in+women&ct=clnk. Last accessed 8-29-2011

Table 24. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Estradiol Baseline-Uncorrected N =47 (female 47, male 0)-exclude subject 14 and subject 25 for analysis of AUCi					
Time (hr)	Test		Reference		T/R Ratio
	Mean (pg/mL)	% CV	Mean (pg/mL)	% CV	
-48.00	3.69	356.67	1.96	179.68	1.88
-24.00	3.75	372.68	2.02	185.59	1.85
0.00	4.22	355.01	2.42	223.65	1.74
2.00	6.85	231.29	4.00	133.57	1.72
4.00	32.85	108.81	26.32	122.35	1.25
8.00	86.68	64.77	74.61	68.14	1.16
12.00	105.90	50.47	88.50	55.14	1.20
18.00	140.58	44.14	116.70	45.25	1.20
24.00	130.98	35.84	114.45	39.60	1.14
30.00	113.58	33.64	99.05	38.76	1.15
36.00	119.45	36.56	102.45	33.80	1.17
48.00	106.57	31.50	100.62	40.93	1.06
60.00	90.19	34.41	90.44	35.99	1.00
72.00	77.51	34.06	79.60	35.32	0.97
84.00	65.88	36.76	70.96	34.96	0.93
86.00	52.98	35.33	50.52	32.14	1.05
88.00	36.53	45.51	34.06	34.37	1.07
92.00	23.97	59.04	21.98	41.78	1.09
96.00	16.94	93.49	14.76	58.93	1.15
100.00	13.53	113.47	11.61	69.80	1.17
108.00	10.13	131.55	7.93	83.68	1.28
120.00	7.36	226.65	5.76	140.73	1.28

Figure 2. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

N =47 (female 47, male 0)-exclude subject 14 and subject 25 for analysis of AUCi



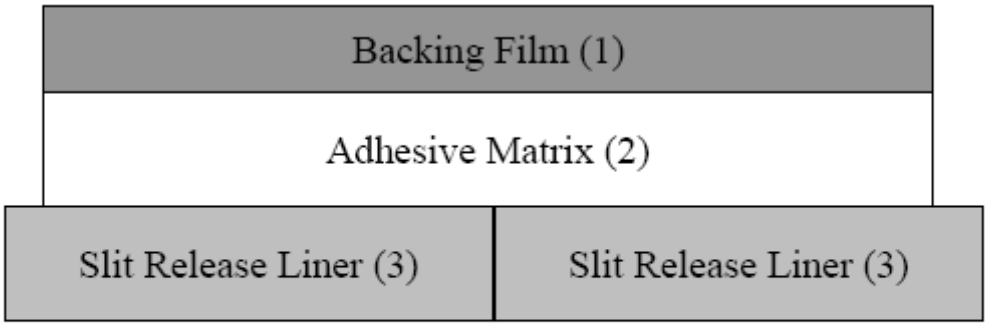
4.2 Formulation Data

Composition and Pharmaceutical Function of Adhesive Matrix Components of Mylan's Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice-Weekly)

Components	Pharmaceutical Function	% w/w	mg per system				
			0.025 mg/ day	0.0375 mg/ day	0.05 mg/ day	0.075 mg/ day	0.1 mg/ day
Active Ingredient							
Estradiol (b) (4) USP (b) (4)	Active Ingredient	(b) (4)	0.41	0.62	0.82	1.23	1.64
Inactive Ingredients							
Oleyl Alcohol (b) (4)	(b) (4)	(b) (4)					(b) (4)
Dipropylene Glycol (b) (4)							
Povidone USP (b) (4)							
Silicone Adhesive (b) (4)	Adhesive						
Acrylic Adhesive (b) (4)	Adhesive						
(b) (4)	(b) (4)						
(b) (4)							
Theoretical Total Matrix							
Components of the Delivery and Packaging System							
Polyolefin Film (b) (4)	Backing						(b) (4)
Brown Ink (b) (4)	Imprinting Ink						
((b) (4) Polyester Film (b) (4)	Oversized Release Liner						

(b) (4)

The Schematic Diagram of Mylan's Estradiol Transdermal System (twice-weekly)



Note: Relative dimensions for 0.1 mg/day; vertical scale exaggerated 50×

The amounts of the inactive ingredient excipients

Inactive Adhesive Matrix Ingredients of Mylan's Estradiol Transdermal System USP, 0.1 mg/day (Twice-Weekly)

Inactive Ingredients	Maximum amount (mg) per system per day	Maximum Level listed in the FDA IIG[11] for transdermal route(mg)	Adjustments	Above or below IIG
Oleyl Alcohol, (b) (4) (b) (4)	(b) (4)	6.03	(b) (4)	below
Dipropylene Glycol (b) (4)		12mg		below
Povidone (b) (4) (b) (4)		7.266 mg		below
Silicone Adhesive (b) (4)		228.23 mg		below
Acrylic Adhesive (b) (4)		Not specified		below
(b) (4)		Not specified		(b) (4)
		36138 mg		below

* (b) (4) is listed in the IIG under the legacy product name (b) (4)

[11] FDA IIG limits. Last accessed 7-28-2011
[12] V:\FIRMSAM\MYLAN\LTRS&REV\75182s12.cr1.new.BBS.doc. submitted 11/26/2003. Last accessed 7-28-2011
[13] DARRTS, DMF (b) (4) (DMF number was provided by the firm). This DMF is (b) (4). Last accessed 7-28-2011.

Component Materials of Mylan's Estradiol Transdermal System, USP (Twice-Weekly)

Components	Maximum amount (mg) per system per day	Maximum Level listed in the FDA IIG[14] (mg)	Adjustments	Above or below IIG
Polyolefin Film (b) (4)	(b) (4)	Not specified	(b) (4)	below
Brown Ink (b) (4)		Not specified		below
(b) (4) Polyester Film (b) (4)		211.8 mg		below

Comment:

1. The firm provided the composition of Brown Ink (b) (4) (b) (4) Brown ink in the test product, the reviewer deems the amounts of the ingredients from the Brown Ink not significant, and therefore, every excipient in the test product is within the acceptable and safe limit.

[14] FDA IIG limits. Last accessed 7-28-2011
[15] EDR, ANDA201675, Module 3.2.P.1 Description and composition of the drug product. Submitted 4/6/2010. Last accessed 7-29-2011
[16] EDR, ANDA201675, Module 2.3 Quality Overall Summary. (b) (4) or polyolefint is, used in the manufacture of 100 ug/hr dosage strength-Mylan's approved Fentanyl Transdermal System (ANDA #076258). (b) (4)
[17] V:\FIRMSAM\MYLAN\LTRS&REV\76258div.sum.doc. ANDA 076258 Fentanyl transdermal patch 10.20 mg/25 cm2 strength has the largest area of polyolefin film. last accessed 7-28-2011

The active pharmaceutical ingredient (API)

	Components	% w/w	mg per system				
			0.025 mg/ day	0.0375 mg/ day	0.05 mg/ day	0.075 mg/ day	0.1 mg/ day
Test product	Estradiol (b) (4), USP,	(b) (4)	0.41 (2.5cm^2)	0.62 (3.75cm^2)	0.82 (5.0cm^2)	1.23 (7.5cm^2)	1.64 (10.0cm^2)
	(b) (4)						
		Mg/cm2					
RLD[18]	Estradiol (b) (4)	(b) (4)	0.39 (2.5cm^2)	0.585 (3.75cm^2)	0.78 (5.0cm^2)	1.17 (7.5cm^2)	1.56 (10.0cm^2)
Difference (%) (Test-RLD)/RLD x 100%			1.8%	2.6%	1.8%	1.8%	1.7%

Comments:

1. Vivelle-Dot® (estradiol transdermal system) contains estradiol in a multipolymeric adhesive. The system is designed to release estradiol continuously upon application to intact skin. Five dosage strengths of Vivelle-Dot are available to provide nominal in vivo delivery rates of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5, 3.75, 5.0, 7.5, or 10.0 cm^2 and contains 0.39, 0.585, 0.78, 1.17, or 1.56 mg of estradiol USP, respectively. The composition of the systems per unit area is identical. [19]

2. The RLD contains the API of estradiol (molecular weight 272.38) and the test product contains API of Estradiol (b) (4) (b) (4) (b) (4) 0.025mg/day, 0.05 mg/day and 0.075 mg/ day, (b) (4) for 0.0375 mg/day and (b) (4) for 0.1mg/day. The reviewer will inform Division of Chemistry this issue. DB I will defer to Division

[18] DARRTS, NDA020538, REV-QUALITY-03(General Review), submitted 10/18/2001. last accessed 7-29-2011
[19] DRUGS@FDA, search vivelle-dot. Last accessed 7-29-2011..

of Chemistry on the decision of this issue. Note: At the time of review, the Division of Chemistry had not yet reviewed the application.

Is there an overage of the active pharmaceutical ingredient (API)?	Yes
If the answer is yes, has the appropriate chemistry division been notified?	The reviewer will notify the chemistry division and DB I will defer to Chemistry Division for the decision of this issue.
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	Pending on Chemistry Division decision.
Comments on the drug product formulation:	Acceptable form bioequivalence point of view. API overage issue will be deferred to Division of Chemistry.

Comments:

1. The test product comprises of three layers and when administered it will be applied to the skin.

2. The formulations of all the strengths of the test product are proportionally similar.

3. The firm provided the composition of Brown Ink (b) (4) Brown ink in the test product, the reviewer deems every excipient in the test product is minimum.

4. The RLD has the API of estradiol (molecular weight 272.38) and the test product contains API of Estradiol (b) (4) (b) (4) (b) (4) . The reviewer will inform Division of Chemistry and rhe DB I defers to the Division of Chemistry to address the API overage issue.

The formulation is acceptable from the bioequivalence point of view.

4.3 Dissolution Data

Dissolution Review Path	DARRTS, ANDA201675, REV-BIOEQ-02(Dissolution Review), submitted 3/29/2011

The DBE did the dissolution review based on the original dissolution testing (DARRTS, ANDA201675, REV-BIOEQ-02(Dissolution Review), submitted 3/29/2011). On 4/15/2011, the DBE issued the deficiency letter on dissolution to the firm (DARRTS, ANDA201675, COR-ANDADE-01(Bio Incomplete Deficiencies), submitted 4/15/2011). The following deficiencies were identified:

1. Please conduct the dissolution test using the following FDA-recommended dissolution method as shown in the current FDA dissolution database at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm:

USP Apparatus :	VI (Cyclinder) attach the patch to a disk at the bottom of the cylinder
Speed (rpm) :	50
Medium :	Water
Volume (mL) :	500 mL (0.025 mg/24 hr and 0.0375 mg/24 hr); 900 mL (0.05 mg/24 hr , 0.075 mg/24 hr and 0.1 mg/24 hr)
Temperature :	32°C ± 0.5°C
Sampling Times :	1, 2, 4, 6, 8, 10 and 12 hours

2. In addition, as recommended in the current Bioequivalence Guidance for Estradiol Transdermal System (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234963.pdf), dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatuses for transdermal systems in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be conducted. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The dissolution test should include early sampling times of 0.5, 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

3. Please clarify which of the following two parameters: the delivered dose (i.e, 0.025 mg/day) or the loading amount (i.e. 0.41 mg), was used in your calculation for the percentage of drug release in your dissolution data.

On 7/28/2011, the firm submitted an amendment on dissolution.

To the deficiency 3, the firm indicated that the drug release profile is calculated as a percentage of the loading drug amount (ie, 0.025mg/day patch contains 0.41 mg API. The dissolution is based on percentage of 0.41 mg). The firm's response to this deficiency is acceptable.

As response to deficiencies 1 and 2, the firm provided the dissolution testing using the FDA recommended method and additional dissolution testing in the media of pH 1, 4.5 and 6.8 buffers. The new dissolution data and review are as follows:

Dissolution testing using the FDA recommended method

Drug Release Conditions	**Apparatus:**	VI (Cylinder)											
	Speed of Rotation:	50 rpm											
	Medium:	Water											
	Volume:	900 mL											
	Temperature:	32 °C ± 0.5 °C											
Firm's Proposed Specifications	2 hours: (b) (4)		8 hours: (b) (4)		(b) (4)								
Dissolution Testing Site (Name, Address)	Mylan Technologies, 110 Lake Street, Saint Albans, Vermont 05478												
Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						1 hr	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**	
N/A	May. 2011	**Estradiol Transdermal System, USP 0.1 mg/day (Twice-Weekly) Lot R6A0030 Mfg. Date – Aug. 2009**	0.1 mg/day	12	Mean (%)	19	30	45	56	67	74	80	Section 3.2.P.5.4
					Range (%)	(b) (4)							

					% CV	2.4	1.7	1.4	1.2	0.8	0.8	1.2	
N/A	May. 2011	**Vivelle Dot® 0.1 mg/day Lot 51508 Exp. Date – Jan. 2012**	0.1 mg/day	12	Mean (%)	18	29	43	54	62	69	73	
					Range (%)	(b) (4)							
					% CV	2.7	3.0	2.1	2.3	1.4	2.1	1.6	

Table 1. Mylan ETS, 0.1 mg/day

Dosage: Estradiol Transdermal System, 0.1 mg/day (1.64mg / 10.0cm²)
Lot: R6A0030
Test Method: FDA Dissolution Method for Estradiol TS (Test 1)
Apparatus: VI - Cylinder
Drug Release Medium: 900 mL Water
32 °C ± 0.5 °C

Quantity Of Drug Released, % of claim							
Sample #	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	19	30	45	56	67	74	80
RSD, %	2.4	1.7	1.4	1.2	0.8	0.8	1.2
Range	(b) (4)						

Table 2. Vivelle Dot ETS, 0.1 mg/day

Dosage: Estradiol Transdermal System, 0.1 mg/day (1.56mg / 10.0cm²)
Lot: 51508
Test Method: FDA Dissolution Method for Estradiol TS (Test 1)
Apparatus: VI - Cylinder
Drug Release Medium: 900 mL Water
32 °C ± 0.5 °C

Quantity Of Drug Released, % of claim							
Sample #	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	18	29	43	54	62	69	73
RSD, %	2.7	3.0	2.1	2.3	1.4	2.1	1.6
Range	(b) (4)						

Drug Release Conditions	**Apparatus:**	VI (Cylinder)		
	Speed of Rotation:	50 rpm		
	Medium:	Water		
	Volume:	900 mL		
	Temperature:	32 °C ± 0.5 °C		
Firm's Proposed Specifications	2 hours: (b) (4)	8 hours: (b) (4)	(b) (4)	
Dissolution Testing Site (Name, Address)	Mylan Technologies, 110 Lake Street, Saint Albans, Vermont 05478			

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength	No. of Dosage Units		Collection Times (minutes or hours)							Study Report Location
						1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr	
N/A	May. 2011	**Estradiol Transdermal System, USP 0.075 mg/day (Twice-Weekly) Lot R6A0038 Mfg. Date – Sept. 2009**	0.075 mg/day	12	Mean (%)	19	30	46	58	68	75	80	Section 3.2.P.5.4
					Range (%)	(b) (4)							
					% CV	1.5	1.6	1.3	1.1	0.8	1.0	1.2	
N/A	May. 2011	**Vivelle Dot® 0.075 mg/day Lot 51509 Exp. Date – Oct. 2012**	0.075 mg/day	12	Mean (%)	18	29	44	54	62	67	73	
					Range (%)	(b) (4)							
					% CV	2.7	1.0	1.5	1.9	1.6	1.3	1.1	

Table 1. Mylan ETS, 0.075 mg/day

Dosage: Estradiol Transdermal System, 0.075 mg/day (1.23mg / 7.5cm²)
Lot: R6A0038
Test Method: FDA Dissolution Method for Estradiol TS (Test 1)
Apparatus: VI - Cylinder
Drug Release Medium: 900 mL Water
32 °C ± 0.5 °C

Quantity Of Drug Released, % of claim							
Sample #	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	19	30	46	58	68	75	80
RSD, %	1.5	1.6	1.3	1.1	0.8	1.0	1.2
Range	(b) (4)						

Table 2. Vivelle Dot ETS, 0.075 mg/day

Dosage: Estradiol Transdermal System, 0.075 mg/day (1.17mg / 7.5cm²)
Lot: 51509
Test Method: FDA Dissolution Method for Estradiol TS (Test 1)
Apparatus: VI - Cylinder
Drug Release Medium: 900 mL Water
32 °C ± 0.5 °C

Quantity Of Drug Released, % of claim							
Sample #	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	18	29	44	54	62	67	73
RSD, %	2.7	1.0	1.5	1.9	1.6	1.3	1.1
Range	(b) (4)						

Drug Release Conditions	**Apparatus:**	VI (Cylinder)
	Speed of Rotation:	50 rpm
	Medium:	Water
	Volume:	900 mL
	Temperature:	32 °C ± 0.5 °C
Firm's Proposed Specifications	2 hours: (b) (4)	8 hours: (b) (4) (b) (4)
Dissolution Testing Site (Name, Address)	Mylan Technologies, 110 Lake Street, Saint Albans, Vermont 05478	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength	No. of Dosage Units		Collection Times (minutes or hours)							Study Report Location
						1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr	
N/A	May. 2011	**Estradiol Transdermal System, USP 0.05 mg/day (Twice-Weekly) Lot R6A0037 Mfg. Date – Sept. 2009**	0.05 mg/day	12	Mean (%)	20	30	45	58	68	76	80	Section 3.2.P.5.4
					Range (%)	(b) (4)							
					% CV	4.0	2.2	1.5	0.9	1.0	1.0	1.1	
N/A	May. 2011	**Vivelle Dot® 0.05 mg/day Lot 51510 Exp. Date – Oct. 2012**	0.05 mg/day	12	Mean (%)	19	29	44	54	62	69	74	
					Range (%)	(b) (4)							
					% CV	5.2	2.1	1.8	2.0	2.2	2.3	1.2	

Table 1. Mylan ETS, 0.05 mg/day

Dosage: Estradiol Transdermal System, 0.05 mg/day (0.82mg / 5.0cm²)
Lot: R6A0037
Test Method: FDA Dissolution Method for Estradiol TS (Test 1)
Apparatus: VI - Cylinder
Drug Release Medium: 900 mL Water
32 °C ± 0.5 °C

Quantity Of Drug Released, % of claim							
Sample #	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	20	30	45	58	68	76	80
RSD, %	4.0	2.2	1.5	0.9	1.0	1.0	1.1
Range	(b) (4)						

Table 2. Vivelle Dot ETS, 0.05 mg/day

Dosage: Estradiol Transdermal System, 0.05 mg/day (0.78mg / 5.0cm²)
Lot: 51510
Test Method: FDA Dissolution Method for Estradiol TS (Test 1)
Apparatus: VI - Cylinder
Drug Release Medium: 900 mL Water
32 °C ± 0.5 °C

Quantity Of Drug Released, % of claim							
Sample #	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	19	29	44	54	62	69	74
RSD, %	5.2	2.1	1.8	2.0	2.2	2.3	1.2
Range	(b) (4)						

Drug Release Conditions	**Apparatus:**	VI (Cylinder)											
	Speed of Rotation:	50 rpm											
	Medium:	Water											
	Volume:	500 mL											
	Temperature:	32 °C ± 0.5 °C											
Firm's Proposed Specifications	2 hours: (b) (4)			8 hours: (b) (4)			(b) (4)						
Dissolution Testing Site (Name, Address)	Mylan Technologies, 110 Lake Street, Saint Albans, Vermont 05478												

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength**	**No. of Dosage Units**		**Collection Times (minutes or hours)**							**Study Report Location**
						1 hr	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**	
N/A	June. 2011	**Estradiol Transdermal System, USP 0.0375 mg/day (Twice-Weekly) Lot R6A0036 Mfg. Date – Sept. 2009**	0.0375 mg/day	12	Mean (%)	20	30	46	58	67	76	81	Section 3.2.P.5.4
					Range (%)	(b) (4)							
					% CV	3.6	2.8	2.8	2.4	1.1	1.4	1.9	
N/A	June. 2011	**Vivelle Dot® 0.0375 mg/day Lot 50548 Exp. Date – Sep. 2012**	0.0375 mg/day	12	Mean (%)	19	29	43	53	61	68	73	
					Range (%)	(b) (4)							
					% CV	2.7	2.1	1.9	2.0	1.7	1.6	1.2	

Table 1. Mylan ETS, 0.0375 mg/day

Dosage: Estradiol Transdermal System, 0.0375 mg/day (0.62mg / 3.75cm²)
Lot: R6A0036
Test Method: FDA Dissolution Method for Estradiol TS (Test 1)
Apparatus: VI - Cylinder
Drug Release Medium: 500 mL Water
32 °C ± 0.5 °C

Quantity Of Drug Released, % of claim							
Sample #	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**
1							(b) (4)
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	20	30	46	58	67	76	81
RSD, %	3.6	2.8	2.8	2.4	1.1	1.4	1.9
Range							(b) (4)

Table 2. Vivelle Dot ETS, 0.0375 mg/day

Dosage: Estradiol Transdermal System, 0.0375 mg/day (0.585mg / 3.75cm²)
Lot: 50548
Test Method: FDA Dissolution Method for Estradiol TS (Test 1)
Apparatus: VI - Cylinder
Drug Release Medium: 500 mL Water
32 °C ± 0.5 °C

Quantity Of Drug Released, % of claim							
Sample #	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	19	29	43	53	61	68	73
RSD, %	2.7	2.1	1.9	2.0	1.7	1.6	1.2
Range	(b) (4)						

Drug Release Conditions	**Apparatus:**	VI (Cylinder)
	Speed of Rotation:	50 rpm
	Medium:	Water
	Volume:	500 mL
	Temperature:	32 °C ± 0.5 °C
Firm's Proposed Specifications	2 hours: (b) (4)	8 hours: (b) (4) (b) (4)
Dissolution Testing Site (Name, Address)	Mylan Technologies, 110 Lake Street, Saint Albans, Vermont 05478	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength	No. of Dosage Units		Collection Times (minutes or hours)							Study Report Location
						1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr	
N/A	June. 2011	**Estradiol Transdermal System, USP 0.025 mg/day (Twice-Weekly) Lot R6A0028 Mfg. Date – Aug. 2009**	0.025 mg/day	12	Mean (%)	20	31	47	59	68	75	81	Section 3.2.P.5.4
					Range (%)	(b) (4)							
					% CV	2.9	3.2	2.6	2.6	2.1	2.0	1.5	
N/A	June. 2011	**Vivelle Dot® 0.025 mg/day Lot 49382 Exp. Date – Jul. 2012**	0.025 mg/day	12	Mean (%)	19	29	43	53	61	64	70	
					Range (%)	(b) (4)							
					% CV	2.7	3.1	2.5	1.9	2.0	2.5	2.6	

Table 1. Mylan ETS, 0.025 mg/day

Dosage: Estradiol Transdermal System, 0.025 mg/day (0.41mg / 2.5cm²)
Lot: R6A0028
Test Method: FDA Dissolution Method for Estradiol TS (Test 1)
Apparatus: VI - Cylinder
Drug Release Medium: 500 mL Water
32 °C ± 0.5 °C

Quantity Of Drug Released, % of claim							
Sample #	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	20	31	47	59	68	75	81
RSD, %	2.9	3.2	2.6	2.6	2.1	2.0	1.5
Range	(b) (4)						

Table 2. Vivelle Dot ETS, 0.025 mg/day

Dosage: Estradiol Transdermal System, 0.025 mg/day (0.39mg / 2.5cm^2)

Lot: 49382

Test Method: FDA Dissolution Method for Estradiol TS (Test 1)

Apparatus: VI - Cylinder

Drug Release Medium: 500 mL Water

32 °C ± 0.5 °C

Quantity Of Drug Released, % of claim							
Sample #	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	19	29	43	53	61	64	70
RSD, %	2.7	3.1	2.5	1.9	2.0	2.5	2.6
Range	(b) (4)						

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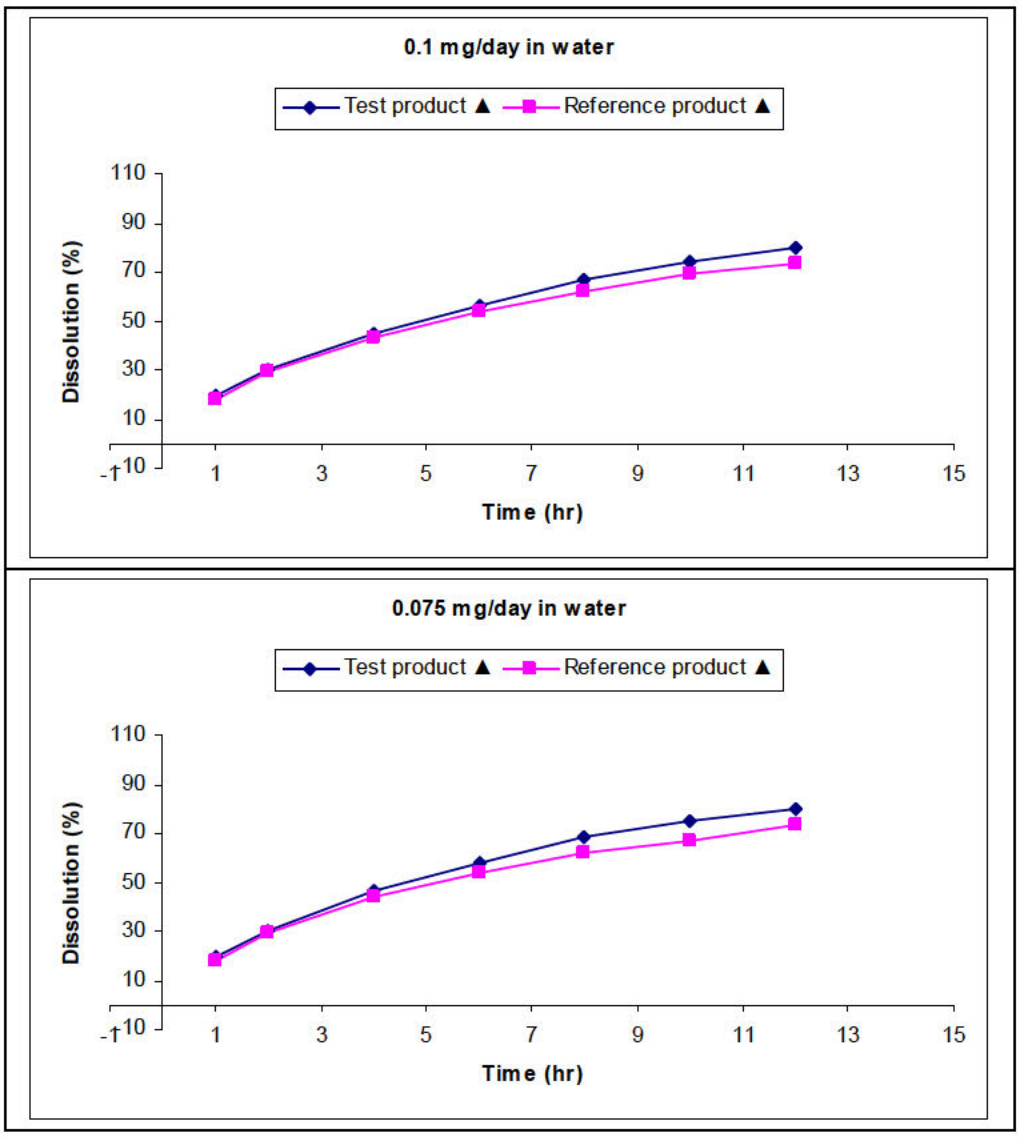
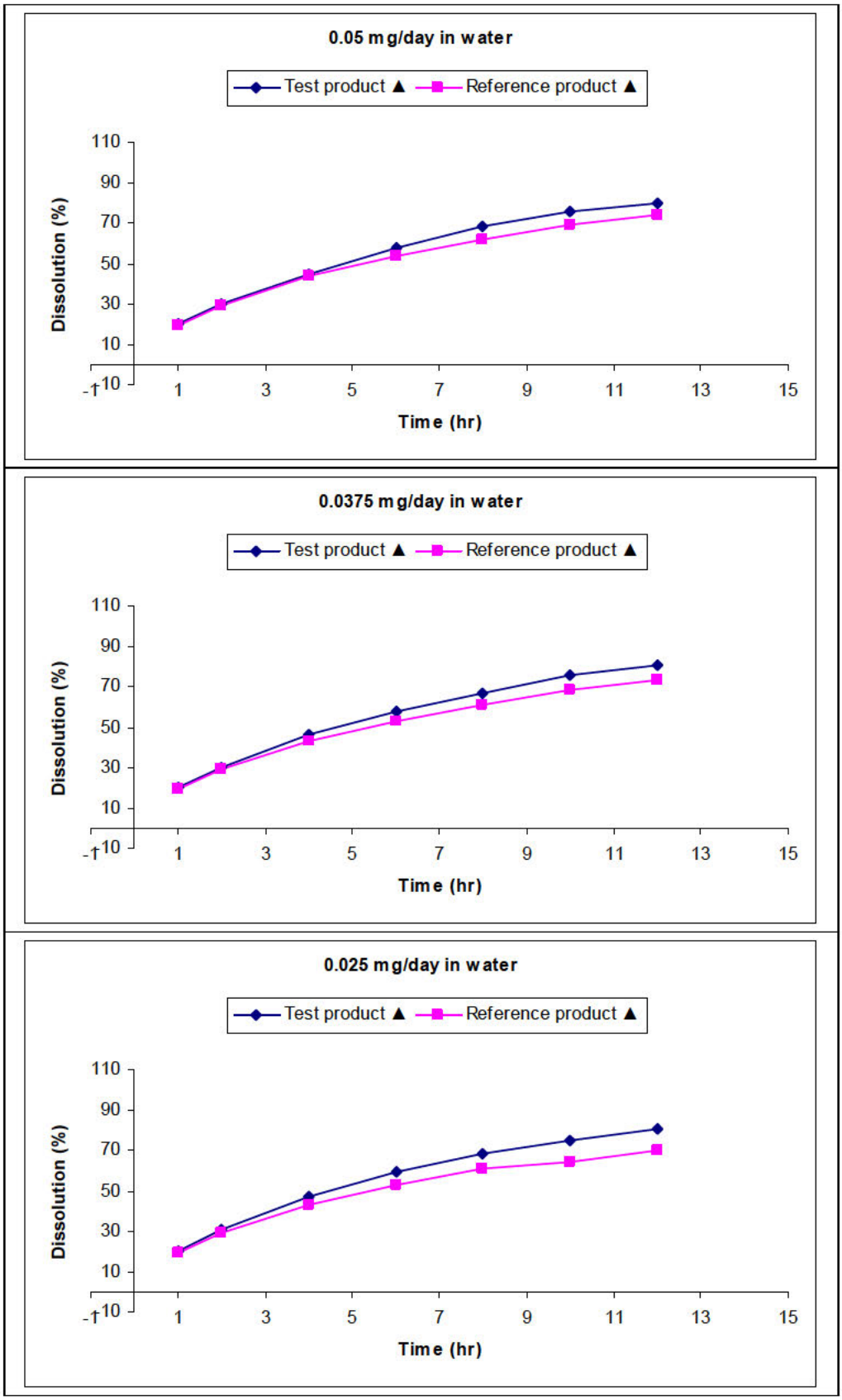
Figure 2. Dissolution Profiles




0.05 mg/day in water
Test product ▲
Reference product ▲
Dissolution (%)
110
90
70
50
30
10
-10
1
3
5
7
9
11
13
15
Time (hr)
0.0375 mg/day in water
Test product ▲
Reference product ▲
Dissolution (%)
110
90
70
50
30
10
-10
1
3
5
7
9
11
13
15
Time (hr)
0.025 mg/day in water
Test product ▲
Reference product ▲
Dissolution (%)
110
90
70
50
30
10
-10
1
3
5
7
9
11
13
15
Time (hr)

The f2 factor calculation (comparing with the corresponding strength of RLD)

Strength (mg/day)	Media condition	F2
0.1	Water	69.5
0.075	Water	64.9
0.05	Water	66.9
0.0375	Water	63.2
0.025	Water	57.4

Reviewer's Comments:

1. The FDA-recommended dissolution method uses the same dissolution medium, rotation speed and temperature as that of the RLD product except for the dissolution apparatus and sampling times (Clinical Pharmacology & Biopharmaceutics (OCPB) review of NDA 020538 dated 8/18/1997 (suppl. 006)). According the OCPB review of supplement 006, the dissolution apparatus was USP Apparatus 5 and the sampling times were 2, 4 an 6 hours. The dissolution specifications of the RLD products were: 2hr: (b) (4) 4 hr: (b) (4) and 6hr (b) (4) (b) (4). In the innovator's supplement SCS-023 with the letter date of 2/13/2004 and 2/17/2004, the innovator proposed to change the dissolution apparatus to a modified Apparatus 6 (involving use of a double sided tape to attach the patch to a disk at the bottom of the cylinder, thereby removing all barriers between the surface of the patch and the release medium and paddle). The OCPB accepted the change in the dissolution method and indicated that this is a more suitable release method and currently the method of choice for most transdermal patch release testing.[20] The new innovator's drug release specifications are 2 hr: (b) (4); 4 hr: (b) (4); 6 hr: (b) (4)[21]

2. The firm conducted the dissolution using the FDA-recommended method and also conducted additional dissolution in various pH media (pH 1, 4.5 and 6.8) using Apparatus 5. The test and reference products have the similar drug release in these media. However, these media with different pH do not have relevance to the biological environment in the skin.

3. The reviewer calculated the f2 factors for all the strengths of drug products tested under the FDA recommended method and found that all these strengths have f2 factors more than 50.

4. The firm proposed the specifications- 2 hr: (b) (4) 8 hr: (b) (4); 24 hr: NLT (b) (4). After consulting the dissolution focal contact (see details in Section 4.5 Consult Reviews), the DB will recommend the following specifications to the firm: 2 hr: (b) (4); 6 hr: (b) (4); 12 hr: 70-90%. The dissolution testing is pending on the firm's acceptance and acknowledgement of the FDA-recommended specifications.

The dissolution testing is incomplete upon the firm's acknowledgement of the FDA recommended specifications.

[20] DARRTS, NDA 020538, REV-CLINPHARM-01 (General Review), finalized date: 7/9/2004. last accessed 7-30-2011

[21] EDR, NDA020538, Module 3.2.P.8.1 Stability-summary. Submitted 9/27/2008. Last accessed 7-30-2011.

4.4 Division of Scientific Investigation (OSI) Inspection Report Review

4.4.1 Review on OSI Inspection of Clinical Site

Clinical site:

Cetero Research
1405 NW 167 Street
Miami Gardens, FL33169

The clinical site was recently inspected on (b) (4) (b) (4). It resulted as Voluntary Action Indicated (VAI) (DARRTS, (b) (4) (b) (4). The clinical study dates for (b) (4) which is prior to the study dates of current application 11/4/2009 to 11/21/2009.

The findings during the inspection and the relevance to the current application are reviewed as follows:

1. Failure to follow the protocol.
The protocol's inclusion/exclusion criteria required that subjects with a serum estradiol concentration ≥ 20 pg/mL be excluded from the study. At the time of screening, Subject 10066 had a serum estradiol concentration of 48pg/mL. However, this test was invalidated and the subject was retested one week later which yielded a serum Estradiol concentration of 13 pg/mL. The subject was later enrolled. The firm did not provide documented justification for the retest of Subject 10066 and the reasons for invalidating the initial test. Although the firm should have provided documented justification for invalidating the initial serum Estradiol concentration test, the subject appears to have met the inclusion criteria with the subsequent test. Therefore, this finding should not significantly affect study outcome.

Firm's response: During the inspection, the firm acknowledged the finding and promised corrective actions for future studies.

OSI: Based on OSI's assessment of the clinical inspection for (b) (4), the clinical portion of this study is acceptable for review.

Relevance to current application: (b) (4) (b) (4) The inclusion/exclusion criteria included a restriction on the baseline Estradiol concentration. The current application does not have a restriction for Estradiol concentration in the inclusion/exclusion criteria. The reviewer checked the concentration, C1 (concentration at Time zero) for all subjects in the current study and found out that subject 25 in test treatment has concentration C1 of 88.97ng/mL. All the rest of the subjects have no more than 13 ng/mL of C1. The endogenous Estradiol concentration is 0-36 pg/mL in post-menopausal females.[22] Subject 25

[22] Internet, http://webcache.googleusercontent.com/search?hl=en&safe=active&q=cache:v9sW5-DbjU4J:http://www.earlymenopause.com/tests.htm+estradiol+levels+in+women&ct=clnk. Last accessed 8-29-2011

in test treatment had abnormally high pre-dose estradiol value. This subject was included in the statistical analysis for Cmax and AUCt but not AUCi due to the undeterminable elimination phase. The study met the acceptance criteria with inclusion of this subject. The reviewer also reanalyzed the study data excluding Cmax and AUCt data of Subject 25 (but with Subject 14 Cmax and AUCt included). It was found that the 90% CIs of three PK parameters are still within the acceptable range of 80-125%. However, the 90%CI of AUCt shift from 104-116% to 90-108%, AUCi from 103-115% to 90-109% and Cmax from 108-124% to 85-110%. The abnormal high pre-dose value of subject 25 does have significant impact on the 90% CIs, but not significantly impact the bioequivalence outcome. The calculation results are as follows:

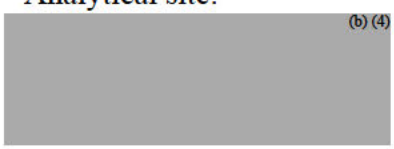
Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 (female 47, male 0)-exclude subject 14 and subject 25 for analysis of AUCi Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Uncorrected Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	8364.33	7616.83	1.10	104.04	115.91
AUC∞ (hr *pg/ml)	8468.48	7746.11	1.09	103.53	115.44
Cmax (pg/ml)	137.77	119.10	1.16	108.31	123.55

Drug: Estradiol Extended Release Film Dose: 1 x 0.1 mg/day N =47 (female 47, male 0)-exclude subject 14 AUCi and subject 25 AUCi, AUCt and Cmax * Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. EDOT-0922 Baseline-Unadjusted Analysis					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	7952.04	8061.48	0.99	89.85	108.30
AUC∞ (hr *pg/ml)	8107.01	8205.71	0.99	89.88	108.60
Cmax (pg/ml)	126.25	130.57	0.97	85.06	109.91

Therefore, this finding does not have relevance to the current application.

4.4.2 Review on OSI Inspection of Analytical Site

Analytical site:



The analytical site recently inspected on [redacted] and resulted as Voluntary Action Indicated (VAI) for [redacted]. The inspection result is recorded in DARRTS (DARRTS, [redacted]). The inspection findings and the relevance to the current application are reviewed as follows:

[redacted]

Firm's response: In response to this observation, [redacted] initiated evaluation of long term stability at -80°C. OSI awaits the results and an evaluation will be submitted separately. The firm also updated the SOP to require that freshly prepared calibration standards and quality controls must be used for the evaluation of stability.

OSI: OSI is waiting for the firm's results on the long term stability study.

Relevance to the current application: This is a systemic finding. The OSI inspected analytical study was performed on [redacted] which is prior to the current analytical study duration of [redacted] Since the OSI inspection was on [redacted], by that time the firm still had not updated the related SOP yet. The reviewer checked the LTSS data the firm submitted as an amendment and found that "Some aliquots of quality control samples (comparison samples) and a freshly prepared calibration curve were processed and analyzed in a single run. Remaining aliquots were stored at -80°C (stability samples). Stability samples were processed with a freshly prepared calibration curve and analyzed in a single run. Mean concentrations of the stability samples were compared to the mean concentrations of the comparison samples". Therefore, this finding does not have impact on the current application.

[redacted]

Firm's response: In response to the observation, [redacted] has revised the validation report to include the results from run 8NYO. As a corrective action, [redacted] revised their SOP to record the hemolyzed samples in future studies.

Relevance to the current application: This finding is specific to the OSI inspected drug product. It should not have any impact on the current application.

[redacted]

Firm's response: [redacted] acknowledged the observation and repeated the assay with whole blood without added anticoagulant to assess impact of adsorption on collection device. The

results presented in their written response show no significant loss of analyte due to adsorption on collection device. However, (b) (4) no longer performs this assay as part of their validation studies.

Relevance to the current application: This would have no impact on the current application since the firm indicated that during each study period, blood samples were collected (10 mL each) from each subject by direct venipuncture using tubes containing K2 EDTA.

(b) (4)

Firm's response: In response to this observation, (b) (4) has implemented additional login requirement for accessing Analyst software.

Relevance to the current application: This should not have significant impact on the bioequivalence outcome.

(b) (4)

OSI: The analytical data for (b) (4) can be accepted for agency review subject to adequate long term fluoxetine stability data to be submitted by (b) (4) to cover the duration of sample storage.

Currently there is no necessary or pending OSI inspection for the clinical and analytical sites. The DBE will determine whether there is necessity for OSI inspection upon the firm's response to the deficiencies issues to the firm.

4.5 Consult Reviews

Dissolution Consult:

From: Munshi, Utpal
Sent: Monday, August 08, 2011 12:39 PM
To: Lu, Dongmei
Subject: FW: Dissolution consult on ANDA201675

Dongmei:

One additional point: As I stated below, drug release methods for transdermals are generally not reflective of in vivo performance. Nonetheless, I would always encourage reviewers to look at all relevant databases and reviews for this and similar products to see if there are better methods out there that the firm can try.

From: Munshi, Utpal
Sent: Monday, August 08, 2011 12:15 PM
To: Lu, Dongmei

Subject: RE: Dissolution consult on ANDA201675

Hi Dongmei:

Per our conversation this morning, here are my thoughts on your consult request:

1) The firm's proposed method uses USP apparatus V, while that proposed by the firm uses USP VI. Based on what I see, there is little difference in terms of the data, both in terms of absolute levels of release, as well as in terms of acceptable method variation.

2) Based on point 1 alone, I see little reason to ask the firm to use USP VI instead of V. However, you might want to ask them to submit data at additional time points before you provide a specification. The other thing to consider is the use of surfactant by the firm (b) (4). You might want to ask them to justify the use of surfactant in their dissolution medium (the use of surfactant seems unjustified if we look at the multimedia release profiles). As we discussed, neither the firm's method nor the FDA method are particularly physiological (nor, for that matter, are transdermal release methods in general thought to be really meaningful in terms of predicting in vivo performance), and therefore I think we can be a little more lenient in terms of the method that we ultimately accept. That being said, the firm could be asked to justify specifications (with data at addnl. time points), use of surfactant, speed, etc. as appropriate. As to how "tough" you want to be with the firm on these conditions is up to you, April, and Hoai.

3) Regarding the specification, the firm proposed "NLT (b) (4) at the final time point, while you propose a range of (b) (4). Irrespective of what method you ultimately recommend, the format of the neither specification is satisfactory. The former is not satisfactory as it does not conform with USP <724>. The latter is not satisfactory per the reasons described in the DBE review of ANDA 075182 (final date: 3/29/2011). As we discussed, you could use the approach from the 3/2011 review of ANDA 075182 (release rate), or you could avoid the issue altogether by adding a time point or two to the specification before 24 h and removing the 24 h time point . The latter approach is probably less cumbersome than the release rate approach in that no additional calculations are involved. Moreover, given the incomplete release of API from the dosage form in vivo, there really is no requirement to have a specification that ensures "complete" release.

4) Please consider the in vivo BE data for Test vs. Reference when you determine the range of the specifications that you provide at each time point.

Please let me know if there are additional questions.

Please note that the above is just my opinion, please consult April for additional input.

Thanks,
Utpal

From: Lu, Dongmei
Sent: Monday, August 01, 2011 9:13 AM
To: Munshi, Utpal
Cc: Braddy, April
Subject: Dissolution consult on ANDA201675

Hello, Utpal:

Currently I am reviewing ANDA201675, including the dissolution new data. In the original submission, the firm did not use the FDA recommended method and only had data using its own method. In the amendment, the firm generated dissolution data using the FDA recommended method. Please find the dissolution data enclosed in this email.

<< File: New Dissolution Data.doc >>
My findings are as follows:

1. The firm proposed the specifications: 2hr (b) (4); 8 hr (b) (4); 24 hr NLT (b) (4)
The RLD specifications: 2 hr (b) (4); 4hr: (b) (4); 6hr: (b) (4)

2. The f2 factors are all more than 50 using FDA recommended method.

3. According to the firm's data, it could not meet the RLD's specifications at 4 and 6 hour (firm has higher values than the high end specification at these two time points).

Based on the submitted data, I propose the following specifications:

2hr: (b) (4); 6 hr: (b) (4); 24 hr: (b) (4)

Would you mind to take a look whether this proposal is reasonable or not? Any suggestion is highly appreciated.

Thanks.

Dongmei

4.6 SAS Output

4.6.1 Baseline-Corrected Fasting Study Data

FASTING CONCENTRATION DATASET

Obs	SUB	SEQ	PER	TREAT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17
1	1	1	1	A	.	.	0	0.0000	0.000	16.410	32.670	50.230	55.250	56.680	52.260	54.870	43.800	42.920	32.770	52.4400	22.7800
2	1	1	2	B	.	.	0	5.5400	0.000	18.260	33.650	47.000	60.290	49.140	50.560	52.360	56.880	48.030	51.250	40.3800	23.9400
3	2	1	1	A	.	.	0	0.3233	2.743	24.243	28.443	57.453	64.043	48.923	54.353	56.833	44.473	43.033	28.083	24.2733	21.8533
4	2	1	2	B	.	.	0	0.9433	1.163	25.303	44.293	65.183	80.903	56.853	60.893	67.623	58.003	49.623	42.883	34.9833	27.5733
5	3	2	1	B	.	.	0	0.9033	7.363	46.523	62.483	81.823	136.013	116.643	116.053	141.723	90.763	83.503	57.533	49.7333	35.5033
6	3	2	2	A	.	.	0	0.1000	19.750	56.540	70.460	109.830	131.330	116.580	122.270	115.250	86.090	91.560	99.340	65.9600	52.3100
7	4	2	1	B	.	.	0	6.2600	46.540	81.340	132.590	143.080	126.220	89.850	111.620	60.360	46.620	34.180	23.140	19.0800	15.3000
8	4	2	2	A	.	.	0	9.5233	83.073	156.773	172.633	196.063	185.173	153.823	160.743	91.473	60.543	38.223	31.323	26.9533	13.7933
9	5	2	1	B	.	.	0	5.6700	59.370	140.210	133.490	211.450	189.450	126.680	146.770	147.250	118.420	128.090	104.790	68.6300	45.9000
10	5	2	2	A	.	.	0	0.0000	54.670	119.120	172.780	190.410	198.010	142.910	203.010	152.980	146.000	136.040	119.940	98.9900	60.0000
11	6	1	1	A	.	.	0	3.8500	55.590	132.340	182.060	201.220	206.160	182.990	192.170	156.220	129.800	109.900	83.090	57.1600	42.6000
12	6	1	2	B	.	.	0	7.1533	81.673	185.933	151.923	200.053	204.243	202.003	177.563	180.503	139.283	130.203	113.803	72.6033	48.6333

13	7	1	1	A	.	.	0	5.0700	7.820	38.660	48.500	93.580	99.660	67.790	79.740	82.130	67.690	74.870	48.660	42.9900	30.3900
14	7	1	2	B	.	.	0	0.0000	8.430	34.150	59.700	77.300	102.140	83.140	73.360	97.210	78.480	75.520	68.050	45.1400	33.9300
15	8	1	1	A	.	.	0	11.9900	79.200	173.960	138.290	228.530	179.340	147.790	155.620	138.090	113.450	89.220	83.140	74.2500	50.2700
16	8	1	2	B	.	.	0	5.4800	39.880	92.600	99.420	133.240	104.370	96.090	97.410	136.970	99.500	101.840	83.690	50.6300	38.3700
17	9	2	1	B	.	.	0	5.4300	20.600	82.060	94.730	102.930	106.190	61.780	83.200	66.370	61.680	39.300	31.540	18.9100	13.5300
18	9	2	2	A	.	.	0	0.0000	7.790	41.790	74.020	108.190	105.280	110.730	88.770	94.140	83.950	70.990	59.220	51.1700	32.5300
19	10	2	1	B	.	.	0	3.8400	17.860	50.940	58.490	114.040	93.060	49.570	55.800	30.820	19.490	17.810	15.560	13.4000	9.1700
20	10	2	2	A	.	.	0	0.2733	9.023	50.773	66.493	100.883	82.663	63.253	43.463	31.693	16.693	15.123	9.663	7.0133	6.5233
21	11	1	1	A	.	.	0	11.590	77.650	136.190	141.180	169.920	144.080	125.860	120.740	102.830	98.930	77.340	67.510	46.7600	28.5800
22	11	1	2	B	.	.	0	0.0000	27.650	67.710	83.570	130.620	103.730	89.060	89.410	91.960	79.250	74.340	67.650	49.3800	32.0700
23	12	2	1	B	.	.	0	0.0000	7.560	53.170	52.630	99.510	117.970	90.690	100.510	102.200	103.110	93.830	78.730	60.8600	43.6000
24	12	2	2	A	.	.	0	5.1500	40.940	144.000	153.160	179.570	176.780	144.440	139.650	153.180	137.960	124.170	94.120	81.6700	46.9700
25	13	2	1	B	.	.	0	0.0000	21.150	116.650	170.030	185.930	164.490	145.360	170.780	141.860	129.780	108.040	98.960	58.4400	36.6300
26	13	2	2	A	.	.	0	0.0000	19.540	103.010	194.250	214.070	172.660	163.450	178.620	130.890	135.440	100.290	95.130	74.5800	43.1500
27	14	1	1	A	.	.	0	0.1700	2.410	23.990	37.890	56.490	66.860	58.380	62.670	58.090	58.900	52.040	51.420	41.8300	33.9000

28	14	1	2	B	.	.	0	1.6900	3.160	14.280	32.400	49.320	52.920	55.790	61.840	58.020	67.600	62.660	63.290	50.8100	41.3500
29	15	1	1	A	.	.	0	0.0000	11.830	37.650	60.120	78.000	74.860	78.460	75.060	76.180	59.350	55.630	47.520	39.5600	27.4700
30	15	1	2	B	.	.	0	0.0000	26.560	51.740	79.890	80.210	87.410	77.500	79.880	76.350	71.190	56.740	60.050	41.5900	32.4600
31	16	2	1	B	.	.	0	0.0000	9.140	41.860	67.460	93.450	93.740	73.850	94.820	79.760	76.420	63.760	39.550	31.7600	21.7600
32	16	2	2	A	.	.	0	0.0000	11.090	52.450	98.040	131.450	138.780	101.460	123.260	119.750	104.880	95.060	70.120	58.2300	36.3800
33	17	1	1	A	.	.	0	0.0000	18.880	70.670	121.680	201.510	172.680	115.300	181.450	142.220	119.920	91.450	70.470	52.7100	34.4100
34	17	1	2	B	.	.	0	0.0000	8.920	57.890	72.990	113.660	112.480	98.440	128.700	113.550	101.160	96.040	91.260	60.4000	38.2600
35	18	2	1	B	.	.	0	0.0000	9.170	45.360	55.900	90.760	91.650	73.890	77.720	94.180	71.820	74.600	61.900	49.8600	40.6800
36	18	2	2	A	.	.	0	0.0000	18.260	65.610	96.940	146.480	119.850	113.730	123.460	90.330	71.080	65.910	49.430	39.8700	32.9400
37	19	1	1	A	.	.	0	1.7133	13.743	39.923	59.573	85.913	102.663	62.533	61.043	60.463	37.113	28.743	22.753	16.5133	14.8533
38	19	1	2	B	.	.	0	9.6933	86.843	145.063	119.863	148.333	178.533	121.673	105.033	128.673	99.653	99.703	75.433	40.2733	32.4133
39	20	1	1	A	.	.	0	0.0000	29.410	96.340	110.610	131.230	126.310	99.810	127.930	105.010	104.390	82.610	87.940	86.4700	52.7700
40	20	1	2	B	.	.	0	8.4500	54.950	155.420	144.430	173.320	180.160	174.560	160.500	242.810	148.470	102.490	97.670	76.7100	43.6300
41	21	1	1	A	.	.	0	0.0000	20.660	81.860	98.110	188.590	116.910	128.120	141.130	80.420	73.100	51.670	49.440	46.9000	30.1400
42	21	1	2	B	.	.	0	0.0000	8.630	45.800	70.210	107.110	72.430	91.330	105.200	65.070	82.390	64.730	81.360	47.7600	30.9200
43	22	2	1	B	.	.	0	0.0000	39.720	88.330	99.940	143.320	119.100	109.120	124.070	102.040	105.130	79.230	81.960	47.0800	31.4900

44	22	2	2	A	.	.	0	11.630	76.830	144.030	148.480	155.470	173.260	158.890	146.940	134.870	100.960	97.670	85.020	60.6800	35.1900
45	23	2	1	B	.	.	0	0.0000	0.000	14.450	23.610	39.990	39.360	52.140	56.090	46.410	49.080	44.610	49.850	37.4700	23.1500
46	23	2	2	A	.	.	0	0.0000	4.427	17.437	44.767	62.527	75.797	78.637	96.857	74.907	64.677	59.837	56.727	48.9967	28.0967
47	24	2	1	B	.	.	0	0.0000	0.000	35.680	49.640	79.120	95.150	75.880	81.970	76.390	63.300	71.210	57.880	39.1500	27.6500
48	24	2	2	A	.	.	0	0.0000	24.520	99.880	97.250	135.200	114.730	103.680	112.050	109.700	89.340	93.310	56.230	43.7700	22.8200
49	25	2	1	B	.	.	0	1.0100	8.760	56.860	75.170	89.640	126.390	120.320	117.690	115.960	119.310	114.630	86.680	72.2100	52.5400
50	25	2	2	A	.	.	0	9.4633	19.253	37.073	51.973	95.673	129.823	111.813	131.193	103.753	49.933	46.563	18.103	15.7933	26.1533
51	26	2	1	B	.	.	0	0.0000	19.320	94.530	97.930	164.890	169.410	122.700	129.200	150.930	148.760	128.230	104.690	75.2400	44.3500
52	26	2	2	A	.	.	0	0.0000	14.840	86.340	108.330	136.300	159.170	122.960	140.060	141.700	102.110	99.210	76.620	54.8800	40.2000
53	27	2	1	B	.	.	0	1.8900	16.710	47.300	51.010	71.880	70.250	57.690	63.620	66.840	58.410	52.750	47.470	41.1400	31.8500
54	27	2	2	A	.	.	0	2.9900	7.860	37.990	46.630	85.170	93.390	68.770	84.820	79.300	62.590	62.030	56.680	49.0000	35.3200
55	28	1	1	A	.	.	0	0.0000	28.650	74.870	79.900	115.690	107.310	96.330	89.600	103.580	95.170	66.410	62.290	46.0000	26.8200
56	28	1	2	B	.	.	0	0.0000	26.150	83.590	82.820	105.130	119.330	120.020	130.680	100.000	100.170	85.820	64.080	48.3200	26.3000
57	30	1	1	A	.	.	0	0.0000	11.400	56.040	61.430	94.900	95.660	79.630	87.660	80.190	57.060	50.710	42.180	32.6300	22.7800
58	30	1	2	B	.	.	0	0.0000	14.690	51.340	69.240	134.950	106.300	95.660	88.800	106.230	98.860	112.940	73.910	50.3200	36.3500
59	31	1	1	A	.	.	0	0.0000	13.600	49.970	101.910	110.930	91.660	101.480	80.050	67.450	54.000	41.440	36.170	35.1400	23.9400

60	31	1	2	B	.	.	0	0.00000	5.940	32.990	39.820	66.500	57.400	70.260	69.320	63.370	70.950	61.900	67.950	56.8600	33.9900
61	32	1	1	A	.	.	0	32.3400	174.020	286.460	171.360	270.960	192.950	145.790	173.320	123.680	117.870	95.640	85.730	55.5100	23.1500
62	32	1	2	B	.	.	0	0.00000	90.210	174.100	179.280	230.390	153.150	176.240	136.160	115.030	123.490	110.770	90.300	38.6000	22.2800
63	33	1	1	A	.	.	0	0.00000	9.417	47.157	76.537	101.097	102.157	68.327	85.787	93.977	93.907	72.777	69.907	47.8467	36.6567
64	33	1	2	B	.	.	0	0.00000	7.513	60.063	64.263	86.333	78.963	80.063	91.053	84.983	80.533	71.683	66.983	59.4633	36.8933
65	34	2	1	B	.	.	0	0.00000	41.360	112.160	123.410	130.280	105.580	109.960	106.940	96.220	91.470	70.870	69.520	44.5000	24.6100
66	34	2	2	A	.	.	0	3.9367	43.017	118.607	158.417	141.277	128.747	151.627	155.057	94.937	80.007	51.647	58.187	37.0667	21.0867
67	35	2	1	B	.	.	0	2.3533	3.793	43.953	46.103	79.293	74.973	56.953	59.773	74.263	70.873	66.253	59.483	44.4833	31.5433
68	35	2	2	A	.	.	0	5.8000	7.110	28.380	49.150	83.520	72.810	69.260	58.440	75.680	58.900	62.440	44.350	44.6900	36.5300
69	36	2	1	B	.	.	0	0.00000	5.890	25.980	43.240	52.220	59.680	56.520	60.970	54.390	53.410	46.400	46.750	31.4000	21.0200
70	36	2	2	A	.	.	0	0.00000	12.420	60.070	79.820	89.240	101.490	99.880	98.870	83.980	80.830	66.580	55.270	46.1300	31.1800
71	37	1	1	A	.	.	0	5.4700	29.400	107.810	137.100	173.510	166.880	149.640	165.410	131.300	101.480	84.150	59.480	51.4200	35.7400
72	37	1	2	B	.	.	0	0.00000	14.710	72.090	103.630	117.200	131.310	111.660	114.130	104.500	101.150	82.100	59.150	43.1900	28.5700
73	38	1	1	A	.	.	0	0.00000	10.850	93.970	76.850	138.390	102.000	104.680	133.380	106.890	92.940	76.510	80.690	56.9800	32.2600
74	38	1	2	B	.	.	0	0.00000	0.000	61.680	93.200	102.440	114.980	82.770	121.610	93.530	91.700	64.670	77.580	63.0000	31.8600
75	39	1	1	A	.	.	0	0.00000	6.640	39.590	51.990	100.820	104.360	79.880	89.920	93.340	82.300	78.720	66.930	55.9900	43.0000

76	39	1	2	B	.	.	0	5.6400	6.980	32.770	44.840	78.760	87.170	101.000	70.160	91.910	63.870	72.850	67.180	52.2200	31.6600
77	40	2	1	B	.	.	0	2.1167	31.247	120.237	117.157	136.817	132.027	116.797	116.117	129.827	83.537	94.917	69.337	52.8567	44.5067
78	40	2	2	A	.	.	0	2.8133	44.673	137.603	140.173	162.713	180.763	144.413	145.603	136.913	92.633	58.733	44.403	36.6033	24.6133
79	41	2	1	B	.	.	0	0.0000	32.260	135.380	184.870	189.790	183.300	167.450	162.870	160.580	129.050	113.620	111.130	66.7500	38.1100
80	41	2	2	A	.	.	0	0.0000	31.170	158.230	153.830	201.380	174.830	135.660	130.640	129.590	104.660	85.600	53.690	54.8300	39.1600
81	42	2	1	B	.	.	0	0.0000	0.000	36.320	73.520	101.360	102.620	100.170	96.090	84.750	134.140	83.540	84.710	61.5900	30.5200
82	42	2	2	A	.	.	0	0.0000	30.080	82.200	147.720	137.670	137.080	172.830	143.530	110.660	111.860	84.940	96.670	60.6200	38.1100
83	43	2	1	B	.	.	0	0.0000	25.310	91.130	105.830	151.450	139.890	84.950	103.700	99.800	57.080	42.070	24.070	21.3200	14.4600
84	43	2	2	A	.	.	0	7.0000	36.540	104.620	112.430	166.710	142.460	119.900	94.480	99.850	63.950	57.560	32.090	20.4200	16.5800
85	44	2	1	B	.	.	0	0.0000	0.000	0.000	16.160	29.650	41.960	34.790	39.960	45.240	42.420	48.730	45.830	38.2300	32.4500
86	44	2	2	A	.	.	0	0.0000	0.000	10.940	32.260	50.450	62.510	62.430	77.910	94.980	65.550	75.640	60.950	52.3100	45.6000
87	45	2	1	B	.	.	0	0.0000	0.000	26.870	44.540	64.600	61.780	71.140	78.370	58.610	82.470	64.440	65.290	43.4400	21.3500
88	45	2	2	A	.	.	0	0.0000	0.000	24.710	47.960	82.740	75.000	71.380	61.960	82.530	68.250	58.440	60.760	41.3300	25.5000
89	46	1	1	A	.	.	0	0.0000	8.380	55.460	110.540	111.430	114.580	133.010	91.980	85.970	96.750	76.610	68.050	68.6900	40.1000
90	46	1	2	B	.	.	0	0.0000	0.000	31.500	65.710	74.850	81.810	78.190	92.970	80.700	69.150	64.660	68.570	52.8300	34.9300
91	47	1	1	A	.	.	0	12.370	122.140	212.710	287.880	374.690	248.870	157.150	159.930	174.060	172.250	126.350	118.010	69.0700	43.4000

92	47	1	2	B	.	.	0	12.4800	172.920	241.320	269.470	284.460	243.120	174.640	168.080	159.270	172.750	111.630	128.760	66.9900	36.6400
93	48	1	1	A	.	.	0	0.00000	10.057	56.887	61.997	126.317	105.627	84.407	108.597	119.507	102.917	94.097	67.227	34.8467	25.5567
94	48	1	2	B	.	.	0	2.1367	26.777	83.467	74.827	130.937	125.287	104.167	86.827	91.467	89.427	75.457	57.507	43.9167	25.9767

Obs	c18	c19	c20	c21	c22	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	t20	t21	t22
1	18.7100	11.8500	9.3500	8.6300	5.8700	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
2	17.0600	13.1000	10.3900	7.4600	5.5100	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
3	16.8833	7.2133	2.1533	3.2533	2.3933	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
4	16.1133	8.2133	4.1233	3.0033	1.1733	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
5	23.4933	15.6533	12.0833	6.2833	5.3833	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
6	33.2200	21.8100	17.3900	7.8800	5.1100	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
7	12.5700	7.9500	7.3900	7.2000	5.0400	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
8	12.2333	6.5133	6.0933	5.2133	2.4433	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
9	26.9500	15.7200	10.1300	6.7400	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
10	41.0100	25.3500	15.3400	9.5600	5.7700	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
11	18.8300	10.4900	9.0800	6.5100	.	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
12	21.8433	12.5833	11.5033	3.4033	2.5833	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
13	22.9200	16.7100	13.3100	9.0900	8.8500	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
14	29.5400	19.7600	13.0200	9.0700	9.1900	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
15	29.3300	17.7100	18.5900	11.9900	8.1800	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
16	24.0500	13.8200	12.3500	7.9200	6.2100	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
17	10.3700	7.6300	6.7600	5.1000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
18	19.5200	14.4300	8.9900	7.4600	6.2400	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
19	7.0800	5.3400	3.9500	3.4000	3.7300	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
20	4.9933	2.3233	0.2833	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
21	16.7400	8.6300	5.9000	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
22	13.9300	7.0200	5.3500	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120

Obs	c18	c19	c20	c21	c22	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	t20	t21	t22
23	26.3100	15.9000	13.9500	11.3900	6.4300	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
24	38.8600	21.1700	15.5200	12.7800	8.6500	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
25	17.3800	8.6600	6.1900	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
26	23.3300	13.2300	9.4300	5.8000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
27	20.8700	12.2900	9.0100	5.6600	2.4800	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
28	28.7700	22.5400	21.0000	14.8200	23.1400	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
29	17.6000	12.3500	11.4200	7.4600	5.8300	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
30	18.1800	10.8300	8.7300	6.0700	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
31	15.4900	11.0900	9.6700	7.2300	5.2500	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
32	24.4300	16.1900	14.7700	9.4300	6.0300	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
33	22.7700	13.8300	8.6100	7.0000	5.4800	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
34	23.0900	15.2200	9.3900	8.5300	5.3700	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
35	28.9600	20.2100	15.1300	10.2000	8.8900	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
36	22.1900	15.5500	14.7800	8.5100	8.0100	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
37	6.7833	6.3433	3.8333	1.5533	1.6433	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
38	21.4933	19.3733	15.2033	6.9733	1.5733	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
39	23.8500	14.9300	9.8500	7.4200	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
40	24.6400	14.0400	9.1800	6.9100	7.2800	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
41	16.8400	10.2900	7.9700	7.3700	6.2200	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
42	20.5300	12.2100	8.7000	6.2400	5.9600	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
43	23.1200	11.0800	10.3500	7.7400	5.8800	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
44	24.2000	16.2900	10.6400	10.5700	6.5100	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
45	16.5900	10.1100	10.5800	7.9300	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
46	16.9067	12.4967	8.7067	6.2467	3.6267	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
47	13.7200	8.6700	6.7100	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
48	18.2700	10.1000	7.5700	5.1200	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
49	39.0000	38.0000	33.5200	18.0700	23.6400	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
50	0.0000	22.9133	16.9833	0.6333	19.0933	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
51	27.5800	16.8900	10.5500	9.9300	5.8200	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120

Obs	c18	c19	c20	c21	c22	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	t20	t21	t22
52	96.6600	14.0600	8.9300	8.5600	4.4700	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
53	19.4400	11.8100	6.4200	3.4100	2.4300	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
54	28.9500	16.2700	13.3400	7.5900	6.6900	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
55	15.9300	12.5700	9.5600	6.9800	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
56	15.4300	8.3000	7.8500	5.5700	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
57	14.4900	7.5600	5.6800	5.1600	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
58	20.1900	10.0200	7.4600	5.7900	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
59	17.3200	12.8500	9.8900	7.9100	5.7100	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
60	26.3800	16.9000	10.6900	8.6000	5.8900	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
61	11.9000	5.2400	0.0000	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
62	12.0200	6.4300	0.0000	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
63	22.5467	11.5067	6.6867	6.0567	2.3967	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
64	28.5833	14.5533	7.5333	4.5233	3.2833	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
65	14.1800	11.6000	9.2800	7.3300	5.1500	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
66	11.5367	7.2367	4.9867	5.8667	2.4667	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
67	20.1133	11.1433	7.9733	5.9433	3.2833	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
68	27.5200	17.5200	13.7000	9.8700	6.4100	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
69	11.4400	6.7700	5.3200	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
70	18.9400	11.8700	8.6400	5.8800	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
71	17.7400	13.4000	10.8400	7.5000	5.1200	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
72	19.3700	13.8400	10.3900	8.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
73	20.1900	13.8200	8.6900	8.8100	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
74	21.7600	12.0700	8.7800	7.9100	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
75	26.7600	20.5900	13.8900	9.5500	6.5600	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
76	29.6300	17.9600	12.8500	8.1800	7.0600	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
77	22.4067	14.2867	7.6767	3.3367	2.3067	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
78	14.8333	10.0233	8.3933	3.7233	2.6833	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
79	15.1800	9.4900	6.9700	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
80	14.8100	8.9400	7.4300	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120

Obs	c18	c19	c20	c21	c22	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	t20	t21	t22
81	14.0200	7.5200	6.7500	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
82	17.0800	10.5000	9.7100	5.1500	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
83	9.6600	7.2100	6.2200	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
84	13.3800	9.7100	7.4400	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
85	17.5200	11.8300	9.0900	6.4100	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
86	28.2700	19.3100	14.5700	8.7200	6.0700	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
87	11.8000	9.2000	5.6100	0.0000	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
88	18.0000	13.7500	8.1900	5.6600	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
89	23.5200	15.5800	12.8700	7.8700	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
90	20.3500	11.0900	7.8700	6.6200	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
91	17.5600	11.9000	8.7800	6.3900	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
92	18.5200	10.4500	7.1000	6.0600	0.0000	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
93	14.3967	8.4667	5.2667	1.2967	0.6467	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120
94	16.9567	9.2367	7.4067	3.1767	2.9667	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96	100	108	120

Baseline-corrected PHARMACOKINETIC DATASET

Obs	SUB	SEQ	PER	TREAT	CMAX	AUCT	AUCI	TMAX	KE	THALF
1	1	1	1	A	56.680	4073.84	4291.85	30.0000	0.02693	25.7428
2	1	1	2	B	60.290	4335.20	4511.78	24.0000	0.03120	22.2137
3	2	1	1	A	64.043	3958.74	3991.18	24.0000	0.07377	9.3962
4	2	1	2	B	80.903	4808.73	4827.04	24.0000	0.06406	10.8198
5	3	2	1	B	141.723	8298.58	8379.15	48.0000	0.06682	10.3739
6	3	2	2	A	131.330	8818.19	8884.58	24.0000	0.07697	9.0051
7	4	2	1	B	143.080	6469.20	6611.83	18.0833	0.03533	19.6165
8	4	2	2	A	196.063	9191.35	9245.14	18.0000	0.04542	15.2595
9	5	2	1	B	211.450	11894.28	11993.73	18.0681	0.06777	10.2284
10	5	2	2	A	203.010	13444.96	13564.29	36.0000	0.04835	14.3355
11	6	1	1	A	206.160	12659.38	12822.05	24.0000	0.04002	17.3204

Obs	SUB	SEQ	PER	TREAT	CMAX	AUCT	AUCI	TMAX	KE	THALF
12	6	1	2	B	204.243	13742.42	13768.80	24.0000	0.09792	7.0786
13	7	1	1	A	99.660	6311.01	6483.95	24.0000	0.05117	13.5451
14	7	1	2	B	102.140	6800.21	6971.53	24.0000	0.05364	12.9216
15	8	1	1	A	228.530	11821.02	12023.89	18.0722	0.04032	17.1904
16	8	1	2	B	136.970	9080.95	9260.24	48.0000	0.03464	20.0117
17	9	2	1	B	106.190	5688.73	5839.59	24.0000	0.03381	20.5033
18	9	2	2	A	110.730	7209.97	7556.83	30.0000	0.01799	38.5292
19	10	2	1	B	114.040	3710.12	3819.03	18.0000	0.03425	20.2388
20	10	2	2	A	100.883	3328.34	3329.13	18.0000	0.35865	1.9326
21	11	1	1	A	169.920	9346.92	9390.66	18.0000	0.13490	5.1384
22	11	1	2	B	130.620	7226.41	7258.25	18.0000	0.16805	4.1246
23	12	2	1	B	117.970	8048.47	8220.53	24.0000	0.03737	18.5473
24	12	2	2	A	179.570	12196.26	12489.59	18.0000	0.02949	23.5054
25	13	2	1	B	185.930	11484.09	11522.05	18.0000	0.16308	4.2505
26	13	2	2	A	214.070	11920.55	12006.37	18.0000	0.06758	10.2565
27	14	1	1	A	66.860	4779.23	4816.94	24.0000	0.06576	10.5405
28	14	1	2	B	67.600	5283.06	.	60.0000	.	.
29	15	1	1	A	78.460	5636.14	5813.46	30.0000	0.03288	21.0816
30	15	1	2	B	87.410	6120.70	6247.57	24.0000	0.04784	14.4877
31	16	2	1	B	94.820	6264.85	6432.80	36.0000	0.03126	22.1745
32	16	2	2	A	138.780	9007.05	9148.17	24.0000	0.04273	16.2216
33	17	1	1	A	201.510	10763.67	11008.12	18.0000	0.02242	30.9192
34	17	1	2	B	128.700	8659.55	8846.14	36.0000	0.02878	24.0848
35	18	2	1	B	94.180	6710.79	6878.67	48.0000	0.05296	13.0893
36	18	2	2	A	146.480	7818.63	7974.78	18.0000	0.05130	13.5121
37	19	1	1	A	102.663	4416.43	4438.96	24.0000	0.07291	9.5063
38	19	1	2	B	178.533	10073.05	10086.97	24.0000	0.11307	6.1305
39	20	1	1	A	131.230	9016.96	9081.64	18.0000	0.11471	6.0424
40	20	1	2	B	242.810	13354.14	13468.86	48.0000	0.06346	10.9228

Obs	SUB	SEQ	PER	TREAT	CMAX	AUCT	AUCI	TMAX	KE	THALF
41	21	1	1	A	188.590	8011.80	8508.08	18.0000	0.01253	55.3048
42	21	1	2	B	107.110	6717.56	6809.90	18.0000	0.06454	10.7397
43	22	2	1	B	143.320	8828.78	9044.03	18.0000	0.02732	25.3736
44	22	2	2	A	173.260	11015.08	11114.93	24.0000	0.06520	10.6313
45	23	2	1	B	56.090	3846.39	3950.87	36.0000	0.07589	9.1330
46	23	2	2	A	96.857	5706.82	5789.42	36.0000	0.04391	15.7860
47	24	2	1	B	95.150	5829.74	5904.79	24.0000	0.08941	7.7527
48	24	2	2	A	135.200	8326.63	8418.87	18.0000	0.05551	12.4869
49	25	2	1	B	126.390	9645.86	10318.36	24.0000	0.03515	19.7182
50	25	2	2	A	131.193	6643.66	7452.32	36.0000	.	.
51	26	2	1	B	169.410	11357.33	11545.63	24.0000	0.03091	22.4260
52	26	2	2	A	159.170	10194.47	10299.41	24.0000	0.04260	16.2727
53	27	2	1	B	71.880	5128.08	5155.11	18.0000	0.08989	7.7108
54	27	2	2	A	93.390	6087.52	6192.64	24.0000	0.06364	10.8918
55	28	1	1	A	115.690	7495.52	7630.75	18.0339	0.05162	13.4287
56	28	1	2	B	130.680	8290.19	8451.09	36.0000	0.03462	20.0232
57	30	1	1	A	95.660	5802.89	5857.40	24.0000	0.09466	7.3227
58	30	1	2	B	134.950	8148.47	8280.96	18.0000	0.04370	15.8613
59	31	1	1	A	110.930	5938.53	6146.56	18.0000	0.02745	25.2526
60	31	1	2	B	70.950	5542.30	5739.03	60.0000	0.02994	23.1512
61	32	1	1	A	286.460	12692.40	12720.62	8.0000	0.18571	3.7324
62	32	1	2	B	230.390	11476.11	11517.50	18.0000	0.15534	4.4621
63	33	1	1	A	102.157	7075.33	7115.61	24.0000	0.05950	11.6504
64	33	1	2	B	91.053	6703.32	6784.68	36.0000	0.04035	17.1769
65	34	2	1	B	130.280	8242.34	8417.27	18.0000	0.02944	23.5436
66	34	2	2	A	158.417	8771.27	8823.82	12.0000	0.04694	14.7669
67	35	2	1	B	79.293	5616.36	5689.70	18.0000	0.04476	15.4845
68	35	2	2	A	83.520	5544.88	5714.37	18.0000	0.03782	18.3283
69	36	2	1	B	60.970	4284.03	4322.55	36.0000	0.13811	5.0187

Obs	SUB	SEQ	PER	TREAT	CMAX	AUCT	AUCI	TMAX	KE	THALF
70	36	2	2	A	101.490	6858.10	6961.17	24.0000	0.05705	12.1503
71	37	1	1	A	173.510	10369.65	10507.82	18.0000	0.03706	18.7059
72	37	1	2	B	131.310	8305.15	8487.72	24.0000	0.04382	15.8183
73	38	1	1	A	138.390	8378.59	8470.60	18.0000	0.09575	7.2389
74	38	1	2	B	121.610	7591.43	7669.80	36.0000	0.10093	6.8677
75	39	1	1	A	104.360	7127.28	7304.49	24.0000	0.03702	18.7244
76	39	1	2	B	101.000	6425.38	6545.25	30.0000	0.05890	11.7689
77	40	2	1	B	136.817	9187.58	9210.32	18.0000	0.10143	6.8336
78	40	2	2	A	180.763	9749.05	9792.10	24.0000	0.06233	11.1209
79	41	2	1	B	189.790	12249.08	12320.72	18.0000	0.09730	7.1241
80	41	2	2	A	201.380	10293.59	10345.47	18.0000	0.14321	4.8402
81	42	2	1	B	134.140	7739.12	7779.18	60.0000	0.16852	4.1132
82	42	2	2	A	172.830	9925.58	9998.44	30.0850	0.07068	9.8067
83	43	2	1	B	151.450	6882.47	6995.50	18.0000	0.05503	12.5963
84	43	2	2	A	166.710	7607.76	7709.18	18.0000	0.07336	9.4484
85	44	2	1	B	48.730	3407.72	3535.90	72.0000	0.05001	13.8608
86	44	2	2	A	94.980	5863.10	5990.58	48.0000	0.04761	14.5579
87	45	2	1	B	82.470	5389.94	5442.64	60.0367	0.10646	6.5109
88	45	2	2	A	82.740	5564.90	5638.03	18.0000	0.07740	8.9559
89	46	1	1	A	133.010	7892.71	8029.43	30.0000	0.05756	12.0414
90	46	1	2	B	92.970	6164.40	6227.89	36.0000	0.10427	6.6476
91	47	1	1	A	374.690	15767.44	15895.01	18.0000	0.05009	13.8384
92	47	1	2	B	284.460	15234.13	15289.99	18.0000	0.10849	6.3890
93	48	1	1	A	126.317	7998.26	8003.54	18.0000	0.12238	5.6637
94	48	1	2	B	130.937	7580.37	7617.00	18.0000	0.08100	8.5573

4.6.2 Baseline-Corrected Fasting Study Codes

```
/*=============================================================================
====
/ Program   : TWOWAYCONTINU(2)07MAR2009.SAS (Updated: 27 March 2007)
/ SubMacros : macrolib.sas, continu2.sas, continu.sas,
/ Purpose   : To analyze two-way crossover bioequivalence studies.
/ Notes     :
/
/=============================================================================
===
/ PARAMETERS:
/-------name------- ------------------------description----------------------
---

/=============================================================================
===
/ AMENDMENT HISTORY:
/ Init --Date--  ----------------------Description------------------------
/ ELIMINATE CALCKE OPTION FROM THIS SAS PROGRAM,
  FOR CALCKE OPTION, PLEASE USE TWOWAYCALCKE07MAR2009.SAS
/=============================================================================
===*/
**** NODATE OPTION generates error in word document.. with bodytitle ods ****;

**********FOLLOW THE STEPS 1-15 TO RUN THIS PROGRAM**********;

OPTIONS PS=60;

****** LOCATION OF MACRO FILE (MACROLIB.SAS). CHANGE LOCATION IF APPLICABLE
********;
%INCLUDE "M:\SAS\MACRO 2009\MACROLIB.SAS";

/*********************************************************
  ASSIGN WHETHER HAVE GROUP EFFECT:
   TRTGROUP = 1      TRT*GROUP INTERACTION IN GLM MODEL
   TRTGROUP = 2      TRT*GROUP INTERACTION NOT IN GLM MODEL
   TRTGROUP =        NO GROUP EFFECT IN STUDY
 NOTE:  group variable has to be named GRP in the dataset.
*********************************************************/;

*****STEP 1:  ASSIGN FLAG FROM ABOVE FOR TREAT*GROUP INTERACTION*****;
%let trtgroup=;

*****STEP 2: ENTER ANDA INFORMATION *****;
%let level = Estradiol;
%let drug=Estradiol Transdermal Patch;
%let dose=1 x 0.1 MG/day;
%let anda=201675;
%let studytype=Baseline-corrected;
```

```
***** STEP 3: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
%let studydir=M:\assignment\2011-7\201675-estradiol transdermal
system\SAS\baseline adjusted\remove S14-reference\remv_S14_AUCI only;

*****STEP 4: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = ng hr/mL;
%let cmaxunit = ng/mL;
%let timeunit = hr;

***** STEP 5: SPECIFY NAME OF THE CONCENTRATION SAS DATASET *****;
***** IGNORE THIS STEP IF DATA IS FROM EXCEL *****;
%let cdata=conc;

*****STEP 6: SPECIFY NAME OF THE PK SAS DATASET *****;
***** IGNORE THIS STEP IF DATA IS FROM EXCEL *****;
%let pdata=pk;


**** DO NOT CHANGE: NAME OF MS WORD STATISTICAL OUTPUT FILE ****;
%LET ODSFILE=&studydir\&anda._&studytype._stat_&level..doc;

**** DO NOT CHANGE: NAME OF MS WORD REVIEW TABLES OUTPUT FILE ****;
%LET ODSFILE1=&studydir\&anda._&studytype._table_&level..doc;

**** DO NOT CHANGE: NAME OF PLASMA CONCENTRATION PLOT IN CGM GRAPHIC FILE****;
%LET PLOTFILE=&studydir\&anda._&studytype._plot_&level..cgm;

**** DO NOT CHANGE: NAME OF CONC AND PK DATASETS OUTPUT ****;
%LET CONCOUTPUT=&studydir\&anda._&studytype._Datasets_&level..doc;


%LET VARSORT=SUB PER;

%GLOBAL SUB PER SEQ TRT GRP TREAT C T AUCT CMAX TMAX AUCI KE DF NNAME
THALF CLAST KE_FIRST KE_LAST OLDNAME NEWNAME;


*****STEP 7: SELECT TYPE OF ANALYSIS FROM BOTTOM******;

/***SELECT CALCKE.SAS IF YOU WANT TO CALCULATE KE AND OTHER PARAMETERS ***/
/***SELECT CONTINU.SAS IF YOU DO NOT WANT TO RECALCULATE KE.  SPONSOR'S KE
WILL BE
USED FOR CALCULATION OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR SUPPLIED
PARAMETERS.  FOR STATISTICS ON CALCULATED PARAMETERS USE CONTINU2.SAS ***/

*%LET FNAME=%QUOTE(C:\Documents and
Settings\munshiu\Desktop\BEPRG\CONTINU.SAS);
%LET FNAME=%QUOTE(M:\SAS\MACRO\CONTINU2.SAS);
/*** WRITE DATA FILE NAMES  ***/

*****STEP 8: BLOOD LEVEL DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE
LIST *****;

/*** IF NO BLOOD DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 3 ***/
/*** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
```

```
FILENAME ORGPLASM DDE 'EXCEL|conc!R2C1:R95C48';
* FILENAME ORGPLASM "&studydir.\&plasmadata";
 %LET FIRSTOBS=1; /* FIRST OBSERVATION */
 %LET VARPLASM=SUB SEQ PER TREAT $ c1-c22 t1-t22;  /* VARIABLE LIST FOR THE
PLASMA DATA FILE */
%LET PLASMLS=500;   /* INCREASE LINE SIZE IF NEEDED */
 %READDATA(ORGPLASM,PLASMA,&FIRSTOBS,&VARPLASM,&PLASMLS)
 RUN;


*** IF EXCEL FILE, ACTIVATE THESE STATEMENTS ***;
 *FILENAME ORGPLASM DDE 'EXCEL|conc!R2C1:R73C26';
 *%LET FIRSTOBS=1; /* FIRST OBSERVATION */

** IF INPUT FILE IS A SAS DATASET **;
** SPECIFIY LIBNAME WHERE THE SAS DATASET IS SAVED **;
/*LIBNAME libdata "&studydir";

DATA PLASMA;

** IF USING EXCEL FILE ACTIVATE THESE STATEMENTS **;
*  infile ORGPLASM;
*  input sub seq per trt c1-c23;

** IF SAS DATASET, ACTIVATE THESE STATEMENTS **;

  *SET LIBDATA.&CDATA(RENAME=(TRT=TREAT SEQ=SEQU));

*** STANDARD NAMES:  SUB SEQ PER GRP TRT c1-c23  ****;
******** IF USING EXCEL FILE ACTIVATE THESE STATEMENTS **;
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST SPECIFYING
DATA POINTS TO BE USED FOR CALCULATION OF KE **;
  infile ORGPLASM;
  input sub seq per GRP treat $ c1-c23 KE_FIRST KE_LAST T1-T23;

  if treat = "A" then trt=1;
  else trt=2;
  DROP TREAT;
RUN;

proc print data=plasma;
run;*/


%SORTDS(PLASMA, &VARSORT)
RUN;



*****STEP 9:PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE
LIST *****;

/***IF NO PK PARAMETER DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4 ***/
/*** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
FILENAME ORGPARAM DDE 'EXCEL|pk!R2C1:R95C10';
* FILENAME ORGPARAM "&studydir.\&pkdata";
```

```
%LET FIRSTOBS=1; /* FIRST OBSERVATION */
%LET VARPARAM=SUB SEQ PER TREAT $ CMAX AUCT AUCI TMAX KE THALF; /* VARIABLE
LIST */
%LET PARAMLS=256;  /* INCREASE LINE SIZE IF NEEDED */
%READDATA(ORGPARAM,PARAME,&FIRSTOBS,&VARPARAM,&PARAMLS)
RUN;


*** IF EXCEL FILE, ACTIVATE THESE STATEMENTS ***;
 *FILENAME ORGPARAM DDE 'EXCEL|PK!R2C1:R73C26';
 *%LET FIRSTOBS=1; /* FIRST OBSERVATION */

/*DATA PARAME;

** IF USING EXCEL FILE ACTIVATE THESE STATEMENTS **;
infile ORGPARAM;
input sub seq per GRP TREAT $ TMAX CMAX AUCT AUCI KE THALF;

** IF SAS DATASET, ACTIVATE THESE STATEMENTS **;

  *SET libdata.&PDATA(RENAME=(TRT=TREAT SEQ=SEQU));


  IF TREAT = "A" THEN TRT=1;
  ELSE TRT=2;

  DROP TREAT;

 RUN;*/


%SORTDS(PARAME, &VARSORT)
RUN;



/***FILENAME OF THE MERGED DATA***/
/***IF NO MERGED DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4 ***/
/*** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
*FILENAME ORGMERGE DDE 'EXCEL|SHEET1!R2C1:R101C29';
* FILENAME ORGMERGE 'C:\Data\Firms\ivax\76634\Fasting\FDA.1';
*%LET FIRSTOBS=1;  /***WRITE LINE NUMBER FOR THE FIRST OBSERVATION***/
*%LET VARMERGE=SUB PER SEQ TREAT $ C1-C18 AUCT AUCI CMAX TMAX THALF KE GRP;
*%LET MERGELS=300;  /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGMERGE,MERGED,&FIRSTOBS,&VARMERGE,&MERGELS)
*RUN;
*%SORTDS(MERGED, &VARSORT)
*RUN;

*****STEP 10: ADD OR REDUCE THE BLOOD SAMPLE NUMBER TO FIT THE STUDY *****;
%LET CONCENT=%STR(C1, C2, C3, C4, C5, C6, C7, C8, C9, C10,
            C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22);


/***STEP 11: USE THIS STEP IF COMMON SAMPLING TIMES ARE USED,
                  ADD OR REDUCE THE SAMPLING TIME POINTS AND CHANGE THE TIME,
```

```
                    OR ADD FEW DEVIATED SAMPLING TIME POINTS,
                    ALSO MAKE SURE TO DEACTIVATE "SET TIME" AND ACTIVATE
"&TIME" UNDER STEP 15***/

/*%LET TIME=%STR(T1=0; T2=1; T3=2; T4=3; T5=4;
T6=5; T7=6; T8=7; T9=8; T10=9; T11=10; T12=12;
T13=16; T14=24; T15=36; T16=48; T17=72; T18=96; T19=120; T20=144; T21=168;
T22=192; T23=216);


/*IF SUB=1 AND PER=2 THEN T12=5;
*IF SUB=12 AND PER=2 THEN T7=1.8);*/

/***STEP 11A:  USE THIS STEP INSTEAD OF STEP 11 IF ACTUAL SAMPLING TIME
DATASET INCLUDED
                    IN THE CONCENTRATION DATASET,
                   ALSO, MAKE SURE TO ACTIVATE "SET TIME" AND DEACTIVATE
"&TIME" UNDER STEP 15***/;

DATA TIME;
SET PLASMA;
*FILE'DESKTOP\TIME';
PUT T1-T22;
KEEP T1-T22;

*PROC PRINT DATA=TIME;
*RUN;

*****STEP 12: WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS *****;
%LET NO_ASSAY=22;


*****STEP 13 : INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF THESE ARE
NOT
IN THE DATA SUBMITTED. *****;
%LET KE_FIRST=&NO_ASSAY-7;
%LET KE_LAST=&NO_ASSAY-4;


*****STEP 14: SUBJECTS/RECORDS TO BE REMOVED FROM CALCULATION *****;
/***VARIOUS SCREENING CONDITIONS CAN BE APPLIED FOR SUBJECT REMOVAL***/
/***LEAVE AS IT IS IF NO CHANGE IS DESIRED***/
/* %LET REMOVSUB=%STR(IF SUB^=10;IF SUB^=15;IF SUB^=34;IF SUB^=37;IF SUB^=49);
*/
*%LET REMOVSUB=%STR(IF SUB^=205);


*****STEP 15: IF SEQ, PER, TRT OR OTHER VARIABLES TO BE ADDED OR MODIFIED
*****;
/***CREATING NUMERIC VARIABLES FROM CHARACTER VARIABLES, ETC  ***/
/***  IF KE_FIRST AND KE_LAST ARE SUBMITTED IN THE DATA SET , KEEP THEM CLOSED
***/
%LET ADD_VAR=%STR(KE_FIRST=&KE_FIRST; KE_LAST=&KE_LAST;
```

```
IF TREAT='A' THEN TRT=1; ELSE TRT=2);
```

4.6.3 Baseline-Corrected Fasting Study Output

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
SUB	47	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48
TRT	2	1 2
PER	2	1 2
SEQ	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	94
Number of Observations Used	94

Data for Analysis of AUCI LAUCI	
Number of Observations Read	94
Number of Observations Used	92

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	48	10.15084403	0.21147592	7.54	<.0001
Error	45	1.26200401	0.02804453		
Corrected Total	93	11.41284804			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.889423	1.875665	0.167465	8.928303

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.02579293	0.02579293	0.92	0.3427
SUB(SEQ)	45	9.84889618	0.21886436	7.80	<.0001
PER	1	0.16840874	0.16840874	6.01	0.0182
TRT	1	0.10774618	0.10774618	3.84	0.0562

Source	DF	Type III SS	Mean Square	F Value	Pr > F

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.02579293	0.02579293	0.92	0.3427
SUB(SEQ)	45	9.84889618	0.21886436	7.80	<.0001
PER	1	0.16265046	0.16265046	5.80	0.0202
TRT	1	0.10774618	0.10774618	3.84	0.0562

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.02579293	0.02579293	0.12	0.7330

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.06772754	0.03455322	1.96	0.0562

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	48	9.92123943	0.20669249	7.93	<.0001
Error	43	1.12018616	0.02605084		
Corrected Total	91	11.04142560			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.898547	1.803477	0.161403	8.949532

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.03474051	0.03474051	1.33	0.2545
SUB(SEQ)	45	9.54942236	0.21220939	8.15	<.0001
PER	1	0.18793466	0.18793466	7.21	0.0102
TRT	1	0.14914190	0.14914190	5.73	0.0212

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00758043	0.00758043	0.29	0.5924
SUB(SEQ)	45	9.59729622	0.21327325	8.19	<.0001
PER	1	0.18047652	0.18047652	6.93	0.0117
TRT	1	0.14914190	0.14914190	5.73	0.0212

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00758043	0.00758043	0.04	0.8513

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.08143589	0.03403509	2.39	0.0212

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	48	13.29700704	0.27702098	7.61	<.0001
Error	45	1.63722200	0.03638271		
Corrected Total	93	14.93422904			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.890371	3.949259	0.190743	4.829830

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.00383345	0.00383345	0.11	0.7470
SUB(SEQ)	45	12.73300467	0.28295566	7.78	<.0001
PER	1	0.12277067	0.12277067	3.37	0.0728
TRT	1	0.43739825	0.43739825	12.02	0.0012

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00383345	0.00383345	0.11	0.7470
SUB(SEQ)	45	12.73300467	0.28295566	7.78	<.0001
PER	1	0.11305440	0.11305440	3.11	0.0847
TRT	1	0.43739825	0.43739825	12.02	0.0012

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00383345	0.00383345	0.01	0.9079

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.13645923	0.03935609	3.47	0.0012

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	SUB	TRT	AUCRATIO
1	1	1	0.95
2	2	1	0.99
3	3	1	0.99
4	4	1	0.99
5	5	1	0.99
6	6	1	0.99
7	7	1	0.97
8	8	1	0.98
9	9	1	0.95
10	10	1	1.00
11	11	1	1.00
12	12	1	0.98
13	13	1	0.99
14	14	1	0.99
15	15	1	0.97
16	16	1	0.98
17	17	1	0.98
18	18	1	0.98
19	19	1	0.99
20	20	1	0.99
21	21	1	0.94
22	22	1	0.99
23	23	1	0.99
24	24	1	0.99
25	25	1	.
26	26	1	0.99
27	27	1	0.98
28	28	1	0.98
29	30	1	0.99
30	31	1	0.97
31	32	1	1.00
32	33	1	0.99
33	34	1	0.99
34	35	1	0.97
35	36	1	0.99
36	37	1	0.99
37	38	1	0.99
38	39	1	0.98

39	40	1	1.00
40	41	1	0.99
41	42	1	0.99
42	43	1	0.99
43	44	1	0.98
44	45	1	0.99
45	46	1	0.98
46	47	1	0.99
47	48	1	1.00
48	1	2	0.96
49	2	2	1.00
50	3	2	0.99
51	4	2	0.98
52	5	2	0.99
53	6	2	1.00
54	7	2	0.98
55	8	2	0.98
56	9	2	0.97
57	10	2	0.97
58	11	2	1.00
59	12	2	0.98
60	13	2	1.00
61	14	2	.
62	15	2	0.98
63	16	2	0.97
64	17	2	0.98
65	18	2	0.98
66	19	2	1.00
67	20	2	0.99
68	21	2	0.99
69	22	2	0.98
70	23	2	0.97
71	24	2	0.99
72	25	2	0.93
73	26	2	0.98
74	27	2	0.99
75	28	2	0.98
76	30	2	0.98
77	31	2	0.97
78	32	2	1.00

79	33	2	0.99
80	34	2	0.98
81	35	2	0.99
82	36	2	0.99
83	37	2	0.98
84	38	2	0.99
85	39	2	0.98
86	40	2	1.00
87	41	2	0.99
88	42	2	0.99
89	43	2	0.98
90	44	2	0.96
91	45	2	0.99
92	46	2	0.99
93	47	2	1.00
94	48	2	1.00

4.6.4 Baseline-Uncorrected Fasting Study Data

Obs	SUB	SEQ	PER	TREAT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
1	1	1	1	A	0.00	0.00	0.00	0.00	0.00	16.41	32.67	50.23	55.25	56.68	52.26	54.87	43.80	42.92	32.7
2	1	1	2	B	0.00	0.00	0.00	5.54	0.00	18.26	33.65	47.00	60.29	49.14	50.56	52.36	56.88	48.03	51.2
3	2	1	1	A	6.22	6.06	5.98	6.41	8.83	30.33	34.53	63.54	70.13	55.01	60.44	62.92	50.56	49.12	34.1
4	2	1	2	B	6.41	5.33	5.83	6.80	7.02	31.16	50.15	71.04	86.76	62.71	66.75	73.48	63.86	55.48	48.7
5	3	2	1	B	7.03	5.83	6.66	7.41	13.87	53.03	68.99	88.33	142.52	123.15	122.56	148.23	97.27	90.01	64.0
6	3	2	2	A	6.66	6.51	7.05	6.84	26.49	63.28	77.20	116.57	138.07	123.32	129.01	121.99	92.83	98.30	106.0
7	4	2	1	B	0.00	0.00	0.00	6.26	46.54	81.34	132.59	143.08	126.22	89.85	111.62	60.36	46.62	34.18	23.1
8	4	2	2	A	0.00	5.29	5.86	13.24	86.79	160.49	176.35	199.78	188.89	157.54	164.46	95.19	64.26	41.94	35.0
9	5	2	1	B	0.00	0.00	0.00	5.67	59.37	140.21	133.49	211.45	189.45	126.68	146.77	147.25	118.42	128.09	104.7
10	5	2	2	A	0.00	0.00	0.00	0.00	54.67	119.12	172.78	190.41	198.01	142.91	203.01	152.98	146.00	136.04	119.9
11	6	1	1	A	6.89	6.05	5.72	10.07	61.81	138.56	188.28	207.44	212.38	189.21	198.39	162.44	136.02	116.12	89.3
12	6	1	2	B	5.47	7.00	6.54	13.49	88.01	192.27	158.26	206.39	210.58	208.34	183.90	186.84	145.62	136.54	120.1
13	7	1	1	A	0.00	0.00	0.00	5.07	7.82	38.66	48.50	93.58	99.66	67.79	79.74	82.13	67.69	74.87	48.6
14	7	1	2	B	0.00	0.00	0.00	0.00	8.43	34.15	59.70	77.30	102.14	83.14	73.36	97.21	78.48	75.52	68.0
15	8	1	1	A	0.00	0.00	0.00	11.99	79.20	173.96	138.29	228.53	179.34	147.79	155.62	138.09	113.45	89.22	83.1
16	8	1	2	B	0.00	0.00	0.00	5.48	39.88	92.60	99.42	133.24	104.37	96.09	97.41	136.97	99.50	101.84	83.6
17	9	2	1	B	0.00	0.00	0.00	5.43	20.60	82.06	94.73	102.93	106.19	61.78	83.20	66.37	61.68	39.30	31.5
18	9	2	2	A	0.00	0.00	0.00	0.00	7.79	41.79	74.02	108.19	105.28	110.73	88.77	94.14	83.95	70.99	59.2
19	10	2	1	B	0.00	5.52	0.00	5.68	19.70	52.78	60.33	115.88	94.90	51.41	57.64	32.66	21.33	19.65	17.4
20	10	2	2	A	5.84	5.77	5.12	5.85	14.60	56.35	72.07	106.46	88.24	68.83	49.04	37.27	22.27	20.70	15.2
21	11	1	1	A	0.00	0.00	0.00	11.59	77.65	136.19	141.18	169.92	144.08	125.86	120.74	102.83	98.93	77.34	67.5
22	11	1	2	B	0.00	0.00	0.00	0.00	27.65	67.71	83.57	130.62	103.73	89.06	89.41	91.96	79.25	74.34	67.6
23	12	2	1	B	0.00	0.00	0.00	0.00	7.56	53.17	52.63	99.51	117.97	90.69	100.51	102.20	103.11	93.83	78.7
24	12	2	2	A	0.00	0.00	0.00	5.15	40.94	144.00	153.16	179.57	176.78	144.44	139.65	153.18	137.96	124.17	94.1
25	13	2	1	B	0.00	0.00	0.00	0.00	21.15	116.65	170.03	185.93	164.49	145.36	170.78	141.86	129.78	108.04	98.9
26	13	2	2	A	0.00	0.00	0.00	0.00	19.54	103.01	194.25	214.07	172.66	163.45	178.62	130.89	135.44	100.29	95.1
27	14	1	1	A	7.41	6.06	8.10	7.36	9.60	31.18	45.08	63.68	74.05	65.57	69.86	65.28	66.09	59.23	58.6
28	14	1	2	B	8.71	8.56	10.45	10.93	12.40	23.52	41.64	58.56	62.16	65.03	71.08	67.26	76.84	71.90	72.5
29	15	1	1	A	0.00	0.00	0.00	0.00	11.83	37.65	60.12	78.00	74.86	78.46	75.06	76.18	59.35	55.63	47.5
30	15	1	2	B	0.00	0.00	0.00	0.00	26.56	51.74	79.89	80.21	87.41	77.50	79.88	76.35	71.19	56.74	60.0
31	16	2	1	B	0.00	0.00	0.00	0.00	9.14	41.86	67.46	93.45	93.74	73.85	94.82	79.76	76.42	63.76	39.5
32	16	2	2	A	0.00	0.00	0.00	0.00	11.09	52.45	98.04	131.45	138.78	101.46	123.26	119.75	104.88	95.06	70.1
33	17	1	1	A	0.00	0.00	0.00	0.00	18.88	70.67	121.68	201.51	172.68	115.30	181.45	142.22	119.92	91.45	70.4
34	17	1	2	B	0.00	0.00	0.00	0.00	8.92	57.89	72.99	113.66	112.48	98.44	128.70	113.55	101.16	96.04	91.2
35	18	2	1	B	0.00	0.00	0.00	0.00	9.17	45.36	55.90	90.76	91.65	73.89	77.72	94.18	71.82	74.60	61.9
36	18	2	2	A	0.00	0.00	0.00	0.00	18.26	65.61	96.94	146.48	119.85	113.73	123.46	90.33	71.08	65.91	49.4

37	19	1	1	A	8.68	8.83	9.78	10.81	22.84	49.02	68.67	95.01	111.76	71.63	70.14	69.56	46.21	37.84	31.8
38	19	1	2	B	10.87	10.06	8.70	19.57	96.72	154.94	129.74	158.21	188.41	131.55	114.91	138.55	109.53	109.58	85.3
39	20	1	1	A	0.00	0.00	0.00	0.00	29.41	96.34	110.61	131.23	126.31	99.81	127.93	105.01	104.39	82.61	87.9
40	20	1	2	B	0.00	0.00	0.00	8.45	54.95	155.42	144.43	173.32	180.16	174.56	160.50	242.81	148.47	102.49	97.6
41	21	1	1	A	0.00	0.00	0.00	0.00	20.66	81.86	98.11	188.59	116.91	128.12	141.13	80.42	73.10	51.67	49.4
42	21	1	2	B	0.00	0.00	0.00	0.00	8.63	45.80	70.21	107.11	72.43	91.33	105.20	65.07	82.39	64.73	81.3
43	22	2	1	B	0.00	0.00	0.00	0.00	39.72	88.33	99.94	143.32	119.10	109.12	124.07	102.04	105.13	79.23	81.9
44	22	2	2	A	0.00	0.00	0.00	11.63	76.83	144.03	148.48	155.47	173.26	158.89	146.94	134.87	100.96	97.67	85.0
45	23	2	1	B	0.00	0.00	0.00	0.00	0.00	14.45	23.61	39.99	39.36	52.14	56.09	46.41	49.08	44.61	49.8
46	23	2	2	A	0.00	0.00	5.89	0.00	6.39	19.40	46.73	64.49	77.76	80.60	98.82	76.87	66.64	61.80	58.6
47	24	2	1	B	0.00	0.00	0.00	0.00	0.00	35.68	49.64	79.12	95.15	75.88	81.97	76.39	63.30	71.21	57.8
48	24	2	2	A	0.00	0.00	0.00	0.00	24.52	99.88	97.25	135.20	114.73	103.68	112.05	109.70	89.34	93.31	56.2
49	25	2	1	B	11.43	15.19	31.43	20.36	28.11	76.21	94.52	108.99	145.74	139.67	137.04	135.31	138.66	133.98	106.0
50	25	2	2	A	88.97	95.26	102.35	104.99	114.78	132.60	147.50	191.20	225.35	207.34	226.72	199.28	145.46	142.09	113.6
51	26	2	1	B	8.94	10.32	8.34	9.00	28.52	103.73	107.13	174.09	178.61	131.90	138.40	160.13	157.96	137.43	113.8
52	26	2	2	A	9.78	10.15	7.97	8.55	24.14	95.64	117.63	145.60	168.47	132.26	149.36	151.00	111.41	108.51	85.9
53	27	2	1	B	6.75	7.24	6.74	8.80	23.62	54.21	57.92	78.79	77.16	64.60	70.53	73.75	65.32	59.66	54.3
54	27	2	2	A	6.06	0.00	7.05	7.36	12.23	42.36	51.00	89.54	97.76	73.14	89.19	83.67	66.96	66.40	61.0
55	28	1	1	A	0.00	0.00	0.00	0.00	28.65	74.87	79.90	115.69	107.31	96.33	89.60	103.58	95.17	66.41	62.2
56	28	1	2	B	0.00	0.00	0.00	0.00	26.15	83.59	82.82	105.13	119.33	120.02	130.68	100.00	100.17	85.82	64.0
57	30	1	1	A	0.00	0.00	0.00	0.00	11.40	56.04	61.43	94.90	95.66	79.63	87.66	80.19	57.06	50.71	42.1
58	30	1	2	B	0.00	0.00	0.00	0.00	14.69	51.34	69.24	134.95	106.30	95.66	88.80	106.23	98.86	112.94	73.9
59	31	1	1	A	0.00	0.00	0.00	0.00	13.60	49.97	101.91	110.93	91.66	101.48	80.05	67.45	54.00	41.44	36.1
60	31	1	2	B	0.00	0.00	0.00	0.00	5.94	32.99	39.82	66.50	57.40	70.26	69.32	63.37	70.95	61.90	67.9
61	32	1	1	A	0.00	0.00	0.00	32.34	174.02	286.46	171.36	270.96	192.95	145.79	173.32	123.68	117.87	95.64	85.7
62	32	1	2	B	0.00	0.00	0.00	0.00	90.21	174.10	179.28	230.39	153.15	176.24	136.16	115.03	123.49	110.77	90.3
63	33	1	1	A	6.20	5.79	6.05	5.71	15.43	53.17	82.55	107.11	108.17	74.34	91.80	99.99	99.92	78.79	75.9
64	33	1	2	B	7.94	5.95	7.01	5.94	14.48	67.03	71.23	93.30	85.93	87.03	98.02	91.95	87.50	78.65	73.9
65	34	2	1	B	0.00	0.00	0.00	0.00	41.36	112.16	123.41	130.28	105.58	109.96	106.94	96.22	91.47	70.87	69.5
66	34	2	2	A	0.00	5.06	5.90	7.59	46.67	122.26	162.07	144.93	132.40	155.28	158.71	98.59	83.66	55.30	61.8
67	35	2	1	B	5.06	0.00	6.21	6.11	7.55	47.71	49.86	83.05	78.73	60.71	63.53	78.02	74.63	70.01	63.2
68	35	2	2	A	0.00	0.00	0.00	5.80	7.11	28.38	49.15	83.52	72.81	69.26	58.44	75.68	58.90	62.44	44.3
69	36	2	1	B	0.00	0.00	0.00	0.00	5.89	25.98	43.24	52.22	59.68	56.52	60.97	54.39	53.41	46.40	46.7
70	36	2	2	A	0.00	0.00	0.00	0.00	12.42	60.07	79.82	89.24	101.49	99.88	98.87	83.98	80.83	66.58	55.2
71	37	1	1	A	0.00	0.00	0.00	5.47	29.40	107.81	137.10	173.51	166.88	149.64	165.41	131.30	101.48	84.15	59.4
72	37	1	2	B	0.00	0.00	0.00	0.00	14.71	72.09	103.63	117.20	131.31	111.66	114.13	104.50	101.15	82.10	59.1
73	38	1	1	A	0.00	0.00	0.00	0.00	10.85	93.97	76.85	138.39	102.00	104.68	133.38	106.89	92.94	76.51	80.6
74	38	1	2	B	0.00	0.00	0.00	0.00	0.00	61.68	93.20	102.44	114.98	82.77	121.61	93.53	91.70	64.67	77.5

75	39	1	1	A	0.00	0.00	0.00	0.00	6.64	39.59	51.99	100.82	104.36	79.88	89.92	93.34	82.30	78.72	66.9
76	39	1	2	B	0.00	0.00	0.00	5.64	6.98	32.77	44.84	78.76	87.17	101.00	70.16	91.91	63.87	72.85	67.1
77	40	2	1	B	6.19	6.73	7.10	8.79	37.92	126.91	123.83	143.49	138.70	123.47	122.79	136.50	90.21	101.59	76.0
78	40	2	2	A	7.45	7.52	7.31	10.24	52.10	145.03	147.60	170.14	188.19	151.84	153.03	144.34	100.06	66.16	51.8
79	41	2	1	B	0.00	0.00	0.00	0.00	32.26	135.38	184.87	189.79	183.30	167.45	162.87	160.58	129.05	113.62	111.1
80	41	2	2	A	0.00	0.00	0.00	0.00	31.17	158.23	153.83	201.38	174.83	135.66	130.64	129.59	104.66	85.60	53.6
81	42	2	1	B	0.00	0.00	0.00	0.00	0.00	36.32	73.52	101.36	102.62	100.17	96.09	84.75	134.14	83.54	84.7
82	42	2	2	A	0.00	0.00	0.00	0.00	30.08	82.20	147.72	137.67	137.08	172.83	143.53	110.66	111.86	84.94	96.6
83	43	2	1	B	0.00	0.00	0.00	0.00	25.31	91.13	105.83	151.45	139.89	84.95	103.70	99.80	57.08	42.07	24.0
84	43	2	2	A	0.00	0.00	0.00	7.00	36.54	104.62	112.43	166.71	142.46	119.90	94.48	99.85	63.95	57.56	32.0
85	44	2	1	B	0.00	0.00	0.00	0.00	0.00	0.00	16.16	29.65	41.96	34.79	39.96	45.24	42.42	48.73	45.8
86	44	2	2	A	0.00	0.00	0.00	0.00	0.00	10.94	32.26	50.45	62.51	62.43	77.91	94.98	65.55	75.64	60.9
87	45	2	1	B	0.00	0.00	0.00	0.00	0.00	26.87	44.54	64.60	61.78	71.14	78.37	58.61	82.47	64.44	65.2
88	45	2	2	A	0.00	0.00	0.00	0.00	0.00	24.71	47.96	82.74	75.00	71.38	61.96	82.53	68.25	58.44	60.7
89	46	1	1	A	0.00	0.00	0.00	0.00	8.38	55.46	110.54	111.43	114.58	133.01	91.98	85.97	96.75	76.61	68.0
90	46	1	2	B	0.00	0.00	0.00	0.00	0.00	31.50	65.71	74.85	81.81	78.19	92.97	80.70	69.15	64.66	68.5
91	47	1	1	A	0.00	0.00	0.00	12.37	122.14	212.71	287.88	374.69	248.87	157.15	159.93	174.06	172.25	126.35	118.0
92	47	1	2	B	0.00	0.00	0.00	12.48	172.92	241.32	269.47	284.46	243.12	174.64	168.08	159.27	172.75	111.63	128.7
93	48	1	1	A	13.34	7.92	8.15	8.70	19.86	66.69	71.80	136.12	115.43	94.21	118.40	129.31	112.72	103.90	77.0
94	48	1	2	B	7.34	7.33	8.77	9.95	34.59	91.28	82.64	138.75	133.10	111.98	94.64	99.28	97.24	83.27	65.3

Obs	c18	c19	c20	c21	c22	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19
1	18.71	11.85	9.35	8.63	5.87	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
2	17.06	13.10	10.39	7.46	5.51	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
3	22.97	13.30	8.24	9.34	8.48	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
4	21.97	14.07	9.98	8.86	7.03	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
5	30.00	22.16	18.59	12.79	11.89	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
6	39.96	28.55	24.13	14.62	11.85	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
7	12.57	7.95	7.39	7.20	5.04	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
8	15.95	10.23	9.81	8.93	6.16	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
9	26.95	15.72	10.13	6.74	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
10	41.01	25.35	15.34	9.56	5.77	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
11	25.05	16.71	15.30	12.73	.	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
12	28.18	18.92	17.84	9.74	8.92	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
13	22.92	16.71	13.31	9.09	8.85	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
14	29.54	19.76	13.02	9.07	9.19	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
15	29.33	17.71	18.59	11.99	8.18	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
16	24.05	13.82	12.35	7.92	6.21	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
17	10.37	7.63	6.76	5.10	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96

Obs	c18	c19	c20	c21	c22	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19
18	19.52	14.43	8.99	7.46	6.24	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
19	8.92	7.18	5.79	5.24	5.57	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
20	10.57	7.90	5.86	5.50	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
21	16.74	8.63	5.90	0.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
22	13.93	7.02	5.35	0.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
23	26.31	15.90	13.95	11.39	6.43	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
24	38.86	21.17	15.52	12.78	8.65	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
25	17.38	8.66	6.19	0.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
26	23.33	13.23	9.43	5.80	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
27	28.06	19.48	16.20	12.85	9.67	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
28	38.01	31.78	30.24	24.06	32.38	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
29	17.60	12.35	11.42	7.46	5.83	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
30	18.18	10.83	8.73	6.07	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
31	15.49	11.09	9.67	7.23	5.25	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
32	24.43	16.19	14.77	9.43	6.03	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
33	22.77	13.83	8.61	7.00	5.48	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
34	23.09	15.22	9.39	8.53	5.37	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
35	28.96	20.21	15.13	10.20	8.89	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
36	22.19	15.55	14.78	8.51	8.01	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
37	15.88	15.44	12.93	10.65	10.74	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
38	31.37	29.25	25.08	16.85	11.45	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
39	23.85	14.93	9.85	7.42	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
40	24.64	14.04	9.18	6.91	7.28	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
41	16.84	10.29	7.97	7.37	6.22	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
42	20.53	12.21	8.70	6.24	5.96	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
43	23.12	11.08	10.35	7.74	5.88	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
44	24.20	16.29	10.64	10.57	6.51	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
45	16.59	10.11	10.58	7.93	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
46	18.87	14.46	10.67	8.21	5.59	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
47	13.72	8.67	6.71	0.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
48	18.27	10.10	7.57	5.12	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
49	58.35	57.35	52.87	37.42	42.99	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
50	35.70	118.44	112.51	96.16	114.62	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
51	36.78	26.09	19.75	19.13	15.02	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
52	105.96	23.36	18.23	17.86	13.77	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
53	26.35	18.72	13.33	10.32	9.34	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
54	33.32	20.64	17.71	11.96	11.06	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
55	15.93	12.57	9.56	6.98	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
56	15.43	8.30	7.85	5.57	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
57	14.49	7.56	5.68	5.16	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96

Obs	c18	c19	c20	c21	c22	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19
58	20.19	10.02	7.46	5.79	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
59	17.32	12.85	9.89	7.91	5.71	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
60	26.38	16.90	10.69	8.60	5.89	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
61	11.90	5.24	0.00	0.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
62	12.02	6.43	0.00	0.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
63	28.56	17.52	12.70	12.07	8.41	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
64	35.55	21.52	14.50	11.49	10.25	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
65	14.18	11.60	9.28	7.33	5.15	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
66	15.19	10.89	8.64	9.52	6.12	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
67	23.87	14.90	11.73	9.70	7.04	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
68	27.52	17.52	13.70	9.87	6.41	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
69	11.44	6.77	5.32	0.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
70	18.94	11.87	8.64	5.88	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
71	17.74	13.40	10.84	7.50	5.12	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
72	19.37	13.84	10.39	8.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
73	20.19	13.82	8.69	8.81	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
74	21.76	12.07	8.78	7.91	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
75	26.76	20.59	13.89	9.55	6.56	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
76	29.63	17.96	12.85	8.18	7.06	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
77	29.08	20.96	14.35	10.01	8.98	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
78	22.26	17.45	15.82	11.15	10.11	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
79	15.18	9.49	6.97	0.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
80	14.81	8.94	7.43	0.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
81	14.02	7.52	6.75	0.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
82	17.08	10.50	9.71	5.15	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
83	9.66	7.21	6.22	0.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
84	13.38	9.71	7.44	0.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
85	17.52	11.83	9.09	6.41	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
86	28.27	19.31	14.57	8.72	6.07	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
87	11.80	9.20	5.61	0.00	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
88	18.00	13.75	8.19	5.66	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
89	23.52	15.58	12.87	7.87	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
90	20.35	11.09	7.87	6.62	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
91	17.56	11.90	8.78	6.39	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
92	18.52	10.45	7.10	6.06	0.00	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
93	24.20	18.27	15.07	11.10	10.45	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96
94	24.77	17.05	15.22	10.99	10.78	-48	-24	0	2	4	8	12	18	24	30	36	48	60	72	84	86	88	92	96

Obs	SUB	SEQ	PER	TREAT	CMAX	AUCT	AUCI	TMAX	KE	THALF
1	1	1	1	A	56.680	4073.84	4291.85	30.0000	0.02693	25.7428
2	1	1	2	B	60.290	4335.20	4511.78	24.0000	0.03120	22.2137
3	2	1	1	A	64.043	3958.74	3991.18	24.0000	0.07377	9.3962
4	2	1	2	B	80.903	4808.73	4827.04	24.0000	0.06406	10.8198
5	3	2	1	B	141.723	8298.58	8379.15	48.0000	0.06682	10.3739
6	3	2	2	A	131.330	8818.19	8884.58	24.0000	0.07697	9.0051
7	4	2	1	B	143.080	6469.20	6611.83	18.0833	0.03533	19.6165
8	4	2	2	A	196.063	9191.35	9245.14	18.0000	0.04542	15.2595
9	5	2	1	B	211.450	11894.28	11993.73	18.0681	0.06777	10.2284
10	5	2	2	A	203.010	13444.96	13564.29	36.0000	0.04835	14.3355
11	6	1	1	A	206.160	12659.38	12822.05	24.0000	0.04002	17.3204
12	6	1	2	B	204.243	13742.42	13768.80	24.0000	0.09792	7.0786
13	7	1	1	A	99.660	6311.01	6483.95	24.0000	0.05117	13.5451
14	7	1	2	B	102.140	6800.21	6971.53	24.0000	0.05364	12.9216
15	8	1	1	A	228.530	11821.02	12023.89	18.0722	0.04032	17.1904
16	8	1	2	B	136.970	9080.95	9260.24	48.0000	0.03464	20.0117
17	9	2	1	B	106.190	5688.73	5839.59	24.0000	0.03381	20.5033
18	9	2	2	A	110.730	7209.97	7556.83	30.0000	0.01799	38.5292
19	10	2	1	B	114.040	3710.12	3819.03	18.0000	0.03425	20.2388
20	10	2	2	A	100.883	3328.34	3329.13	18.0000	0.35865	1.9326
21	11	1	1	A	169.920	9346.92	9390.66	18.0000	0.13490	5.1384
22	11	1	2	B	130.620	7226.41	7258.25	18.0000	0.16805	4.1246
23	12	2	1	B	117.970	8048.47	8220.53	24.0000	0.03737	18.5473
24	12	2	2	A	179.570	12196.26	12489.59	18.0000	0.02949	23.5054
25	13	2	1	B	185.930	11484.09	11522.05	18.0000	0.16308	4.2505
26	13	2	2	A	214.070	11920.55	12006.37	18.0000	0.06758	10.2565
27	14	1	1	A	66.860	4779.23	4816.94	24.0000	0.06576	10.5405
28	14	1	2	B	67.600	5283.06	.	60.0000	.	.
29	15	1	1	A	78.460	5636.14	5813.46	30.0000	0.03288	21.0816
30	15	1	2	B	87.410	6120.70	6247.57	24.0000	0.04784	14.4877
31	16	2	1	B	94.820	6264.85	6432.80	36.0000	0.03126	22.1745
32	16	2	2	A	138.780	9007.05	9148.17	24.0000	0.04273	16.2216
33	17	1	1	A	201.510	10763.67	11008.12	18.0000	0.02242	30.9192
34	17	1	2	B	128.700	8659.55	8846.14	36.0000	0.02878	24.0848
35	18	2	1	B	94.180	6710.79	6878.67	48.0000	0.05296	13.0893
36	18	2	2	A	146.480	7818.63	7974.78	18.0000	0.05130	13.5121
37	19	1	1	A	102.663	4416.43	4438.96	24.0000	0.07291	9.5063
38	19	1	2	B	178.533	10073.05	10086.97	24.0000	0.11307	6.1305
39	20	1	1	A	131.230	9016.96	9081.64	18.0000	0.11471	6.0424
40	20	1	2	B	242.810	13354.14	13468.86	48.0000	0.06346	10.9228

Obs	SUB	SEQ	PER	TREAT	CMAX	AUCT	AUCI	TMAX	KE	THALF
41	21	1	1	A	188.590	8011.80	8508.08	18.0000	0.01253	55.3048
42	21	1	2	B	107.110	6717.56	6809.90	18.0000	0.06454	10.7397
43	22	2	1	B	143.320	8828.78	9044.03	18.0000	0.02732	25.3736
44	22	2	2	A	173.260	11015.08	11114.93	24.0000	0.06520	10.6313
45	23	2	1	B	56.090	3846.39	3950.87	36.0000	0.07589	9.1330
46	23	2	2	A	96.857	5706.82	5789.42	36.0000	0.04391	15.7860
47	24	2	1	B	95.150	5829.74	5904.79	24.0000	0.08941	7.7527
48	24	2	2	A	135.200	8326.63	8418.87	18.0000	0.05551	12.4869
49	25	2	1	B	126.390	9645.86	10318.36	24.0000	0.03515	19.7182
50	25	2	2	A	131.193	6643.66	.	36.0000	.	.
51	26	2	1	B	169.410	11357.33	11545.63	24.0000	0.03091	22.4260
52	26	2	2	A	159.170	10194.47	10299.41	24.0000	0.04260	16.2727
53	27	2	1	B	71.880	5128.08	5155.11	18.0000	0.08989	7.7108
54	27	2	2	A	93.390	6087.52	6192.64	24.0000	0.06364	10.8918
55	28	1	1	A	115.690	7495.52	7630.75	18.0339	0.05162	13.4287
56	28	1	2	B	130.680	8290.19	8451.09	36.0000	0.03462	20.0232
57	30	1	1	A	95.660	5802.89	5857.40	24.0000	0.09466	7.3227
58	30	1	2	B	134.950	8148.47	8280.96	18.0000	0.04370	15.8613
59	31	1	1	A	110.930	5938.53	6146.56	18.0000	0.02745	25.2526
60	31	1	2	B	70.950	5542.30	5739.03	60.0000	0.02994	23.1512
61	32	1	1	A	286.460	12692.40	12720.62	8.0000	0.18571	3.7324
62	32	1	2	B	230.390	11476.11	11517.50	18.0000	0.15534	4.4621
63	33	1	1	A	102.157	7075.33	7115.61	24.0000	0.05950	11.6504
64	33	1	2	B	91.053	6703.32	6784.68	36.0000	0.04035	17.1769
65	34	2	1	B	130.280	8242.34	8417.27	18.0000	0.02944	23.5436
66	34	2	2	A	158.417	8771.27	8823.82	12.0000	0.04694	14.7669
67	35	2	1	B	79.293	5616.36	5689.70	18.0000	0.04476	15.4845
68	35	2	2	A	83.520	5544.88	5714.37	18.0000	0.03782	18.3283
69	36	2	1	B	60.970	4284.03	4322.55	36.0000	0.13811	5.0187
70	36	2	2	A	101.490	6858.10	6961.17	24.0000	0.05705	12.1503
71	37	1	1	A	173.510	10369.65	10507.82	18.0000	0.03706	18.7059
72	37	1	2	B	131.310	8305.15	8487.72	24.0000	0.04382	15.8183
73	38	1	1	A	138.390	8378.59	8470.60	18.0000	0.09575	7.2389
74	38	1	2	B	121.610	7591.43	7669.80	36.0000	0.10093	6.8677
75	39	1	1	A	104.360	7127.28	7304.49	24.0000	0.03702	18.7244
76	39	1	2	B	101.000	6425.38	6545.25	30.0000	0.05890	11.7689
77	40	2	1	B	136.817	9187.58	9210.32	18.0000	0.10143	6.8336
78	40	2	2	A	180.763	9749.05	9792.10	24.0000	0.06233	11.1209
79	41	2	1	B	189.790	12249.08	12320.72	18.0000	0.09730	7.1241
80	41	2	2	A	201.380	10293.59	10345.47	18.0000	0.14321	4.8402

Obs	SUB	SEQ	PER	TREAT	CMAX	AUCT	AUCI	TMAX	KE	THALF
81	42	2	1	B	134.140	7739.12	7779.18	60.0000	0.16852	4.1132
82	42	2	2	A	172.830	9925.58	9998.44	30.0850	0.07068	9.8067
83	43	2	1	B	151.450	6882.47	6995.50	18.0000	0.05503	12.5963
84	43	2	2	A	166.710	7607.76	7709.18	18.0000	0.07336	9.4484
85	44	2	1	B	48.730	3407.72	3535.90	72.0000	0.05001	13.8608
86	44	2	2	A	94.980	5863.10	5990.58	48.0000	0.04761	14.5579
87	45	2	1	B	82.470	5389.94	5442.64	60.0367	0.10646	6.5109
88	45	2	2	A	82.740	5564.90	5638.03	18.0000	0.07740	8.9559
89	46	1	1	A	133.010	7892.71	8029.43	30.0000	0.05756	12.0414
90	46	1	2	B	92.970	6164.40	6227.89	36.0000	0.10427	6.6476
91	47	1	1	A	374.690	15767.44	15895.01	18.0000	0.05009	13.8384
92	47	1	2	B	284.460	15234.13	15289.99	18.0000	0.10849	6.3890
93	48	1	1	A	126.317	7998.26	8003.54	18.0000	0.12238	5.6637
94	48	1	2	B	130.937	7580.37	7617.00	18.0000	0.08100	8.5573

4.6.5 Baseline-Uncorrected Study Codes

```
/*=============================================================================
====
/ Program   : TWOWAYCONTINU(2)07MAR2009.SAS (Updated: 27 March 2007)
/ SubMacros : macrolib.sas, continu2.sas, continu.sas,
/ Purpose   : To analyze two-way crossover bioequivalence studies.
/ Notes     :
/
/=============================================================================
===
/ PARAMETERS:
/-------name------- ------------------------description----------------------
---

/=============================================================================
===
/ AMENDMENT HISTORY:
/ Init --Date--  ----------------------Description-------------------------
/ ELIMINATE CALCKE OPTION FROM THIS SAS PROGRAM,
  FOR CALCKE OPTION, PLEASE USE TWOWAYCALCKE07MAR2009.SAS
/=============================================================================
===*/
**** NODATE OPTION generates error in word document.. with bodytitle ods ****;

**********FOLLOW THE STEPS 1-15 TO RUN THIS PROGRAM**********;

OPTIONS PS=60;

****** LOCATION OF MACRO FILE (MACROLIB.SAS). CHANGE LOCATION IF APPLICABLE
********;
%INCLUDE "M:\SAS\MACRO 2009\MACROLIB.SAS";

/*********************************************************
  ASSIGN WHETHER HAVE GROUP EFFECT:
   TRTGROUP = 1      TRT*GROUP INTERACTION IN GLM MODEL
   TRTGROUP = 2      TRT*GROUP INTERACTION NOT IN GLM MODEL
   TRTGROUP =        NO GROUP EFFECT IN STUDY
 NOTE:  group variable has to be named GRP in the dataset.
*********************************************************/;

*****STEP 1:  ASSIGN FLAG FROM ABOVE FOR TREAT*GROUP INTERACTION*****;
%let trtgroup=;

*****STEP 2: ENTER ANDA INFORMATION *****;
%let level = Estradiol;
%let drug=Estradiol Transdermal Patch;
%let dose=1 x 0.1 MG/day;
%let anda=201675;
%let studytype=Baseline-uncorrected;


***** STEP 3: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
```

```
%let studydir=M:\assignment\2011-7\201675-estradiol transdermal
system\SAS\unadjusted\remove 25_14 AUCi;

*****STEP 4: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = ng hr/mL;
%let cmaxunit = ng/mL;
%let timeunit = hr;

***** STEP 5: SPECIFY NAME OF THE CONCENTRATION SAS DATASET *****;
***** IGNORE THIS STEP IF DATA IS FROM EXCEL *****;
%let cdata=conc;

*****STEP 6: SPECIFY NAME OF THE PK SAS DATASET *****;
***** IGNORE THIS STEP IF DATA IS FROM EXCEL *****;
%let pdata=pk;


**** DO NOT CHANGE: NAME OF MS WORD STATISTICAL OUTPUT FILE ****;
%LET ODSFILE=&studydir\&anda._&studytype._stat_&level..doc;

**** DO NOT CHANGE: NAME OF MS WORD REVIEW TABLES OUTPUT FILE ****;
%LET ODSFILE1=&studydir\&anda._&studytype._table_&level..doc;

**** DO NOT CHANGE: NAME OF PLASMA CONCENTRATION PLOT IN CGM GRAPHIC FILE****;
%LET PLOTFILE=&studydir\&anda._&studytype._plot_&level..cgm;

**** DO NOT CHANGE: NAME OF CONC AND PK DATASETS OUTPUT ****;
%LET CONCOUTPUT=&studydir\&anda._&studytype._Datasets_&level..doc;


%LET VARSORT=SUB PER;

%GLOBAL SUB PER SEQ TRT GRP TREAT C T AUCT CMAX TMAX AUCI KE DF NNAME
THALF CLAST KE_FIRST KE_LAST OLDNAME NEWNAME;


*****STEP 7: SELECT TYPE OF ANALYSIS FROM BOTTOM******;

/***SELECT CALCKE.SAS IF YOU WANT TO CALCULATE KE AND OTHER PARAMETERS ***/
/***SELECT CONTINU.SAS IF YOU DO NOT WANT TO RECALCULATE KE.  SPONSOR'S KE
WILL BE
USED FOR CALCULATION OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR SUPPLIED
PARAMETERS.  FOR STATISTICS ON CALCULATED PARAMETERS USE CONTINU2.SAS ***/

*%LET FNAME=%QUOTE(C:\Documents and
Settings\munshiu\Desktop\BEPRG\CONTINU.SAS);
%LET FNAME=%QUOTE(M:\SAS\MACRO\CONTINU2.SAS);
/*** WRITE DATA FILE NAMES  ***/

*****STEP 8: BLOOD LEVEL DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE
LIST *****;

/*** IF NO BLOOD DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 3 ***/
/*** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
```

```
FILENAME ORGPLASM DDE 'EXCEL|conc!R2C1:R95C48';
* FILENAME ORGPLASM "&studydir.\&plasmadata";
 %LET FIRSTOBS=1; /* FIRST OBSERVATION */
 %LET VARPLASM=SUB SEQ PER TREAT $ c1-c22 t1-t22;  /* VARIABLE LIST FOR THE
PLASMA DATA FILE */
%LET PLASMLS=500;   /* INCREASE LINE SIZE IF NEEDED */
 %READDATA(ORGPLASM,PLASMA,&FIRSTOBS,&VARPLASM,&PLASMLS)
 RUN;


*** IF EXCEL FILE, ACTIVATE THESE STATEMENTS ***;
 *FILENAME ORGPLASM DDE 'EXCEL|conc!R2C1:R73C26';
 *%LET FIRSTOBS=1; /* FIRST OBSERVATION */

** IF INPUT FILE IS A SAS DATASET **;
** SPECIFIY LIBNAME WHERE THE SAS DATASET IS SAVED **;
/*LIBNAME libdata "&studydir";

DATA PLASMA;

** IF USING EXCEL FILE ACTIVATE THESE STATEMENTS **;
*  infile ORGPLASM;
*  input sub seq per trt c1-c23;

** IF SAS DATASET, ACTIVATE THESE STATEMENTS **;

  *SET LIBDATA.&CDATA(RENAME=(TRT=TREAT SEQ=SEQU));

*** STANDARD NAMES:  SUB SEQ PER GRP TRT c1-c23  ****;
******** IF USING EXCEL FILE ACTIVATE THESE STATEMENTS **;
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST SPECIFYING
DATA POINTS TO BE USED FOR CALCULATION OF KE **;
  infile ORGPLASM;
  input sub seq per GRP treat $ c1-c23 KE_FIRST KE_LAST T1-T23;

  if treat = "A" then trt=1;
  else trt=2;
  DROP TREAT;
RUN;

proc print data=plasma;
run;*/


%SORTDS(PLASMA, &VARSORT)
RUN;



*****STEP 9:PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE
LIST *****;

/***IF NO PK PARAMETER DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4 ***/
/*** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
```

```
FILENAME ORGPARAM DDE 'EXCEL|pk!R2C1:R95C10';
* FILENAME ORGPARAM "&studydir.\&pkdata";
%LET FIRSTOBS=1; /* FIRST OBSERVATION */
%LET VARPARAM=SUB SEQ PER TREAT $ CMAX AUCT AUCI TMAX KE THALF; /* VARIABLE
LIST */
%LET PARAMLS=256;  /* INCREASE LINE SIZE IF NEEDED */
%READDATA(ORGPARAM,PARAME,&FIRSTOBS,&VARPARAM,&PARAMLS)
RUN;


*** IF EXCEL FILE, ACTIVATE THESE STATEMENTS ***;
 *FILENAME ORGPARAM DDE 'EXCEL|PK!R2C1:R73C26';
 *%LET FIRSTOBS=1; /* FIRST OBSERVATION */

/*DATA PARAME;

** IF USING EXCEL FILE ACTIVATE THESE STATEMENTS **;
infile ORGPARAM;
input sub seq per GRP TREAT $ TMAX CMAX AUCT AUCI KE THALF;

** IF SAS DATASET, ACTIVATE THESE STATEMENTS **;

  *SET libdata.&PDATA(RENAME=(TRT=TREAT SEQ=SEQU));


  IF TREAT = "A" THEN TRT=1;
  ELSE TRT=2;

  DROP TREAT;

 RUN;*/


%SORTDS(PARAME, &VARSORT)
RUN;



/***FILENAME OF THE MERGED DATA***/
/***IF NO MERGED DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4 ***/
/*** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
*FILENAME ORGMERGE DDE 'EXCEL|SHEET1!R2C1:R101C29';
* FILENAME ORGMERGE 'C:\Data\Firms\ivax\76634\Fasting\FDA.1';
*%LET FIRSTOBS=1;  /***WRITE LINE NUMBER FOR THE FIRST OBSERVATION***/
*%LET VARMERGE=SUB PER SEQ TREAT $ C1-C18 AUCT AUCI CMAX TMAX THALF KE GRP;
*%LET MERGELS=300;  /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGMERGE,MERGED,&FIRSTOBS,&VARMERGE,&MERGELS)
*RUN;
*%SORTDS(MERGED, &VARSORT)
*RUN;

*****STEP 10: ADD OR REDUCE THE BLOOD SAMPLE NUMBER TO FIT THE STUDY *****;
%LET CONCENT=%STR(C1, C2, C3, C4, C5, C6, C7, C8, C9, C10,
             C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22);
```

```
/***STEP 11: USE THIS STEP IF COMMON SAMPLING TIMES ARE USED,
                   ADD OR REDUCE THE SAMPLING TIME POINTS AND CHANGE THE TIME,
                   OR ADD FEW DEVIATED SAMPLING TIME POINTS,
                   ALSO MAKE SURE TO DEACTIVATE "SET TIME" AND ACTIVATE
"&TIME" UNDER STEP 15***/

/*%LET TIME=%STR(T1=0; T2=1; T3=2; T4=3; T5=4;
T6=5; T7=6; T8=7; T9=8; T10=9; T11=10; T12=12;
T13=16; T14=24; T15=36; T16=48; T17=72; T18=96; T19=120; T20=144; T21=168;
T22=192; T23=216);


/*IF SUB=1 AND PER=2 THEN T12=5;
*IF SUB=12 AND PER=2 THEN T7=1.8);*/

/***STEP 11A:  USE THIS STEP INSTEAD OF STEP 11 IF ACTUAL SAMPLING TIME
DATASET INCLUDED
                   IN THE CONCENTRATION DATASET,
                  ALSO, MAKE SURE TO ACTIVATE "SET TIME" AND DEACTIVATE
"&TIME" UNDER STEP 15***/;

DATA TIME;
SET PLASMA;
*FILE'DESKTOP\TIME';
PUT T1-T22;
KEEP T1-T22;

*PROC PRINT DATA=TIME;
*RUN;

*****STEP 12: WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS *****;
%LET NO_ASSAY=22;


*****STEP 13 : INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF THESE ARE
NOT
IN THE DATA SUBMITTED. *****;
%LET KE_FIRST=&NO_ASSAY-7;
%LET KE_LAST=&NO_ASSAY-4;


*****STEP 14: SUBJECTS/RECORDS TO BE REMOVED FROM CALCULATION *****;
/***VARIOUS SCREENING CONDITIONS CAN BE APPLIED FOR SUBJECT REMOVAL***/
/***LEAVE AS IT IS IF NO CHANGE IS DESIRED***/
/* %LET REMOVSUB=%STR(IF SUB^=10;IF SUB^=15;IF SUB^=34;IF SUB^=37;IF SUB^=49);
*/
*%LET REMOVSUB=%STR(IF SUB^=205);


*****STEP 15: IF SEQ, PER, TRT OR OTHER VARIABLES TO BE ADDED OR MODIFIED
*****;
/***CREATING NUMERIC VARIABLES FROM CHARACTER VARIABLES, ETC  ***/
```

```
/***  IF KE_FIRST AND KE_LAST ARE SUBMITTED IN THE DATA SET , KEEP THEM CLOSED
***/
%LET ADD VAR=%STR(KE FIRST=&KE FIRST; KE_LAST=&KE_LAST;
IF TREAT='A' THEN TRT=1; ELSE TRT=2);
```

4.6.6 Baseline-Uncorrected Study Output

BASELINE-UNCORRECTED FASTING STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
SUB	47	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48
TRT	2	1 2
PER	2	1 2
SEQ	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	94
Number of Observations Used	94

Data for Analysis of AUCI LAUCI	
Number of Observations Read	94
Number of Observations Used	92

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	48	10.74147866	0.22378081	9.22	<.0001
Error	45	1.09247845	0.02427730		
Corrected Total	93	11.83395711			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.907683	1.734174	0.155812	8.984783

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.00406690	0.00406690	0.17	0.6843
SUB(SEQ)	45	10.27531438	0.22834032	9.41	<.0001
PER	1	0.25624027	0.25624027	10.55	0.0022

Source	DF	Type I SS	Mean Square	F Value	Pr > F
TRT	1	0.20585711	0.20585711	8.48	0.0056

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00406690	0.00406690	0.17	0.6843
SUB(SEQ)	45	10.27531438	0.22834032	9.41	<.0001
PER	1	0.24644643	0.24644643	10.15	0.0026
TRT	1	0.20585711	0.20585711	8.48	0.0056

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00406690	0.00406690	0.02	0.8944

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.09361541	0.03214879	2.91	0.0056

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	46	9.10289795	0.19788909	8.41	<.0001
Error	43	1.01195539	0.02353385		
Corrected Total	89	10.11485334			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.899954	1.706175	0.153407	8.991307

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.07453067	0.07453067	3.17	0.0822
SUB(SEQ)	43	8.66558017	0.20152512	8.56	<.0001
PER	1	0.18400976	0.18400976	7.82	0.0077
TRT	1	0.17877736	0.17877736	7.60	0.0085

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.07453067	0.07453067	3.17	0.0822
SUB(SEQ)	43	8.66558017	0.20152512	8.56	<.0001
PER	1	0.17594807	0.17594807	7.48	0.0090
TRT	1	0.17877736	0.17877736	7.60	0.0085

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.07453067	0.07453067	0.37	0.5463

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.08916045	0.03234912	2.76	0.0085

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	48	13.20074950	0.27501561	7.62	<.0001
Error	45	1.62390166	0.03608670		
Corrected Total	93	14.82465116			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.890459	3.914616	0.189965	4.852712

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.00043536	0.00043536	0.01	0.9130
SUB(SEQ)	45	12.54977615	0.27888391	7.73	<.0001
PER	1	0.15241577	0.15241577	4.22	0.0457
TRT	1	0.49812223	0.49812223	13.80	0.0006

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00043536	0.00043536	0.01	0.9130
SUB(SEQ)	45	12.54977615	0.27888391	7.73	<.0001
PER	1	0.14084986	0.14084986	3.90	0.0543
TRT	1	0.49812223	0.49812223	13.80	0.0006

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00043536	0.00043536	0.00	0.9687

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.14562380	0.03919566	3.72	0.0006

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	SUB	TRT	AUCRATIO
1	1	1	0.95
2	2	1	0.98
3	3	1	0.98
4	4	1	0.99
5	5	1	0.99
6	6	1	0.98
7	7	1	0.97
8	8	1	0.98
9	9	1	0.95
10	10	1	1.00
11	11	1	1.00
12	12	1	0.98
13	13	1	0.99
14	14	1	0.98
15	15	1	0.97
16	16	1	0.98
17	17	1	0.98
18	18	1	0.98
19	19	1	0.98
20	20	1	0.99
21	21	1	0.94
22	22	1	0.99
23	23	1	0.98
24	24	1	0.99
25	25	1	.
26	26	1	0.97
27	27	1	0.97
28	28	1	0.98
29	30	1	0.99
30	31	1	0.97
31	32	1	1.00
32	33	1	0.98
33	34	1	0.99
34	35	1	0.97
35	36	1	0.99
36	37	1	0.99
37	38	1	0.99
38	39	1	0.98
39	40	1	0.99
40	41	1	0.99
41	42	1	0.99
42	43	1	0.99
43	44	1	0.98
44	45	1	0.99
45	46	1	0.98
46	47	1	0.99
47	48	1	0.99
48	1	2	0.96
49	2	2	0.98
50	3	2	0.98
51	4	2	0.98
52	5	2	0.99
53	6	2	0.99
54	7	2	0.98
55	8	2	0.98
56	9	2	0.97
57	10	2	0.96
58	11	2	1.00
59	12	2	0.98
60	13	2	1.00

61	14	2	.
62	15	2	0.98
63	16	2	0.97
64	17	2	0.98
65	18	2	0.98
66	19	2	0.99
67	20	2	0.99
68	21	2	0.99
69	22	2	0.98
70	23	2	0.97
71	24	2	0.99
72	25	2	0.91
73	26	2	0.96
74	27	2	0.98
75	28	2	0.98
76	30	2	0.98
77	31	2	0.97
78	32	2	1.00
79	33	2	0.97
80	34	2	0.98
81	35	2	0.98
82	36	2	0.99
83	37	2	0.98
84	38	2	0.99
85	39	2	0.98
86	40	2	0.99
87	41	2	0.99
88	42	2	0.99
89	43	2	0.98
90	44	2	0.96
91	45	2	0.99
92	46	2	0.99
93	47	2	1.00
94	48	2	0.99

4.7 Additional Attachments

RLD formulation: [23]

[23] DARRTS, NDA020538, REV-QUALITY-03(General Review), submitted 10/18/2001. last accessed 7-29-2011

1. The patch is die cut to 25 ug/day strength by cutting it to a surface area of 2.5 Cm^2 size. The composition of the patch per unit surface area and the mg/patch composition of all the strengths a provided below*.

Ingredient	Mg/Cm^2	Mg/2.5 Cm^2	Mg/3.75 Cm^2	Mg/5 Cm^2	Mg/7.5 Cm^2	Mg/10 Cm^2
Estradiol (b) (4)	(b) (4)	0.390	0.585	0.780	1.17	1.56
(b) (4) acrylic adhesive	(b) (4)					
(b) (4) (b) (4) silicone						
Oleyl alcohol						
Dipropylene glycol						
Povidone, USP						
(b) (4)						

(b) (4)

BIOEQUIVALENCE DEFICIENCIES

ANDA: 201675

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Estradiol Transdermal System, USP (Twice-weekly), 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day

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

Deficiencies Related to the Fasting BE Study:

1. In the protocol deviation table for the fasting BE study (Report # EDOT-0922 (M1GJ09001), Table 10.3), you stated that "*there were pharmacokinetic (PK) sample processing errors: Period II, 12 hour B samples tubes were out of order at dispensing. It is unknown which subject's samples were in which tube.*" This statement was applied to the Period II, 12-hour samples of subject Nos. 9, 10, 12, 13, 16 (test treatment) and subjects 11, 14 and 15 (reference treatment). Please clarify how the issue was resolved and how you were able to confirm the sample identities.

2. In the protocol deviation table for the fasting BE study (Report # EDOT-0922 (M1GJ09001), Table 10.3), you indicated that there was a deviation in the "*transdermal sample handling*: *the Period 1 Control Sample 1A was found under the freezer*". Please explain how the issue was resolved and whether the found sample was used during the study.

Deficiency Related to Dissolution Testing:

3. You have conducted comparative dissolution testing using the FDA-recommended method. Based on the data submitted, the DB recommends the specifications below. Please acknowledge your acceptance of the FDA recommended dissolution method and specifications as follows:

Apparatus:	USP VI (cylinder, modified)
Speed:	50 rpm
Medium:	Water
Volume:	500 mL for 0.025 mg/day and 0.0375 mg/day; 900 mL for 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day
Temperature:	32°C ± 0.5°C

The test product should meet the following specifications:

2 hr: (b) (4)
6 hr:
12 hr: 70-90%

Sincerely yours,

{See appended electronic signature page}

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

4.8 Outcome Page

ANDA: 201675

Enter Review Productivity and Generate Report

COMPLETED ASSIGNMENT FOR 201675 ID: 15080

Reviewer: Lu, Dongmei **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Estradiol transdermal patch

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
15080	9/10/2010	Bioequivalence Study	Fasting Study	1	1
15080	7/28/2011	Other	Dissolution Amendment	1	1
15080	7/28/2011	Other	Dissolution Waiver	1	1
15080	7/28/2011	Other	Dissolution Waiver	1	1
15080	7/28/2011	Other	Dissolution Waiver	1	1
15080	7/28/2011	Other	Dissolution Waiver	1	1
15080	9/10/2010	Other	DSI Inspection Report – Analytical Site	1	1
15080	9/10/2010	Other	DSI Inspection Report – Clinical Site	1	1
				Bean Total:	8

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONGMEI LU
10/20/2011

APRIL C BRADDY
10/24/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
10/31/2011

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	201675
Drug Product Name	Estradiol Transdermal System, USP (Twice-Weekly)
Strength (s)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day
Applicant Name	Mylan Technologies
Address	110 Lake Street, St. Albans, VT 05478
Applicant's Point of Contact	S. Wayne Talton
Contact's Phone Number	(304) 599-2595, ext. 6551
Contact's Fax Number	(304) 285-6407
Submission Date(s)	April 26, 2010
First Generic	No
Reviewer	Hongling Zhang, Ph.D.
Study Number (s)	EDOT-0922
Study Type (s)	Fasting
Strength(s)	0.1 mg/day
Clinical Site	Cetero Research – Miami
Clinical Site Address	1405 NW 167 Street Miami Gardens, FL 33169
Analytical Site	(b) (4)
Analytical Address	
OUTCOME DECISION	**INADEQUATE**

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT#	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	Dissolution	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day	**INADEQUATE**

EXECUTIVE SUMMARY

There is no USP method for Estradiol Transdermal System, but there is an FDA recommended dissolution method which is the public dissolution database on the Office of Generic Drugs (OGD) website, http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. The current FDA-recommended dissolution methods for Estradiol Transdermal System are as follows (updated on 10/28/2010)[1]:

USP Apparatus :	VI (Cyclinder) attach the patch to a disk at the bottom of the cylinder
Speed (rpm) :	50
Medium :	Water
Volume (mL) :	500 mL (0.025 mg/24 hr and 0.0375 mg/24 hr); 900 mL (0.05 mg/24 hr , 0.075 mg/24 hr and 0.1 mg/24 hr)
Temperature :	32°C ± 0.5°C
Sampling Times :	1, 2, 4, 6, 8, 10 and 12 hours

The firm conducted the dissolution testing using their own method. The firm will be asked to conduct the dissolution testing using FDA-recommended dissolution method. In addition, according to the current BE Guidance (recommended Nov. 2010) for Estradiol Transdermal System, the firm needs to conduct additional dissolution testing in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer). The firm is also asked to clarify if the delivered dose (i.e, 0.025 mg/day) or the loading amount (i.e. 0.41 mg) was used for the calculation of the percentage release of the dissolution data.

NON DISSOLUTION TESTING ITEMS:

The long-term storage stability data that the firm provided is sufficient to cover the maximum storage period of the study samples for the submitted bioequivalence study.

The firm provided the SAS files in the electronic format for the BE study.

The DBE will review the fast BE study and waiver requests at a later date.

The in vitro dissolution testing is **inadequate**.

[1]This method is the same as the dissolution method of the RLD product (NDA 020538, OCPB Review dated 8/18/1997 for supplement 006 and Chemistry Review dated 7/9/2004). The dissolution specifications for the RLD products are: 2 hr (b) (4) 4 hr: (b) (4); 6 hr: (b) (4) (NOT TO BE RELEASED UNDER FOI)

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☒	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☒	☐	☐
Is FDA method in the public dissolution database (on the web)			☒	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples*?			☒	☐	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

* The firm submitted the addendum on 5/25/2010 providing the additional LTSS data.

FDA-Recommended Dissolution Method (External Database)[2]:

Estradiol (Test 1) (0.025 mg/24 hr, 0.0375 mg/24 hr, 0.05 mg/24 hr, 0.075 mg/24 hr and 0.1 mg/24 hr)	Film, Transdermal (Extended Release)	VI (Cylinder) attach the patch to a disk at the bottom of the cylinder	50	Water at 32 ± 0.5°C	0.025 mg/24 hr and 0.0375 mg/24 hr: 500 mL; 0.05 mg/24 hr, 0.075 mg/24 hr and 0.1 mg/24 hr: 900 mL	1, 2, 4, 6, 8, 10 and 12 hours	10/28/2010

[2] According to the external dissolution database, there are four dissolution recommendations for Estradiol Transdermal System. There are four RLD products listed in the current Orange Book. Based on the NDA reviews of the RLD product of the current application (NDA 020538), the method listed above is for the RLD, Vivelle-DOT®, which is used for the current application.

I. COMMENTS

1. There is no USP method for Estradiol Transdermal System, but there is an FDA recommended dissolution method which is listed in the public dissolution database on the Office of Generic Drugs (OGD) website, http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. The current FDA-recommended dissolution methods for Estradiol Transdermal System are as follows (updated on 10/28/2010):

USP Apparatus :	VI (Cyclinder) attach the patch to a disk at the bottom of the cylinder
Speed (rpm) :	50
Medium :	Water
Volume (mL) :	500 mL (0.025 mg/24 hr and 0.0375 mg/24 hr); 900 mL (0.05 mg/24 hr , 0.075 mg/24 hr and 0.1 mg/24 hr)
Temperature :	32°C ± 0.5°C
Sampling Times :	1, 2, 4, 6, 8, 10 and 12 hours

2. The above FDA-recommended dissolution method is the same as the dissolution method of the RLD product as indicated in the Clinical Pharmacology & Biopharmaceutics (OCPB) review of NDA 020538 dated 8/18/1997 (suppl. 006), except the dissolution apparatus and sampling times. According the OCPB review of supplement 006, the dissolution apparatus was USP Apparatus 5 and the sampling times were 2, 4 an 6 hours. The dissolution specifications of the RLD products were: 2hr: (b) (4); 4 hr: (b) (4) and 6hr (b) (4) In the innovator's supplement SCS-023 with the letter date of 2/13/2004 and 2/17/2004, the innovator proposed to change the dissolution apparatus to a modified Apparatus 6 (involving use of a double sided tape to attach the patch to a disk at the bottom of the cylinder, thereby removing all barriers between the surface of the patch and the release medium and paddle). The OCPB accepted the change in the dissolution method and indicated that this is a more suitable release method and currently the method of choice for most transdermal patch release testing [DARRTS, NDA 020538, REV-CLINPHARM-01 (General Review), finalized date: 7/9/2004].

3. The firm conducted the dissolution testing using their own method. The firm proposed dissolution method and specifications for the test product are as followings:

Specifications:

(b) (4)

3. In addition, the firm also conducted the dissolution testing for the 0.1 mg/day strength film using (b) (4) (b) (4)

4. According to the firm's Quality Overall Summary submitted in module 2.3, the firm has the following description of the test product: *'Mylan's Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice-Weekly) are single disk, self-adhering systems for transdermal administration of estradiol. The 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day systems* ***contain 0.41 mg, 0.62 mg, 0.82 mg, 1.23 mg, and 1.64 mg estradiol****, respectively, in a multipolymeric adhesive matrix. The figure below is a schematic representation of Mylan's Estradiol Transdermal System, USP (Twice-Weekly), which is designed to be qualitatively identical and therapeutically equivalent to Novartis' Vivelle-Dot® (estradiol transdermal system'*. The proposed labeling of the test product has the following statements: *'Five dosage strengths of estradiol transdermal system (twice-weekly) are available to provide nominal in vivo delivery rates of 0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5 cm², 3.75 cm², 5.0 cm², 7.5 cm², or 10.0 cm² and* ***contains 0.41 mg, 0.62 mg, 0.82 mg, 1.23 mg, or 1.64 mg*** *of estradiol, USP, respectively'*. The dissolution data (both summary and individual) is expressed as percentage of **label claim**. The firm will be asked to clarify if the delivered dose (i.e, 0.025 mg/day) or the loading amount (i.e. 0.41 mg) was used for the calculation of the percentage release of the dissolution data.

5. The firm will be asked to conduct the dissolution testing using FDA-recommended dissolution method. The BE Guidance (recommended Nov 2010) of the drug product which is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234963.pdf has the following statement for the dissolution testing: *'in addition to the method above, for transdermal system, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatuses for transdermal systems in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 0.5, 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application'.*

II. DEFICIENCY COMMENTS:

1. The firm's dissolution testing is incomplete. The firm is asking to conduct the dissolution testing using the following FDA-recommended method:

USP Apparatus :	VI (Cyclinder) attach the patch to a disk at the bottom of the cylinder
Speed (rpm) :	50
Medium :	Water
Volume (mL) :	500 mL (0.025 mg/24 hr and 0.0375 mg/24 hr); 900 mL (0.05 mg/24 hr , 0.075 mg/24 hr and 0.1 mg/24 hr)
Temperature :	32°C ± 0.5°C
Sampling Times :	1, 2, 4, 6, 8, 10 and 12 hours

2. In addition, for transdermal system, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatuses for transdermal systems in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The dissolution test should include early sampling times of 0.5, 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

3. The firm should clarify whether the delivered dose (i.e, 0.025 mg/day) or the loading amount (i.e. 0.41 mg) was used in its calculation for the percentage release of the dissolution data.

III. RECOMMENDATION:

The *in vitro* dissolution testing conducted by Mylan Technologies, on its test product, Estradiol Transdermal System, USP, 0.025 mg/day (Lot # R6A0028), 0.0375 mg/day (Lot #R6A0036), 0.05 mg (Lot # 3R6A0037), 0.075 mg/day (Lot #R6A0038) and 0.1 mg (Lot # R6A0030) comparing it to Novartis' Vivelle-DOT® (estradiol) Extended-Release Tablets, 0.025 mg/day (Lot # 26018311), 0.0375 mg/day (Lot #25228111), 0.05 mg (Lot # 2386711), 0.075 mg/day (Lot #26317111) and 0.1 mg (Lot # 38967), respectively, is incomplete for the reason stated in the deficiency comments mentioned above.

The firm should be informed of the above deficiency comments and recommendation.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 201675

APPLICANT: Mylan Technologies

DRUG PRODUCT: Estradiol Transdermal System, USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence (BE) study and waiver requests will be conducted later. The following deficiencies have been identified:

1. Please conduct the dissolution test using the following FDA-recommended dissolution method as shown in the current FDA dissolution database at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm:

USP Apparatus :	VI (Cyclinder) attach the patch to a disk at the bottom of the cylinder
Speed (rpm) :	50
Medium :	Water
Volume (mL) :	500 mL (0.025 mg/24 hr and 0.0375 mg/24 hr); 900 mL (0.05 mg/24 hr , 0.075 mg/24 hr and 0.1 mg/24 hr)
Temperature :	32°C ± 0.5°C
Sampling Times :	1, 2, 4, 6, 8, 10 and 12 hours

2. In addition, as recommended in the current Bioequivalence Guidance for Estradiol Transdermal System (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234963.pdf), dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatuses for transdermal systems in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be conducted. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The dissolution test should include early sampling times of 0.5, 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is

released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

3. Please clarify which of the following two parameters: the delivered dose (i.e, 0.025 mg/day) or the loading amount (i.e. 0.41 mg), was used in your calculation for the percentage of drug release in your dissolution data.

Sincerely yours,

{See appended electronic signature page}

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

IV. OUTCOME

ANDA: 201675

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
13400	4/26/2010	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HONGLING ZHANG
03/28/2011

BING V LI
03/28/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
03/29/2011

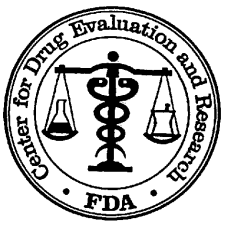
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201675Orig1s000

STATISTICAL REVIEW(S)

Appendix 2



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

ANDA/Serial Number:	201675
Drug Name:	Estradiol transdermal system, USP 0.025mg/day
Reference Listed Drug:	Vivelle-Dot® transdermal system, 0.025mg/day
Applicant:	Mylan Pharmaceuticals Inc.
Date(s):	April 26, 2010 Submission September 10, 2010 Amendment March 11, 2014 additional issue
Biometrics Division:	DB6
Statistical Reviewer:	Huaixiang Li, Ph.D.
Concurring Reviewers:	Stella Grosser, Ph.D.
Medical Division:	Division of Clinical Review (DCR) in OGD
Clinical Team:	Sarah Seung, Pharm.D.
Keywords:	irritation, sensitization, adhesion, non-inferiority, matched pair analysis

1. Introduction

This review is written in response to issues raised by the sponsor, Mylan Pharmaceuticals Inc, in an email to the FDA dated December 30, 2013. These concerns are described in detail in section 4, below .

The purpose of the studies as originally reviewed was to assess the adhesion, irritation, and sensitization properties of the Test: Mylan's Estradiol Transdermal System, USP (0.025 mg/day) versus those of the Reference: Vivelle-Dot® (Estradiol Transdermal System) (Novartis; 0.025 mg/day).

2. Original review

Statistical methodologies

Each subject received the test and reference products simultaneously in the skin irritation, sensitization, and adhesion studies. As a result, observations taken from the same subject might be correlated. For the analysis of continuous data, linear mixed models were used; the random effects in the mixed model structure assessed and reflected the correlation of observations. Also for matched pairs dichotomous data, the McNemar, Clopper-Pearson, and, Schuirmann tests were used to compare the test and reference products in the difference between proportions.

Continuous data – primary endpoint

<Mixed Model>

The statistical reviewer used a mixed model with treatment (TRT) as a fixed effect and SUBJECT as a random effect to analyze the mean cumulative irritation or adhesion score (primary endpoint).

The statistical method for continuous data uses the estimate of the adjusted mean difference $\mu_T - 1.25\mu_R$, to test the hypotheses

$H_0: \mu_T - 1.25\mu_R > 0$ vs $H_1: \mu_T - 1.25\mu_R \leq 0$

where μ_T is the mean response for the test product and μ_R is the mean response for the reference product. One-sided 95% confidence intervals (CIs) for $\mu_T - 1.25\mu_R$ were obtained based on the estimated means. If the upper limit of the CI is less than or equal to 0, the null hypothesis is rejected and the test product may be considered non-inferior to the reference product. Otherwise it is concluded that the test product may be worse than the reference product.

The SAS® (Version 9.2) PROC MIXED statements for the relevant analysis are

```
Proc Mixed Data = <dataset name>;
Class Subject TRT;
Model X = TRT/DDFM = SATTERTH;
```

Repeated TRT / sub = Subject type = fa0(2) r;
Estimate 'Test – 1.25*Reference' int -0.25 TRT 1 -1.25/cl alpha = 0.1;
LSMEANS TRT;
Run;

Results and conclusion

Adhesion
The analysis is based on the 228 subjects in the Adhesion Per Protocol population (ADHPP).

The frequency of cumulative adhesion scores per each patch at each visit is shown in Table below.

Frequency of adhesion scores (ADHPP)

Visit	Treatment	Adhesion score				
		0	1	2	3	4
2	Test	228	0	0	0	0
	Reference	228	0	0	0	0
3	Test	227	1	0	0	0
	Reference	228	0	0	0	0
4	Test	224	4	0	0	0
	Reference	227	1	0	0	0
5	Test	219	5	0	1	3
	Reference	218	6	1	1	2

Primary endpoint: Mean cumulative adhesion score

Analysis for the mean cumulative adhesion scores using mixed model (ADHPP)

Test (Ls mean)	Reference (Ls mean)	Upper limit one-sided 95%CB (test-1.25ref)	Pass the Non-inferiority test
0.027	0.022	0.015	No

Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was greater than zero (0.015) and the non-inferiority test was failed for test versus reference patch. Therefore, the adhesion potential of the test product is worse than that of the reference product.

Irritation
The analysis is based on the 213 subjects in the Irritation Per Protocol population (IRRPP).

Primary endpoint: Mean Cumulative Irritation scores

The table below presents the frequency of irritation and other effects scores for each treatment on each visit.

Frequency of irritation and other effects scores (IRRPP)

	Test							Reference						
Visit	Irritation score					Other effect		Irritation score					Other effect	
	0	1	2	3	7	C	H	0	1	2	3	7	C	H
5	200	8	5	0	0	0	0	198	15	0	0	0	0	0
6	193	18	2	0	0	0	0	195	16	2	0	0	0	0
7	190	16	7	0	0	0	0	187	25	1	0	0	0	0
8	192	12	5	3	1	1	3	190	18	5	0	0	2	0
9	178	21	10	3	1	1	3	167	38	8	0	0	2	0
10	184	21	4	3	1	1	4	184	22	6	1	0	1	0

Analysis for the mean cumulative irritation scores using mixed model (IRRPP)

Test (LS mean μ_T)	Reference (LS mean μ_R)	Upper limit one-sided 95% CB ($\mu_T - 1.25\mu_R$)	Pass the Non-inferiority test
0.1925	0.1495	0.047	No

Non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was greater than zero (0.047) and the non-inferiority test was failed for test versus reference patch. Therefore, the irritation potential of the test product is worse than that of the reference product.

Based on the results from the mixed linear modeling in the 2010 statistical review, the test product was found to be inferior to the reference product for adhesion and irritation.

3. Current considerations (FDA)

Adhesion

There are at least 90% of patches having at least 90% adhesion throughout the entire study for both test and reference products. Both the Test and reference patches have demonstrated very good adhesion.

Based on the Memorandum "Waiver of Statistical Non-Inferiority Analysis for Highly Adhering Patch Drug Products" dated 2/10/2014 by Bryan Newman, Ph.D., the adhesion data were reconsidered. This study meets the new 90/90 analysis criteria, since there are at least 90% of patches having at least 90% adhesion throughout the entire study for both test and reference products. Therefore the statistical non-inferiority analysis of adhesion, comparing the test product with the RLD, can be considered satisfactory, based on this new memorandum by Dr. Newman.

Irritation

There are four outliers, which are defined as values outside the main body of the data. Whether these outliers are gross errors (e.g., due to reading, copying, transmission errors) or "true" but unusual observations is yet to be determined. A list of the four subjects with the combined irritation score per each visit is below.

subject	patch	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Total	Mean
157	Test	0	0	1	6	6	6	19	3.1667
	Ref.	0	0	0	2	3	3	7	1.667
162	Test	0	0	0	6	6	6	18	3
	Ref.	0	0	0	4	4	4	12	2
192	Test	1	1	2	10	10	10	34	5.667
	Ref.	0	0	1	2	2	2	7	1.167
203	Test	0	1	2	5	5	5	18	3
	Ref.	1	1	1	4	1	3	11	1.833

These four outliers are "influential values." If they are removed from the analyses, the analysis result changes.

Analysis for the mean cumulative irritation scores using mixed model (IRRPP*)

Test (LS mean μ_T)	Reference (LS mean μ_R)	Upper limit one-sided 95% CB ($\mu_T - 1.25\mu_R$)	Pass the Non-inferiority test
0.1252	0.1228	-0.0074	Yes

*: Four subjects, 157, 162, 192, and 203, were removed from the analysis

Non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was less than zero (-0.0074) and the non-inferiority test was passed for test versus reference patch when the four outliers were removed. However, as indicated above, no reason has been given for these patients to have outlying values, and therefore they should not be removed from the analysis.

4. Sponsor's view and concerns

Adhesion

Both the Test and reference patches have demonstrated very good adhesion.

Irritation

In the email on December 30, 2013, Mylan described their concern for the approval plan by removal of the 4 outliers. Sponsor insisted the test patch should be passed the non-inferiority test by using the "correct" statistical analysis method. Mylan provided their exploration and research results, and their conclusion.

> *"we find no substantive clinical information that would lead us to support dropping the identified outliers from the analysis at this time."*
>
> *"In closing, Mylan has provided a number of points and supporting data indicating that OGD's method for non-inferiority testing, based on irritation potential for a transdermal drug delivery system, is overly stringent. Additionally, standard approaches to inferring outliers in the related data is highly sensitive in itself, which creates an additional barrier for generic entry."*

Concern

An amendment document was submitted to Office of Generic Drugs (OGD) on September 10, 2010 from Mylan Technologies. The sponsor pointed out the main issues.

> *Mylan has observed that FDA's current method for analysis of cumulative irritation appears to be overly sensitive to differences in data that would otherwise be considered to be of low irritation potential. While the FDA recommended method could be considered to be generally applicable to data for which more definite responses are seen (ie. mean cumulative irritation scores ≥ 1), it becomes overly sensitive in situations of low or minimal irritation response (ie. mean cumulative irritation scores < 1). .... To accommodate the case of low irritation scores, Mylan proposed an additional consideration, such that if the Reference mean irritation score is below the sensitivity of irritation scoring (i.e. mean irritation score < 1), then the upper statistical bound would be based on an absolute value representing 25% of the sensitivity limit of 1 (i.e. absolute change of 0.25, or 25%*1.0). If the mean irritation score of the Reference were to be greater than one, then FDA's recommended limit, based on 25% of Reference, would apply.*

Mylan's proposal changes the non-inferiority test:

FDA $H_0: \mu_T - 1.25\,\mu_R > 0$ vs $H_A: \mu_T - 1.25\,\mu_R \le 0$;

Mylan $H_0: \mu_T - \mu_R > 0.25$ vs $H_A: \mu_T - \mu_R \le 0.25$ when $\overline{x_R} \le 1$

$H_0: \mu_T - 1.25\,\mu_R > 0$ vs $H_A: \mu_T - 1.25\,\mu_R \le 0$ when $\overline{x_R} > 1$

Since, in these irritation data, $\overline{x_R} \le 1$, the Non-inferiority test becomes to check whether the difference of means $(\mu_T - \mu_R)$ is less than or equal to the bound value 0.25.

Conclusion

Both test and reference products are good for the adhesion. The test product was found to be inferior to the reference product for irritation.

_____

Huaixiang Li, Ph.D.
Mathematical Statistician, DB6/OB

_____

Stella G. Grosser, Ph.D.
Team Leader, DB6/OB
cc:
HFD-600 John R Peter, Sarah Seung, Nitin K Patel
HFD-705 Tsong Yi, Stella Grosser, Huaixiang Li
HFD-700 Lillian Patrician OB

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH H Seung
03/26/2014

JOHN R PETERS
03/26/2014

DALE P CONNER
03/27/2014

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA/Serial Number:	201675
Drug Name:	Estradiol transdermal system, USP 0.025mg/day
Reference Listed Drug:	Vivelle-Dot® transdermal system, 0.025mg/day
Applicant:	Mylan Pharmaceuticals Inc.
Date(s):	April 26, 2010 Submission September 10, 2010 Amendment March 11, 2014 additional issue
Biometrics Division:	DB6
Statistical Reviewer:	Huaixiang Li, Ph.D.
Concurring Reviewers:	Stella Grosser, Ph.D.
Medical Division:	Division of Clinical Review (DCR) in OGD
Clinical Team:	Sarah Seung, Pharm.D.
Keywords:	irritation, sensitization, adhesion, non-inferiority, matched pair analysis

1. Introduction

This review is written in response to issues raised by the sponsor, Mylan Pharmaceuticals Inc, in an email to the FDA dated December 30, 2013. These concerns are described in detail in section 4, below .

The purpose of the studies as originally reviewed was to assess the adhesion, irritation, and sensitization properties of the Test: Mylan's Estradiol Transdermal System, USP (0.025 mg/day) versus those of the Reference: Vivelle-Dot® (Estradiol Transdermal System) (Novartis; 0.025 mg/day).

2. Original review

Statistical methodologies

Each subject received the test and reference products simultaneously in the skin irritation, sensitization, and adhesion studies. As a result, observations taken from the same subject might be correlated. For the analysis of continuous data, linear mixed models were used; the random effects in the mixed model structure assessed and reflected the correlation of observations. Also for matched pairs dichotomous data, the McNemar, Clopper-Pearson, and, Schuirmann tests were used to compare the test and reference products in the difference between proportions.

Continuous data – primary endpoint

<Mixed Model>

The statistical reviewer used a mixed model with treatment (TRT) as a fixed effect and SUBJECT as a random effect to analyze the mean cumulative irritation or adhesion score (primary endpoint).

The statistical method for continuous data uses the estimate of the adjusted mean difference $\mu_T - 1.25\mu_R$, to test the hypotheses

$H_0: \mu_T - 1.25\mu_R > 0$ vs $H_1: \mu_T - 1.25\mu_R \leq 0$

where μ_T is the mean response for the test product and μ_R is the mean response for the reference product. One-sided 95% confidence intervals (CIs) for $\mu_T - 1.25\mu_R$ were obtained based on the estimated means. If the upper limit of the CI is less than or equal to 0, the null hypothesis is rejected and the test product may be considered non-inferior to the reference product. Otherwise it is concluded that the test product may be worse than the reference product.

The SAS® (Version 9.2) PROC MIXED statements for the relevant analysis are

```
Proc Mixed Data = <dataset name>;
Class Subject TRT;
Model X = TRT/DDFM = SATTERTH;
```

Repeated TRT / sub = Subject type = fa0(2) r;
Estimate 'Test – 1.25*Reference' int -0.25 TRT 1 -1.25/cl alpha = 0.1;
LSMEANS TRT;
Run;

Results and conclusion

Adhesion

The analysis is based on the 228 subjects in the Adhesion Per Protocol population (ADHPP).

The frequency of cumulative adhesion scores per each patch at each visit is shown in Table below.

Frequency of adhesion scores (ADHPP)

Visit	Treatment	Adhesion score				
		0	1	2	3	4
2	Test	228	0	0	0	0
	Reference	228	0	0	0	0
3	Test	227	1	0	0	0
	Reference	228	0	0	0	0
4	Test	224	4	0	0	0
	Reference	227	1	0	0	0
5	Test	219	5	0	1	3
	Reference	218	6	1	1	2

Primary endpoint: Mean cumulative adhesion score

Analysis for the mean cumulative adhesion scores using mixed model (ADHPP)

Test (Ls mean)	Reference (Ls mean)	Upper limit one-sided 95%CB (test-1.25ref)	Pass the Non-inferiority test
0.027	0.022	0.015	No

Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was greater than zero (0.015) and the non-inferiority test was failed for test versus reference patch. Therefore, the adhesion potential of the test product is worse than that of the reference product.

Irritation

The analysis is based on the 213 subjects in the Irritation Per Protocol population (IRRPP).

Primary endpoint: Mean Cumulative Irritation scores

The table below presents the frequency of irritation and other effects scores for each treatment on each visit.

Frequency of irritation and other effects scores (IRRPP)

	Test							Reference						
Visit	Irritation score					Other effect		Irritation score					Other effect	
	0	1	2	3	7	C	H	0	1	2	3	7	C	H
5	200	8	5	0	0	0	0	198	15	0	0	0	0	0
6	193	18	2	0	0	0	0	195	16	2	0	0	0	0
7	190	16	7	0	0	0	0	187	25	1	0	0	0	0
8	192	12	5	3	1	1	3	190	18	5	0	0	2	0
9	178	21	10	3	1	1	3	167	38	8	0	0	2	0
10	184	21	4	3	1	1	4	184	22	6	1	0	1	0

Analysis for the mean cumulative irritation scores using mixed model (IRRPP)

Test (LS mean μ_T)	Reference (LS mean μ_R)	Upper limit one-sided 95% CB ($\mu_T - 1.25\mu_R$)	Pass the Non-inferiority test
0.1925	0.1495	0.047	No

Non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was greater than zero (0.047) and the non-inferiority test was failed for test versus reference patch. Therefore, the irritation potential of the test product is worse than that of the reference product.

Based on the results from the mixed linear modeling in the 2010 statistical review, the test product was found to be inferior to the reference product for adhesion and irritation.

3. Current considerations (FDA)

Adhesion

There are at least 90% of patches having at least 90% adhesion throughout the entire study for both test and reference products. Both the Test and reference patches have demonstrated very good adhesion.

Based on the Memorandum "Waiver of Statistical Non-Inferiority Analysis for Highly Adhering Patch Drug Products" dated 2/10/2014 by Bryan Newman, Ph.D., the adhesion data were reconsidered. This study meets the new 90/90 analysis criteria, since there are at least 90% of patches having at least 90% adhesion throughout the entire study for both test and reference products. Therefore the statistical non-inferiority analysis of adhesion, comparing the test product with the RLD, can be considered satisfactory, based on this new memorandum by Dr. Newman.

Irritation

There are four outliers, which are defined as values outside the main body of the data. Whether these outliers are gross errors (e.g., due to reading, copying, transmission errors) or "true" but unusual observations is yet to be determined. A list of the four subjects with the combined irritation score per each visit is below.

subject	patch	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Total	Mean
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	Ref.	0	0	0	2	3	3	7	1.667
162	Test	0	0	0	6	6	6	18	3
	Ref.	0	0	0	4	4	4	12	2
192	Test	1	1	2	10	10	10	34	5.667
	Ref.	0	0	1	2	2	2	7	1.167
203	Test	0	1	2	5	5	5	18	3
	Ref.	1	1	1	4	1	3	11	1.833

These four outliers are "influential values." If they are removed from the analyses, the analysis result changes.

Analysis for the mean cumulative irritation scores using mixed model (IRRPP*)

Test (LS mean μ_T)	Reference (LS mean μ_R)	Upper limit one-sided 95% CB ($\mu_T - 1.25\mu_R$)	Pass the Non-inferiority test
0.1252	0.1228	-0.0074	Yes

*: Four subjects, 157, 162, 192, and 203, were removed from the analysis

Non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was less than zero (-0.0074) and the non-inferiority test was passed for test versus reference patch when the four outliers were removed. However, as indicated above, no reason has been given for these patients to have outlying values, and therefore they should not be removed from the analysis.

4. Sponsor's view and concerns

Adhesion

Both the Test and reference patches have demonstrated very good adhesion.

Irritation

In the email on December 30, 2013, Mylan described their concern for the approval plan by removal of the 4 outliers. Sponsor insisted the test patch should be passed the non-inferiority test by using the "correct" statistical analysis method. Mylan provided their exploration and research results, and their conclusion.

> *"we find no substantive clinical information that would lead us to support dropping the identified outliers from the analysis at this time."*
>
> *"In closing, Mylan has provided a number of points and supporting data indicating that OGD's method for non-inferiority testing, based on irritation potential for a transdermal drug delivery system, is overly stringent. Additionally, standard approaches to inferring outliers in the related data is highly sensitive in itself, which creates an additional barrier for generic entry."*

Concern

An amendment document was submitted to Office of Generic Drugs (OGD) on September 10, 2010 from Mylan Technologies. The sponsor pointed out the main issues.

> *Mylan has observed that FDA's current method for analysis of cumulative irritation appears to be overly sensitive to differences in data that would otherwise be considered to be of low irritation potential. While the FDA recommended method could be considered to be generally applicable to data for which more definite responses are seen (ie. mean cumulative irritation scores ≥ 1), it becomes overly sensitive in situations of low or minimal irritation response (ie. mean cumulative irritation scores < 1). .... To accommodate the case of low irritation scores, Mylan proposed an additional consideration, such that if the Reference mean irritation score is below the sensitivity of irritation scoring (i.e. mean irritation score < 1), then the upper statistical bound would be based on an absolute value representing 25% of the sensitivity limit of 1 (i.e. absolute change of 0.25, or 25%*1.0). If the mean irritation score of the Reference were to be greater than one, then FDA's recommended limit, based on 25% of Reference, would apply.*

Mylan's proposal changes the non-inferiority test:

FDA $H_0: \mu_T - 1.25\,\mu_R > 0$ vs $H_A: \mu_T - 1.25\,\mu_R \le 0$;

Mylan $H_0: \mu_T - \mu_R > 0.25$ vs $H_A: \mu_T - \mu_R \le 0.25$ when $\overline{x_R} \le 1$

$H_0: \mu_T - 1.25\,\mu_R > 0$ vs $H_A: \mu_T - 1.25\,\mu_R \le 0$ when $\overline{x_R} > 1$

Since, in these irritation data, $\overline{x_R} \le 1$, the Non-inferiority test becomes to check whether the difference of means $(\mu_T - \mu_R)$ is less than or equal to the bound value 0.25.

Conclusion

Both test and reference products are good for the adhesion. The test product was found to be inferior to the reference product for irritation.

_____
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_____
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HUAIXIANG LI
03/12/2014

STELLA C GROSSER
03/12/2014

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA/Serial Number: 201675

Drug Name: Estradiol transdermal system, USP 0.025mg/day

Reference Listed Drug: Vivelle-Dot® transdermal system, 0.025mg/day

Applicant: Mylan Pharmaceuticals Inc.

Date(s): April 26, 2010 Submission
September 10, 2010 Amendment

Biometrics Division: DB6

Statistical Reviewer: Huaixiang Li, Ph.D.

Concurring Reviewers: Stella Grosser, Ph.D.

Medical Division: Division of Clinical Review (DCR) in OGD

Clinical Team: Nicole Lee, Pharm.D.

Keywords: irritation, sensitization, adhesion, non-inferiority, matched pair analysis

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1 EXECUTIVE SUMMARY

1.1 Conclusions and recommendations

The purpose of the studies reviewed here was to assess the adhesion, irritation, and sensitization properties of the Test: Mylan's Estradiol Transdermal System, USP (0.025 mg/day) versus those of the Reference: Vivelle-Dot® (Estradiol Transdermal System) (Novartis; 0.025 mg/day).

Based on the results from the mixed linear modeling, the test product was found to be inferior to the reference product for adhesion and irritation.

The dichotomized adhesion, irritation, and sensitization scores were also analyzed using binary analysis methods. The 95% upper confidence bound for difference in proportions of test versus reference could be: (1) At most 3.2% for the difference of the mean adhesion score in detachment rates of greater than or equal to 10% detached (score≥1). (2) At most 4.7% with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1; a similar result held for those with the mean cumulative irritation scores greater than or equal to 3. (3) At most 1.9% for the proportion of subjects potentially sensitized[1].

The test product was found to be inferior to the reference product for adhesion and irritation based on the mixed linear model. Those 95% upper confidence bounds (CB) for the adjusted mean difference ($\mu_T - 1.25\mu_R$) were close to zero for adhesion (0.015) and irritation (0.047). The least mean cumulative scores were 0.027 (Test) and 0.022 (Reference) for adhesion, and 0.1925 (Test) and 0.1495 (Reference) for irritation. In addition, the 95% upper confidence bound for difference in proportions of test versus reference based on the dichotomized adhesion and irritation scores were at most 3.2% for the difference of the mean adhesion score in detachment rates of greater than or equal to 10% detached (score≥1) and at most 4.7% with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1 or to 3.

Given the borderline results, the clinical decision should be made using medical judgment as well as statistics.

1.2 Brief overview of clinical studies

Objectives

The objective of this study was the comparative evaluation of the adhesion, cumulative irritation and contact sensitization potential of Mylan's Estradiol Transdermal System, USP (twice-weekly) (0.025 mg/day) to Vivelle-Dot® (Estradiol Transdermal System) (Novartis; 0.025 mg/day) in healthy post-menopausal women.

[1] The definition of "subject potentially sensitized" is in the FDA Draft Guidance on Estradiol, November 2010. Please find the detail in the "Sensitization Data Tables and Analyses" on page 21-22.

Design

This was an open-label, multiple-dose, randomized application site, two-treatment, three-phase, one-period, study of the human dermal safety and adhesion of estradiol transdermal systems (TDS) in healthy post-menopausal female volunteers.

The study was conducted at one clinical site and consisted of three phases: an Induction/irritation phase (21 days, 6 applications), a 14-day Rest phase, and a Challenge/sensitization phase (5 days, one phase application).

During the induction phase, the transdermal systems were removed at 84 hours ± 2 hours after placement. On each day the patch was removed, signs and symptoms of localized irritation were evaluated and new patches were applied to the same sites.

During the challenge phase, the transdermal systems were removed at 48 hours ± 2 hours after placement, which was followed by 3 days of observation and irritation evaluation.

Adhesion of the estradiol transdermal systems during Induction application 1 was assessed every 24 hours (± 2 hours) and within 1 hour prior to patch removal. Adhesion assessment during Induction applications 2 through 6, and the Challenge application was performed within 1 hour prior to patch removal.

Remark: Based on the FDA Draft Guidance on Estradiol, November 2010: "*After the first application, the adhesion performance of subsequent same site applications could be affected by skin stripping or residual adhesive. Therefore, [the applicant should] formally evaluate and compare the adhesion performance of only the first applied test product and RLD for 3.5 days (84 hours) after application. Daily adhesion evaluations are recommended during the first 3.5 day application*". The adhesion analysis is carried out based on the four adhesion scores assessed every 24 hours (± 2 hours) and within 1 hour prior to the first patch removal per each patch regardless of the other adhesion scores collected in the study.

1.3 Statistical issues and findings

Remark

The original submission was received on April 26, 2010.

On September 10, 2010, Mylan submitted an amendment in response to OGD deficiency letter provided on August 6, 2010. The Clinical Review Team refused to file this application because the sponsor did not submit the statistical results using the OGD recommended statistical method to show that the skin irritation potential and adhesion performance of their product are at least as good as those of the reference product. OGD requested that the sponsor provide the one-sided 95% CI for the mean cumulative irritation score of the test product minus 1.25 X mean cumulative irritation score of the reference product in the PP population. OGD also requested that the dermal response and "other effects" scores be combined for the irritation analysis. The frequency distribution of the irritation scores provided by the sponsor in the original submission

based on the greater of the dermal response and "other effects" scores showed considerably more scores of 3 or higher for the test product than the reference product. The one-sided 95% CI for the mean adhesion score of the test product minus 1.25 times the mean adhesion score of the reference product in the PP population was also requested.

Adhesion

I) The mean cumulative adhesion scores (primary endpoint) were analyzed using a mixed linear model. The 95% upper confidence bound (CB) for the adjusted mean difference (μ_T -1.25μ_R) was greater than zero (0.015), thus the test product was found to be inferior to the reference.

II) Based on the 95% upper confidence bound for the difference in detachment rates of greater than or equal to 10% detached (score≥1), the test might exceed the reference by at most 3.2 percentage points for the mean of the adhesion score.

Irritation

I) Non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was greater than zero (0.047). Thus non-inferiority test was failed for the test patch versus reference patch and the irritation potential of the test patch product is considered worse than that of the reference patch product.

II) Analyses based on dichotomized mean cumulative irritation scores:
In addition to the primary endpoint analyses, analyses for the secondary endpoints were conducted to compare the test and reference products with regard to the proportions of subjects who had mean cumulative irritation score greater than or equal to 1, to 2, and, to 3. Based on the 95% upper confidence bound for the difference in proportions, the test product might exceed the reference product by at most 4.7, 4.1, and 4.7 percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1, to 2, and, to 3.

Sensitization

The test might exceed the reference by at most 1.9 percentage points based on the 95% upper confidence bound for the difference in sensitization rates. The non-inferiority standard such as order of magnitude of the possible range of p_T - p_R has not yet been specified by OGD to date. If the non-inferiority limit were established as low as 2%, the Test products have been shown to be non-inferior to the reference products.

2 INTRODUCTION

2.1 Overview

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and

estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women. Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue. Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

Ortho Evra® is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception. The Ortho Evra® transdermal patch was designed to deliver EE (Ethinyl Estradiol) and NGMN (Norelgestromin) over a seven-day period, while oral contraceptives (containing NGM 250 µg / EE 35 µg) are administered on a daily basis. According to the approved label, in general, overall exposure for NGMN and EE (AUC and Css) was higher in subjects treated with Ortho Evra® for both Cycle 1 and Cycle 2, compared to that for the oral contraceptive, while Cmax values were higher in subjects administered the oral contraceptive.

2.2 Data sources

The data were submitted electronically. The data files are located in the following directory:

\\cdsesub1\EVSPROD\ANDA201675\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\edot2-cln-0908\&data

In this review, all tables, unless otherwise specified, are taken from FDA clinical reviewer's report. Analysis results and tables calculated by FDA statistical reviewer are noted as such in the text and/or the title of the tables.

3 STATISTICAL EVALUATION

3.1 Statistical methodologies

Each subject received the test and reference products simultaneously in the skin irritation, sensitization, and adhesion studies. As a result, observations taken from the same subject might be correlated. For the analysis of continuous data, linear mixed models were used; the random effects in the mixed model structure assessed and reflected the correlation of observations. Also for matched pairs dichotomous data, the McNemar, Clopper-Pearson, and, Schuirmann tests were used to compare the test and reference products in the difference between proportions.

3.1.1 Continuous data

<Mixed Model>

The statistical reviewer used a mixed model with treatment (TRT) as a fixed effect and SUBJECT as a random effect to analyze the mean cumulative irritation or adhesion score (primary endpoint).

The statistical method for continuous data uses the estimate of the adjusted mean difference $\mu_T - 1.25\mu_R$, to test the hypotheses

$H_0: \mu_T - 1.25\mu_R > 0$ vs $H_1: \mu_T - 1.25\mu_R \leq 0$

where μ_T is the mean response for the test product and μ_R is the mean response for the reference product. One-sided 95% confidence intervals (CIs) for $\mu_T - 1.25\mu_R$ were obtained based on the estimated means. If the upper limit of the CI is less than or equal to 0, the null hypothesis is rejected and the test product may be considered non-inferior to the reference product. Otherwise it is concluded that the test product may be worse than the reference product.

The SAS® (Version 9.2) PROC MIXED statements for the relevant analysis are

```
Proc Mixed Data = <dataset name>;
Class Subject TRT;
Model X = TRT/DDFM = SATTERTH;
Repeated TRT / sub = Subject type = fa0(2) r;
Estimate 'Test – 1.25*Reference' int -0.25 TRT 1 -1.25/cl alpha = 0.1;
LSMEANS TRT;
Run;
```

3.1.2 Binary data

<Matched pairs dichotomized analysis>

Additional (secondary) endpoints considered were the dichotomized mean cumulative irritation score and irritation score per evaluation day, rate of sensitization, and dichotomized mean of cumulative adhesion score and adhesion score per evaluation day. Methods based on the work of McNemar, Clopper-Pearson, and Schuirmann were used to compare the test and reference products with regard to the binary endpoints (proportions). The McNemar test is a common method for matched pair dichotomized analysis. The Clopper-Pearson method is considered as an "exact" test specifically for small proportions. Schuirmann (2008) examined another method and showed it better preserves type I error for small proportions. The testing procedure was as follows.

For each method used to assess the non-inferiority of the test product to the reference product, a 95% upper confidence bound for the difference of the proportions between test and reference was calculated.

Let
p_T = rate of the test product, p_R = rate of the reference product (p_T and p_R might be irritation rates, sensitization rate, or adhesion rates, depending on the analysis);
n = total number of subjects;

b = number of subjects with a negative outcome (irritation, sensitization or detachment) using the test product but not the reference product;
and c = number of subjects with a negative outcome (irritation, sensitization or detachment) using the reference product but not the test product.

Hypotheses: H_0: $p_T - p_R > \delta$ vs H_1: $p_T - p_R \leq \delta$

Data on two outcomes from matched pairs

		Reference	
		Score≥crit	Score<crit
Test	Score≥crit	a	b
	Score<crit	c	d
Total n=a+b+c+d			

*: Critical value (crit) was used to dichotomize the score.

The difference of $p_T - p_R$ may be estimated by the quantity (b – c)/n.

Based on McNemar's test, the 95% upper confidence bound (U) for the quantity $p_T - p_R$ was calculated as

$$U = \frac{(b-c)}{n} + \frac{1}{n} + 1.645\frac{\sqrt{(b+c) - \frac{(b-c)^2}{n}}}{n}$$

This formula for the upper confidence bound is algebraically the same as that given by Fleiss (1981, p117).

Based on the Clopper-Pearson test (1934), the 95% upper confidence bound (U) for the quantity $p_T - p_R$ was calculated as:

$$U = \left[1 + \frac{n-x}{(x+1)F_{2(x+1),2(n-x),\alpha/2}}\right]^{-1} \qquad \text{if } b \geq c$$

or,

$$U = -\left[1 + \frac{n-x+1}{xF_{2x,2(n-x+1),1-\alpha/2}}\right]^{-1} \qquad \text{if } b < c$$

where x = | b-c | and α=0.10. $F_{2(x+1),\ 2(n-x),\ \alpha/2}$ denotes the (1-α/2) quantile from the F distribution with degrees of freedom 2(x+1) and 2(n-x). $F_{2x,\ 2(n-x+1),\ 1-\alpha/2}$ denotes the α/2 quantile from the F distribution with degrees of freedom 2x and 2(n-x+1).

Based on the Schuirmann (2008) test, the 95% upper confidence bound (U) for the quantity p_T - p_R was calculated as follows.

Let $Z = \dfrac{\hat{\delta} + CC - U}{\sqrt{\dfrac{\xi^* - U^2}{n}}}$,

Here, $\hat{\delta} = \dfrac{b-c}{n}, CC = \dfrac{1}{n}, \xi^* = \max(\dfrac{b+c}{n}, |U|)$.

The value of U is the 95% upper confidence bound for the quantity p_T - p_R when Z is equal to $Z_{\alpha/2}$ = -1.645, α=0.10.

For any given non-inferiority bound δ, the null hypothesis H_0 may be rejected if this 95% upper confidence bound U for the quantity p_T - p_R is less than or equal to δ, that is: $U \leq \delta$. Rejection of the null hypothesis H_0 supports the conclusion of non-inferiority of the test product to the reference product. The non-inferiority standard δ is yet to be decided by OGD.

3.2 Study #EDOT-0908: Evaluation of adhesion, irritation, and sensitization

3.2.1 Study design and endpoints

Objectives

The primary objective of this study was to compare the adhesion, cumulative dermal irritation and contact sensitization of Mylan's Estradiol Transdermal System, USP (Twice-Weekly) (0.025 mg/day) to Vivelle-Dot® (Estradiol Transdermal System) (Novartis; 0.025 mg/day) in 200 healthy post-menopausal female volunteers.

Study design

This was an open-label, multiple-dose, randomized application site, two-treatment, three-phase, one-period, study of the human dermal safety and adhesion of estradiol transdermal systems (TDS) in healthy post-menopausal female volunteers.

The study was conducted at one clinical site and consisted of three phases: an Induction (21 days, 6 applications) phase, a 14-day Rest phase, and a Challenge (5 days, one application) phase. During the induction phase, the transdermal systems were removed at 84 hours ± 2 hours after placement. During the challenge phase, the transdermal systems were removed at 48 hours

± 2 hours after placement.

Irritation Induction period (Study Days 1 to 21)	Rest period (14 days)	Sensitization Challenge period (Study Days 37 to 40)

Subjects received a 0.025 mg/day estradiol transdermal system (Mylan) and a 0.025 mg/day Vivelle- Dot® transdermal system simultaneously applied to a clean, dry area of the skin on the abdomen according to the randomization scheme. Patches were applied for a 3.5-day wear cycle per application with a total of 6 applications during the Induction phase (21 days), followed by a 14-day Rest phase. Following the Rest Phase, one Challenge application of a 0.025 mg/day estradiol transdermal system (Mylan) and a 0.025 mg/day Vivelle Dot® transdermal system was simultaneously applied to a clean, dry area of the skin on the abdomen (naïve site) for a 48-hour period according to the randomization scheme described.

Adhesion evaluation

Adhesion of the estradiol transdermal systems during Induction application 1 was assessed every 24 hours (± 2 hours) and within 1 hour prior to patch removal. Adhesion assessment during Induction applications 2 through 6, and the Challenge application were performed within 1 hour prior to patch removal.

Based on the FDA Draft Guidance on Estradiol, November 2010, the adhesion analysis was carried out based on the four adhesion scores assessed every 24 hours (± 2 hours) and within 1 hour prior to the first patch removal per each patch regardless of the other adhesion scores collected in the study.

Irritation period

The patches were removed 84 hours ± 2 hours after application. The six induction applications (per transdermal system) were done twice weekly for 21 days. The six applications performed during the three-week phase were designated applications 1 – 6 respectively. The appropriate transdermal system was re-applied to the identical site until after the sixth patch application, when patch applications were completed. If a subject developed an edematous reaction or a reaction of 3 or greater, according to the Irritation rating scale, the subject did not have any further transdermal systems applied to that same application site during the Induction phase of the study. In this case, any re-applications for Induction were made at a designated alternate site and were appropriately documented and diagrammed.

On each day the patch was removed, signs and symptoms of localized irritation were evaluated and new patches were applied to the same sites.

Sensitization period

The irritation induction phase was followed by a 14-day rest period and a subsequent 48-hr Challenge phase, which was followed by 3 days of observation and irritation evaluation.

Treatments

A total of two hundred twenty-eight (228) subjects were randomized to receive Mylan's Estradiol Transdermal System, USP (Twice-Weekly) (0.025 mg/day) and Vivelle-Dot® (Estradiol Transdermal System) (Novartis; 0.025 mg/day) simultaneously for the skin adhesion, irritation and sensitization.

A. Estradiol Transdermal System, 0.025mg, Lot No: R6A0028, Mfg Date: August 2009, Mylan Pharmaceuticals, Inc.
B. Vivelle-Dot® transdermal system, 0.025 mg/day, Lot No: 36393, Exp. Date: Oct 2010, Manufactured by: Novartis Pharmaceutical Corporation

Outcome variables

The following scales were used by the sponsor for evaluating adhesion, irritation, and sensitization:

ADHERENCE

System Adherence	
Score	**Definitions**
100	Adhesion: 100%
95	Adhesion: >90% to <100%
85	Adhesion: >80% to 90%
75	Adhesion: >70% to 80%
65	Adhesion: >60% to 70%
55	Adhesion: >50% to 60%
45	Adhesion: >40% to 50%
35	Adhesion: >30% to 40%
25	Adhesion: >20% to 30%
15	Adhesion: >10% to 20%
5	Adhesion: >0% to 10%
0	Adhesion: Fall-off

FDA clinical Reviewer's comments*: The sponsor used a different adhesion scale for assessing adhesion performance than that generally recommended by the OGD. The statistician was asked to evaluate adhesion using the following scale:*

System Adherence	
Score	**Definitions**
0	≥90% adhered (essentially no lift off the skin)
1	≥75% to <90% adhered (some edges only lifting off the skin)
2	≥50% to <75% adhered (less than half of the system lifting off the skin)
3	>0% to <50% adhered but not detached (more than half of the system lifting off the skin without falling off)
4	0% adhered-test system detached (test system completely off the skin)

Based upon FDA's comments, the adhesion score was converted as below.

	Mylan adhesion scale	**Conversion to FDA adhesion scale**
Definition	**Score**	**Score**
Adhesion: 100%	100	0
Adhesion: >90% to <100%	95	0
Adhesion: >80% to 90%	85	1
Adhesion: >70% to 80%	75	1
Adhesion: >60% to 70%	65	2
Adhesion: >50% to 60%	55	2
Adhesion: >40% to 50%	45	3
Adhesion: >30% to 40%	35	3
Adhesion: >20% to 30%	25	3
Adhesion: >10% to 20%	15	3
Adhesion: >0% to 10%	5	3
Adhesion: Fall-off	0	4

IRRITATION AND SENSITIZATION:

Dermal Response**:**

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 test site

Other Effects:

A (0)	Slight glazed appearance
B (1)	Marked glazing appearance
C (2)	Glazing with peeling and cracking
F (3)	Glazing with fissures
G (3)	Film of dried serous exudates covering all or part of the patch site
H (3)	Small petechial erosions and/or scabs

Endpoints

Adhesion

Primary endpoint: Mean cumulative adhesion scores were obtained by adding four observations every 24 hours (± 2 hours) and within 1 hour prior to the first patch removal and dividing by the number of observations (4).

Secondary endpoints: The clinical reviewer requested a comparison of test versus reference with regard to the proportion of patch applications with "meaningful detachment". The analysis was carried out for the dichotomized endpoints defined as mean cumulative adhesion score and by-

visit adhesion scores of ≥ 1, 2, 3, and 4. (Since no adhesion score was greater than 1 until visit 5, these definitions resulted in a total of 7 secondary endpoints.)

Irritation

Primary endpoint: Mean cumulative irritation scores for each test article were obtained by summing and averaging all irritation scores over the induction period.

Secondary endpoint: Proportion of subjects who had mean cumulative irritation scores and by-visit irritation scores of ≥ 1, 2, and 3 (total of 21 secondary endpoints).

Sensitization

Primary endpoint: For each treatment, the proportion of subjects showing a potential sensitizing reaction according to the sensitization definition provided by the clinical reviewer, which was based on the FDA Draft Guidance on Estradiol**,** November 2010.

3.2.2 Patient disposition

Study population

A total of two hundred and twenty-eight (228) healthy postmenopausal female volunteers were enrolled in this study. Each subject received both study treatments simultaneously during the study.

Two hundred and twenty-eight (228) subjects were included in the FDA's and Sponsor's Adhesion Per Protocol (ADHPP) population.

Two hundred and thirteen (213) subjects were included in the FDA's and Sponsor's Irritation Per Protocol (IRRPP) population. Fifteen (15) subjects were excluded from the IRRPPP due to protocol deviation (11) and non-completion (4).

Two hundred and twenty-two (222) subjects were included in the FDA's and Sponsor's Sensitization Per Protocol (SENPP) population. Six (6) subjects were excluded from the SENPP due to protocol deviation (1) and non-completion (5).

FDA clinical reviewer's comments*: "Although it is expected that the "evaluable" irritation population is greater than the "evaluable" sensitization population, those that were excluded from the irritation population were mostly due to not having scores evaluated at the acceptable visit window hours. These subjects still completed the whole induction period, and were thus included in the sensitization population."* Eleven (11) subjects were excluded from the IRRPP, but included in the SENPP. (These subjects were SUBJID = 9, 25, 30, 35, 43, 68, 73, 83, 118, 123, and 137.)

Demographics

Table 1 shows the distribution of age and race for the ADHPP, IRRPP, and SENPP populations.

Table 1: Demographic characteristics (ADHPP, IRRPP, SENPP)

	ADHPP (N=228)	IRRPP (N=213)	SENPP (N=222)
Age (years)			
Mean (Range)	55.1 (44-69)	55.0 (44-69)	55.1 (44-69)
Race			
White Asian	226 (99.1%) 2 (0.9%)	212 (99.5%) 1 (0.5%)	221 (99.6%) 1 (0.5%)

3.2.3 Results and conclusions

3.2.3.1 Sponsor's analysis results

In this section, all of the comments and tables for adhesion and irritation analysis, unless otherwise specified, are taken from Mylan's amendment submitted on September 10, 2010.

Adhesion

The sponsor noted and tabled in their amendment:

> "As noted in the previous discussion of cumulative irritation, FDA's recommended scale indicates that better-performing scores would trend toward zero. Mean adhesion data in this study was based on the mean of 4 adhesion evaluations performed during the first patch application period for each subject in EDOT-0908. For comparative purposes, Mylan's raw adhesion data was transformed according to FDA's scale … and the associated frequency table was generated ... Datasets were then evaluated according to the appropriate statistical test, recommended by FDA versus the modification proposed by Mylan."

Assessment of Mean Adhesion Scores, Based on FDA Recommended Scale, and Analyzed According to Mylan and FDA Statistical Models*

Method	Parameter	Upper 95% CI	Criteria	Pass /Fail
FDA	Test - 1.25*Ref	0.016	<0	Fail
Mylan	Test - Ref	0.020	<0.25	Pass

[*: This table is "Table 12" in Mylan's amendment.]

> "Mylan has thus re-assessed the adhesion data according to the Agency recommendation, which further illustrates the impact of scaling, analogous to the issue of scaling for irritation. The difference with irritation is that it is not a continual scale that can be easily evaluated, and where there is a clinically acknowledged cut-off at which a subject would achieve a meaningful irritation response. In the case of adhesion, the preponderance of scores for both treatments over the first application period trend toward zero in this reanalysis, per FDA recommendation, which makes comparison of mean results by the FDA-recommended analysis overly sensitive to very minor differences.
>
> In either case, it is noteworthy that both products have very good adhesion profiles. Therefore, in the case of adhesion results, Mylan contends that adhesion scoring is directly amenable to a scale of 0 (detachment) to 100 (fully adhered) and the previously submitted analysis allows for

a more-appropriate comparison. To further illustrate the problematic nature of FDA's recommended criteria, additional Bootstrap Simulations were performed in a similar manner as conducted for the cumulative irritation evaluation."

Irritation

The sponsor noted and tabled in their amendment:

Summary of Irritation Scores of 3 or Higher, by subject (213 total), based on Sum of Dermal Response and Other Effects Scores*

		Test - Mylan	
		< 3	≥ 3
Reference – Vivelle Dot®	< 3	208	2
	≥ 3	0	3

[*: This table is "Table 5B" in Mylan's amendment.]

"Individual subjects observed in the study with scores ≥ 3, evaluated as a summed score of dermal response and other effects score, are 5 for Test versus 3 for Reference. … In this case, the data is thus amenable to more standard clinical endpoint types of analyses, such as a modified-Wald analysis, which has been proposed for certain topical evaluations such as recommended for fluorouracil cream or estradiol vaginal tablets. … The conclusion drawn is that there are no differences in population proportions identified as clinically meaningful irritation responders for Test and Reference."

Assessment of Mean Cumulative Irritation Scores based upon Mylan and FDA Statistical Models for EDOT-0908*

Method	Parameter	Upper 95% CI	Criteria	Pass /Fail
FDA	Test – 1.25*Ref	0.050	< 0	Fail
Mylan	Test – Ref	0.082	< 0.25	Pass

[*: This table is "Table 6" in Mylan's amendment.]

"Mylan provides an analysis of the one-sided 95% CI for the mean cumulative irritation scores, based on the sum of the dermal response and other effects scores and evaluated as Test - 1.25*Reference < 0 (Table 6, FDA method). For comparison, Mylan also provides an analysis of one-sided 95% CI for mean cumulative irritation scores, based on the sum of the dermal responses and other scores and evaluated as Test –Reference < 0.25 (Table 6, Mylan method). … Mylan contends that the Agency's recommended statistical analysis is overly sensitive for the evaluation of non-inferiority of non-irritating patches, as observed in Study EDOT-0908. This was realized during the initial review and analysis of the data per statistical plan, and thus the method modification proposed by Mylan was provided as a more appropriate metric for such data."

Sensitization

The sponsor noted in their amendment:

"None of the subjects were considered to be potentially sensitized to either product. The scores for the test and reference products were similar during the challenge phase."

No analysis was performed by the sponsor.

3.2.3.2 Reviewer's results

Adhesion

The analysis is based on the 228 subjects in the Adhesion Per Protocol population (ADHPP).

The frequency of cumulative adhesion scores per each patch at each visit is shown in Table 2.

Table 2: Frequency of adhesion scores (ADHPP)

Visit	Treatment	Adhesion score				
		0	1	2	3	4
2	Test	228	0	0	0	0
	Reference	228	0	0	0	0
3	Test	227	1	0	0	0
	Reference	228	0	0	0	0
4	Test	224	4	0	0	0
	Reference	227	1	0	0	0
5	Test	219	5	0	1	3
	Reference	218	6	1	1	2

Primary endpoint: Mean cumulative adhesion score

The frequency of mean cumulative adhesion scores per each patch is shown in Table 3. The mean cumulative adhesion scores were analyzed using a mixed model and the results are presented in Table 4.

Table 3: Frequency of mean cumulative adhesion scores (ADHPP)

Mean	0	0.25	0.5	0.75	1	1.25	1.5
Test	219	4	1	0	2	1	1
Reference	218	6	1	1	1	1	0

Table 4: Analysis for the mean cumulative adhesion scores using mixed model (ADHPP)

Test (Ls mean)	Reference (Ls mean)	Upper limit one-sided 95%CB (test-1.25ref)	Pass the Non-inferiority test
0.027	0.022	0.015	No

Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was greater than zero (0.015) and the non-inferiority test was failed for test versus reference patch. Therefore, the adhesion potential of the test product is worse than that of the reference product.

Secondary endpoint: Dichotomized adhesion scores

Table 5: Analysis of the dichotomized adhesion score (ADHPP)

Critical value (crit)	Score ≥crit for Test & not for Reference	Score ≥crit for Reference & not for Test	$P_T - P_R$*	95% Upper Bound# for $P_T - P_R$		
				McNemar	Clopper	Schuirmann
Crit = 1						
Mean	3	1	0.009	0.028	0.027	**0.032**
Visit 3	1	0	0.004	0.016	0.021	**0.026**
Visit 4	3	0	0.013	0.030	0.034	**0.039**
Visit 5	6	7	-0.004	0.026	-0.000	**0.026**
Crit = 2						
Visit 5	1	1	0.000	0.015	0.013	**0.019**
Crit = 3						
Visit 5	2	1	0.004	0.021	0.021	**0.026**
Crit = 4						
Visit 5	2	1	0.004	0.021	0.021	**0.026**

*: p_T=P (mean cumulative/daily adhesion score greater than or equal to crit for test), and p_R=P (mean cumulative/daily adhesion score greater than or equal to crit for reference).
#: The highest upper bound is marked in bold.

In addition to the primary endpoint analyses, analyses for the secondary endpoints as defined above were conducted to compare the test and reference products.

Based on the 95% upper confidence bound for the difference in proportions, the test product might exceed the reference product by at most 3.2 percentage points with regard to the proportion of subjects who had mean cumulative adhesion scores greater than or equal to 1. For by-visit scores, the test product might exceed the reference product by at most 3.9 percentage points with regard to the proportion of subjects who had the adhesion scores greater than or equal to 1 at visit 4.

Irritation

The analysis is based on the 213 subjects in the Irritation Per Protocol population (IRRPP).

Primary endpoint: Mean Cumulative Irritation scores

Table 6 presents the frequency of irritation and other effects scores for each treatment on each visit. Table 7 presents the frequency of maximum irritation scores per subject. The frequency of mean cumulative irritation scores per each patch application is shown in Table 8.

Table 6: Frequency of irritation and other effects scores (IRRPP)

	Test							Reference						
Visit	Irritation score					Other effect		Irritation score					Other effect	
	0	1	2	3	7	C	H	0	1	2	3	7	C	H
5	200	8	5	0	0	0	0	198	15	0	0	0	0	0
6	193	18	2	0	0	0	0	195	16	2	0	0	0	0
7	190	16	7	0	0	0	0	187	25	1	0	0	0	0
8	192	12	5	3	1	1	3	190	18	5	0	0	2	0
9	178	21	10	3	1	1	3	167	38	8	0	0	2	0
10	184	21	4	3	1	1	4	184	22	6	1	0	1	0

Table 7: Frequency of the maximum irritation score per subject (IRRPP)

Maximum irritation score	0	1	2	3	4	5	6	10
Test	144	42	22	0	0	2	2	1
Reference	130	69	11	1	2	0	0	0

Table 8: Frequency of the mean cumulative irritation scores per subject (IRRPP)

Mean cumulate score	0	0.17	0.33	0.5	0.67	0.83	1	1.17	1.67	1.83	2	3	3.17	5.67
Test	144	28	15	9	5	3	1	3	1	0	0	2	1	1
Reference	130	40	20	8	7	3	0	3	0	1	1	0	0	0

Table 9: Analysis for the mean cumulative irritation scores using mixed model (IRRPP)

Test (LS mean μ_T)	Reference (LS mean μ_R)	Upper limit one-sided 95% CB ($\mu_T - 1.25\mu_R$)	Pass the Non-inferiority test
0.1925	0.1495	0.047	No

Non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was greater than zero (0.047) and the non-inferiority test was failed for test versus reference patch. Therefore, the irritation potential of the test product is worse than that of the reference product.

Secondary endpoints: dichotomized variables

Secondary endpoints examined consisted of dichotomized mean cumulative irritation scores and dichotomized irritation scores per visit. Analyses of these endpoints are discussed below.

Dichotomized Mean Cumulative Irritation Scores

In addition to the primary endpoint analyses, analyses for the secondary endpoints were conducted to compare the test and reference products with regard to the proportion of subjects who had mean cumulative irritation score greater than or equal to 1, to 2, and, to 3. Based on the 95% upper confidence bound for the difference in proportions, the test product might exceed the reference product by at most 4.7, 4.1, and 4.7 percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1, to 2, and, to 3, respectively.

Table 10: Analysis of the dichotomized mean cumulative irritation score (IRRPP)

Critical value (crit)	Score ≥crit for Test & not for Reference	Score ≥crit for Reference & not for Test	$P_T - P_R$*	95% Upper Bound# for $P_T - P_R$		
				McNemar	Clopper	Schuirmann
1	4	0	0.019	0.039	0.042	**0.047**
2	3	0	0.014	0.032	0.036	**0.041**
3	4	0	0.019	0.039	0.042	**0.047**

*: p_T=P (mean cumulative irritation score greater than or equal to crit for test), and p_R=P (mean cumulative irritation score greater than or equal to crit for reference).
#: The highest upper bound is marked in bold.

Dichotomized Irritation Scores per Visit

Similarly, the test and reference patches were compared with regard to the proportion of patch applications with irritation scores greater than or equal to 1, to 2, and, to 3 for each visit (Table 11). The test product might exceed the reference product by at most 3.9 percentage points for critical value 1 (visit 10), at most 6.0 percentage points for critical value 2 (visit 7), and at most 4.1 percentage points for critical value 3 (visit 10).

Table 11: Analysis of the dichotomized irritation score for each visit (IRRPP)

Critical value (crit) Visit	Score ≥ crit for Test & not for Reference	Score ≥ crit for Reference & not for Test	$P_T - P_R$ *	95% Upper Bound# for $P_T - P_R$		
Crit=1				McNemar	Clopper	Schuirmann
5	6	8	-0.009	**0.024 (0.02418)**	-0.002	0.024 (0.0241)
6	6	4	0.009	**0.038 (0.038484)**	0.029	0.038 (0.0381)
7	8	11	-0.014	**0.024 (0.024237)**	-0.004	0.024 (0.0242)
8	6	8	-0.009	**0.024 (0.02418)**	-0.002	0.024 (0.0241)
9	5	16	-0.052	-0.012	-0.029	**-0.011**
10	10	10	0.000	**0.039 (0.039233)**	0.014	0.039 (0.0389)
Crit=2						
5	5	0	0.023	0.045	0.049	**0.054**
6	2	2	0.000	0.020	0.014	**0.021**
7	6	0	0.028	0.052	0.055	**0.060**
8	4	0	0.019	0.039	0.042	**0.047**
9	6	1	0.023	0.048	0.049	**0.054**
10	1	0	0.005	0.017	0.022	**0.028**
Crit=3						
5	0	0	0.000	0.005	0.014	**0.021**
6	0	0	0.000	0.005	0.014	**0.021**
7	0	0	0.000	0.005	0.014	**0.021**
8	2	0	0.009	0.025	0.029	**0.035**
9	2	0	0.009	0.025	0.029	**0.035**
10	3	0	0.014	0.032	0.036	**0.041**

*: p_T=P (irritation score greater than or equal to crit for test), and p_R=P (irritation score greater than or equal to crit for reference).
#: The highest upper bound is marked in boldface. For certain cases, the precise value is given in parentheses below the listed CB.

Sensitization

The analysis is based on the 222 subjects in the Sensitization Per Protocol population (SENPP).

None of the subjects were considered to be potentially sensitized to either product. The irritation scores in the challenge phase were zero for test and reference products per each visit.

Table 12 presents the 95% upper confidence bounds for the difference of the test versus reference of the proportion of potentially sensitized subjects based on the Sensitization Per-

Protocol population. The test might exceed the reference by at most 1.9 percentage points based on the 95% upper confidence bound for the difference in sensitization rates.

Table 12: Analysis of the proportions of subjects with potentially sensitization (SNSPP)

Test potentially sensitized and reference not potentially sensitized (P_T)	Test not potentially sensitized and reference potentially sensitized (P_R)	Total N	$P_T - P_R$*	95% Upper Bound# for $P_T - P_R$		
				McNemar	Clopper	Schuirmann
0	0	222	0	0.005	0.013	**0.019**

*: p_T=P (Test potentially sensitized and reference not potentially sensitized), and p_R=P (Test not potentially sensitized and reference potentially sensitized).
#: The highest upper bound is marked in bold.

4 SUMMMARY AND CONCLUSIONS

4.1 Statistical Issues and Findings

Adhesion

Primary endpoint: Mean cumulative adhesion scores
The 95% upper confidence bound (0.015) based on the mixed linear model was greater than zero. The test product was found to be inferior to the reference.

Secondary endpoints: Dichotomized adhesion scores
Based on the 95% upper confidence bound for the difference in proportions, the test product might exceed the reference product by at most 3.2 percentage points with regard to the proportion of subjects who had mean cumulative adhesion scores greater than or equal to 10% detached (score≥1). For by-visit scores, the test product might exceed the reference product by at most 3.9 percentage points with regard to the proportion of subjects who had the adhesion scores greater than or equal to 10% detached (score≥1) (at visit 4).

Irritation

Primary endpoint: Mean cumulative irritation scores
Non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was greater than zero (0.047). The non-inferiority test was failed for test patch versus reference patch and the irritation potential of the test patch product is considered worse than that of the reference patch product.

Secondary endpoints: dichotomized irritation scores
Dichotomized endpoints for mean cumulative irritation scores were considered for the secondary analyses. Based on the 95% upper confidence bound for the difference in proportions, the test product might exceed the reference product by at most 4.7, 4.1, and 4.7 percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1, to 2, and, to 3, respectively.

The test and reference patches were compared with regard to the proportion of patch applications with irritation scores greater than or equal to 1, to 2, and, to 3 for each visit. The test product might exceed the reference product by at most 3.9 percentage points for critical value = 1, at most 6.0 percentage points for critical value = 2, and at most 4.1 percentage points for critical value = 3.

Sensitization

No subject was identified to be potentially sensitized to test and reference.

The test might exceed the reference by at most 1.9 percentage points based on the 95% upper confidence bound for the difference in sensitization rates.

Main difference between sponsor's results and our results

The sponsor found the test patch to be equivalent to the reference on all three aspects examined, while the FDA found the test patch to be inferior with respect to adhesion and irritation.

Where the sponsor's results differ from our own results, mainly it is due to two reasons.

a) Different statistical analysis method for continuous data – irritation and adhesion scores:
Mylan provides an analysis of the one-sided 95% CI for the mean cumulative irritation scores and adhesion scores evaluated as Test - 1.25*Reference < 0 based on FDA request. For comparison, Mylan also provides an analysis of one-sided 95% CI for mean cumulative irritation scores and adhesion scores evaluated as Test –Reference < 0.25. Mylan insists the test patch is non-inferior to the reference patch for irritation and adhesion based on their non-inferiority difference test. They also claim that FDA's non-inferiority ratio test is overly sensitive when the irritation and adhesion scores are low, as they are in this ANDA.

b) Different adhesion scoring:
Per protocol, Mylan specified a 100-point scale in the protocol for EDOT-0908, which is directly related to degree of adhesion (i.e. 100 relates to complete adhesion, while 0 denotes detachment). As such, the sponsor's test was based on Test – 0.8*Reference.

4.2 Conclusions

For adhesion and irritation, the test product was found to be, in general, inferior to the reference product based on mixed model analysis. However, the upper confidence bounds for the difference in proportions of test *versus* reference, based on binary analysis, were low, with the test exceeding the reference by no more than 6 percentage points in all cases.

None of the subjects were considered to be potentially sensitized to either product. The test might exceed the reference by at most 1.9 percentage points based on the 95% upper confidence bound for the difference in sensitization rates.

Given the results, the clinical decision should be made using medical judgment as well as statistics.

_____
Huaixiang Li, Ph.D.
Mathematical Statistician, DB6/OB

_____
Stella Grosser, Ph.D
Statistical Team Leader, DB6/OB

_____
Stella G. Machado, Ph.D.
Director, DB6/OB
cc:
HFD-600 John R Peter, Nicole Lee, Nitin K Patel
HFD-705 Stella G. Machado, Stella Grosser, Huaixiang Li
HFD-700 Lillian Patrician OB

5 REFERENCES

Joseph L. Fleiss, Bruce Levin, and MyungHee Cho Paik. (1981). Statistical Methods for Rates and Proportions (2nd edition). New York: Wiley-Interscience.

McNemar, Q. (1947) Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika, 12, 153-157.

Schuirmann, D. J. (2008) One-Sided Tests and Confidence Bounds for the Difference between Probabilities for Matched Pairs Dichotomous Data. Presented at the Spring Meetings of the Eastern North American Region (ENAR) of the International Biometric Society, March 17, 2008 in Crystal City, VA.

Clopper, C. and Pearson, S. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413.

Peter J. Diggle, Kung-Yee Liang, and Scott L. Zeger (1994). Analysis of Longitudial Data. Oxford Science Publications.

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/s/

HUAIXIANG LI
10/22/2012

STELLA C GROSSER
10/22/2012

STELLA G MACHADO
10/22/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201675Orig1s000

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER'S CLINICAL SITE SELECTION REVIEW FOR OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) INSPECTION

ANDA#	201675
Product	Estradiol Transdermal System 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day
Sponsor	Mylan Technologies Inc.
Submission Date	8/19/2014
DCR ANDA Reviewer	Sarah H. Seung, Pharm.D.
Inspection Requestor	Eunjung (Esther) Chuh, Pharm.D. Medical Affairs Coordinator Division of Clinical Review (DCR) Office of Generic Drugs
Date of Review	9/22/2014
Approving Official	Lesley-Anne Furlong, M.D. Director (Acting), Division of Clinical Review Office of Generic Drugs

One clinical study was submitted to compare the irritation potential.

Study Number and Title	EDOT-14030 Comparative Evaluation of the Cumulative Irritation of Estradiol Transdermal System (0.025 mg/day; Mylan) and Vivelle-Dot® Transdermal System (0.025 mg/day; Noven) in Healthy Post-Menopausal Women
Study Period	6/9/2014 – 7/20/2014
Total Number of Subjects Enrolled	120 subjects
Principal Investigators	John V. Murray, M.D. Hill Top Research 4711 34th Street North Saint Petersburg, FL 33714, USA Tel: 727-334-7602

PRINCIPAL INVESTIGATOR	NO INSPECTION HISTORY	LAST INSPECTION VAI & > 5YR	HAS PRIOR INSPECTION HISTORY	DATA UNACCEPTABLE IN PRIOR INSPECTION
John V. Murray, M.D.			NAI on 6/13/2012 at different street address (6699 13th Avenue North) under ANDA 77775/S-007	

RECOMMENDATION:

The following clinical investigator has prior inspectional history, therefore OSI inspection will not be requested at this time.

Principal Investigator	Number of Subjects Enrolled
John V. Murray, M.D. Hill Top Research 4711 34th Street North Saint Petersburg, FL 33714, USA	120

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/s/

EUNJUNG E CHUH
09/23/2014

NITIN K PATEL
09/23/2014
ON BEHALF OF LESLEYANNE FURLONG

M E M O R A N D U M

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

DATE: May 02, 2013

TO: John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs

FROM: Ruben C. Ayala, Pharm.D.
Jyoti B. Patel, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering ANDA 201-675, Estradiol Transdermal System USP, sponsored by Mylan Technologies, Inc., Morgantown, WV

At the request of the Division of Clinical Review, the Division of Bioequivalence and GLP Compliance (DBGC) audited the clinical portion of the following study:

Study Number: EDOT-0908
Study Title: "Comparative evaluation of the adhesion, cumulative irritation and contact sensitization potential of Mylan's estradiol transdermal system, USP (twice weekly) (0.025 mg/day) to Vivelle-Dot™ (estradiol transdermal system) (Novartis; 0.025 mg/day) in healthy post-menopausal women"

The objectives of the study were to compare the adhesion, cumulative dermal irritation, and contact sensitization of Mylan's estradiol transdermal system USP (test) to Vivelle-Dot

estradiol transdermal system (reference) in healthy post-menopausal female volunteers. Two hundred and twenty eight (228) subjects were enrolled and 221 completed the study.

Nathan R. Moon, ORA investigator from the Denver District Office, conducted the inspection of the clinical site at The Federal State Enterprise "Scientific Research Center for Preventive Medicine of Federal Agency of High Technology Medical Care" in Moscow, Russia from 02/25/2013 to 03/01/2013. The inspection covered review of business organization, audit of study records including consent of human subjects, conduct of the clinical study, study data, a tour of the facility, and discussions with the site's management and staff.

Following the inspection at the clinical site, no significant objectionable conditions were observed and Form FDA 483 was not issued.

Conclusions:

Following the review of the inspectional report, **the DBGLPC reviewers recommend that the data for clinical portion of study EDOT-0908 be accepted for further agency review.**

Ruben C. Ayala, Pharm.D.
Jyoti B. Patel, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classification:

NAI: The Federal State Enterprise "Scientific Research Center for Preventive Medicine of Federal Agency of High Technology Medical Care" Moscow, Russia.
FEI: 3010022496

CC:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Skelly/Dejernett/Ayala/Patel
OGD/DCR/Peters/Patel
ORA/SW-FO/DEN-DO/Sykes/Moon
Draft: RCA 05/02/2013
Edit: JBP 05/02/2013
Edit: MFS 5/2/13
File: BE6183; O:\BE\EIRCOVER\201675.myl.est.doc
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/s/

RUBEN C AYALA
05/02/2013

WILLIAM H TAYLOR
05/06/2013

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
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**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 201675 **FIRM NAME**: MYLAN TECHNOLOGIES

PIV: YES **Electronic or Paper Submission:** ELECTRONIC (GATEWAY)

RELATED APPLICATION(S): SEE (b) (4)

MYLAN TECHNOLOGIES RFR 5/18/09 (RLD VIVELLE DOT)

First Generic Product Received? NO

DRUG NAME: ESTRADIOL
DOSAGE FORM: TRANSDERMAL SYSTEM USP, 0.25 MG/DAY, 0.0375 MG/DAY, 0.05 MG/DAY, 0.075 MG/DAY AND 0.1 MG/DAY

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC1 Team 14 ☒ ***Activity***	***Bio Team 10: April Braddy*** ☒ ***Activity***
ANDA/Quality RPM: Ben Danso ☒ ***FYI***	Bio PM: Diana Solana ☐ ***FYI***
Quality Team Leader: Bykadi, Raj No assignment needed in DARRTS	***Clinical Endpoint Team Assignment:*** ☒ ***Activity***
Labeling Reviewer: Ruby Wu ☒ ***Activity***	***Micro Review (No)*** ☐ ***Activity***

*****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). *****

Letter Date: APRIL 26, 2010 **Received Date**: APRIL 27, 2010

Comments: EC - 5 YES **On Cards:** YES
Therapeutic Code: 3011000 ESTROGENS

Archival copy: ELECTRONIC (GATEWAY) **Sections** I
Review copy: NA E-Media Disposition: NA
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

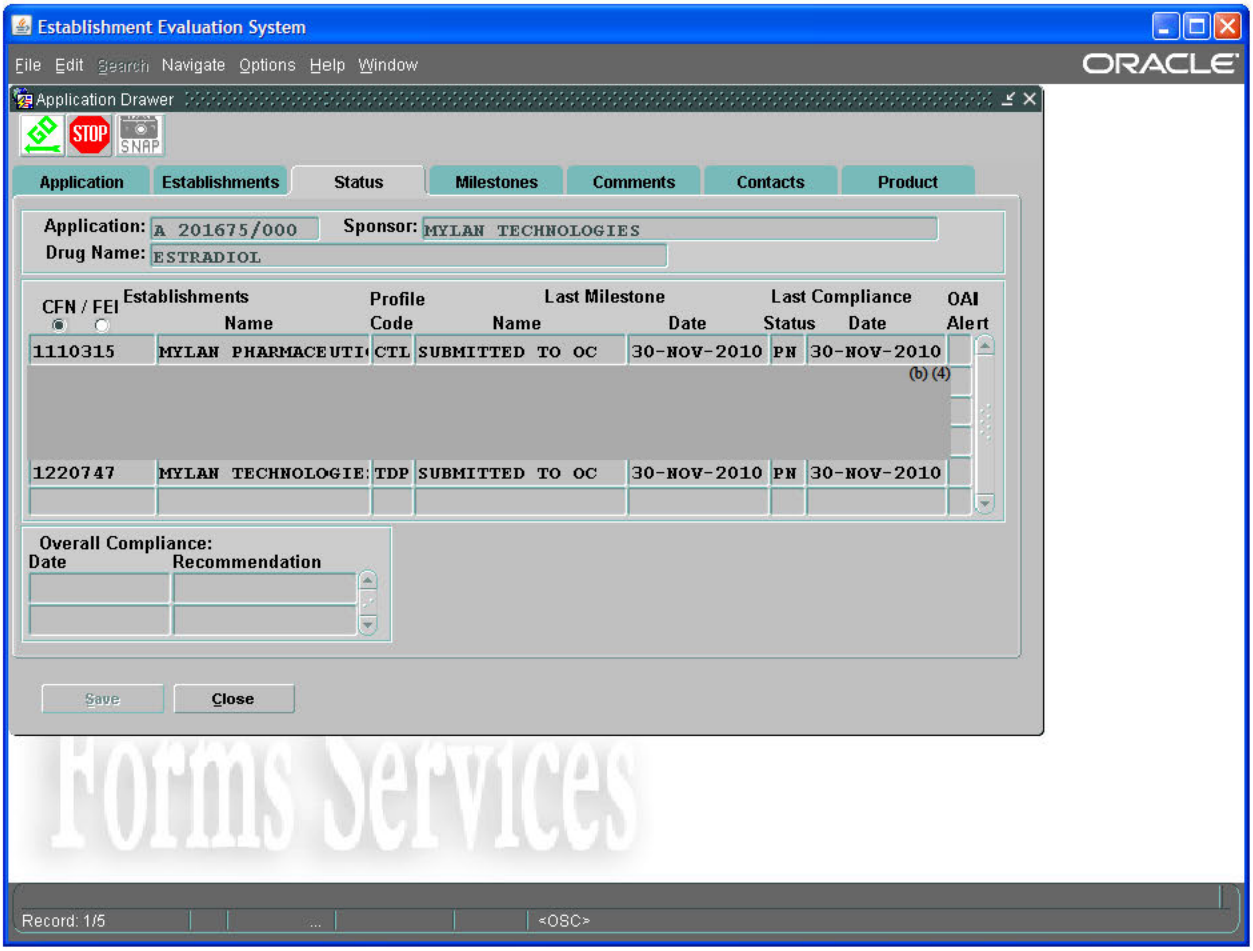
Reviewing CSO/CST Ted Palat Date 11/30/2010	Recommendation: ☒ FILE ☐ REFUSE to RECEIVE

Supervisory Concurrence/Date: _____ **Date:** _____

1. Edit Application Property Type in DARRTS where applicable for
   a. First Generic Received
      ☐ Yes ☒ No
   b. Market Availability
      ☒ Rx ☐ OTC
   c. Pepfar
      ☐ Yes ☒ No
   d. Product Type
      ☐ Small Molecule Drug (usually for most ANDAs except protein drug products)
   e. USP Drug Product (at time of filing review)
      ☒ Yes ☐ No
2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☒ Yes
4. Requested EER
   ☒ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA: 304-599-2595 Wayne Talton
1. failed clinical filing review.
2.

Firm responded to our RTR letter on 09/10/2010. Response is AC for filing per clinical group. Mylan requests their original filing date. Original dated granted. The original submission contained all appropriate data but did not provide the appropriate statistical analysis. As the application contained all the appropriate data it was substantially complete and will be granted the original filing date.



Reference ID: 2882177

AMENDMENT
CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# 201675_____ **FIRM NAME**_Mylan Technologies Inc. _____

DRUG NAME _Estradiol Transdermal System, USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day_____

DOSAGE FORM __Transdermal System_____

REFERENCE LISTED DRUG (RLD)__Vivelle-Dot® (estradiol transdermal system), NDA 020538_____

Requested by: __Eda Howard_____ Date: _9/16/10_____
Regulatory Support Team, (HFD-615)

	Summary of Findings by Clinical Review Team
X	**Study meets statutory requirements** **Please see Comments to be conveyed to the sponsor for details.**
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: _X__COMPLETE __INCOMPLETE

Reviewed by:

_____ Date: _____
Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

_____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

BIOEQUIVALENCE CHECKLIST
FOR APPLICATION COMPLETENESS

ANDA# 201675 **FIRM NAME** **Mylan Technologies Inc.**

DRUG NAME Estradiol

DOSAGE FORM Film, extended release - Transdermal; 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

SUBJ: Request for examination of the bioequivalence study submitted with an ANDA 201675 for Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv)

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason: NOTE: The adhesion, skin irritation and sensitization study should be reviewed for completeness by the OGD Clinical Team. Only the BE study with pharmacokinetic (PK) endpoints is reviewed by the Division of Bioequivalence in the current checklist.
☒	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Vipra Kundoor, Ph.D.
Reviewer

_____ Date: _____
April C. Braddy, Ph.D.
Team Leader

BIO_1G_CHKLST.dot v.4/4/2003

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) YES	☒
1.2	**Cover Letter** Dated: APRIL 26, 2010	☒

1.2.1	**Form FDA 3674 (PDF) YES**	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES SEE SECTION 1.3.3 2. List of Convictions statement (original signature) SAME	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES SEE SECTION 1.3.3, form 3454 Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) PIV – '286 and '976, PIII – '783 and '446 **Patent and Exclusivity Search Results from query on Appl No 020538 Product 005 in the OB_Rx list.**	☒

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020538	005	5474783	Dec 12, 2012				
N020538	005	5656286	Aug 12, 2014				
N020538	005	5958446	Dec 12, 2012				
N020538	005	6024976	Jan 7, 2014				

There is no unexpired exclusivity for this product.

2. Paragraph: (Check all certifications that apply)
   MOU ☐ PI ☐ PII ☐ PIII ☒
   PIV ☒ (Statement of Notification) ☒
3. Expiration of Patent(s): 1/7/2014
   a. Pediatric exclusivity submitted?
   b. Expiration of Pediatric Exclusivity?
4. Exclusivity Statement: YES no exclusivity

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES Type II DMF No. (b) (4) b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA	☒

1.12.11	**Basis for Submission OK** NDA# : 20-538 Ref Listed Drug: VIVELLE DOT Firm: NOVARTIS ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES SEE SECTION 1.12.14	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): YES ON 0.025 MG/DAY, 0.0375 MG/DAY, 0.050 MG/DAY AND 0.075 MG/DAY SEE SECTION 1.12.15	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** YES **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** YES **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation YES Table 6. Formulation Data YES **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution YES **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies YES Table 3. Statistical Summary of the Comparative BA Data YES **2.7.1.4 Appendix** YES **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study YES **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies YES	☒

8 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) **2.3.P.3 Manufacture (Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, 0.1 mg/day (Twice-Weekly))** **Who manufactures the drug product?** Manufacturing, Packaging, Labeling, Quality Control Testing of components, Testing of Finished Dosage Form: **Name and Address** / **Responsibilities** Mylan Technologies 110 Lake Street St. Albans, VT 05478 Manufacturing, Packaging, Labeling, Quality Control Testing of Components and Finished Dosage Form. A cGMP certification letter is provided in Section 3.2.P.3.1. (b) (4) [redacted] 2. CGMP Certification: YES SEE SECTION 3.2.P.3.1 3. Function or Responsibility YES 4. CFN or FEI numbers YES **3.2.P.3.2 Batch Formula** YES **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (b) (4) [redacted] with equipment specified YES (b) (4) [redacted] 3. If sterile product: Aseptic fill / Terminal sterilization NA 4. Reprocessing Statement YES **3.2.P.3.4 Controls of Critical Steps and Intermediates** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation NA 2. Filter validation (if aseptic fill) NA	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA YES	☒

MODULE 3
3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** YES **3.2.P.5.2 Analytical Procedures** YES **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers R6A0028, 30, 36, 37, 38 **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **3.2.P.5.5 Characterization of Impurities** **3.2.P.5.6 Justification of Specifications**	☒

3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes **HOW SUPPLIED: Estradiol Transdermal System USP, 0.025 mg/day (Twice-Weekly) -** each 2.5 cm^2 system contains 0.41 mg of estradiol, USP for nominal* delivery of 0.025 mg of estradiol per day. Patient Calendar Pack of 8 Systems.....NDC 0378-4644-26 **Estradiol Transdermal System USP, 0.0375 mg/day (Twice-Weekly) -** each 3.75 cm^2 system contains 0.62 mg of estradiol, USP for nominal* delivery of 0.0375 mg of estradiol per day. Patient Calendar Pack of 8 Systems .....NDC 0378-4643-26 **Estradiol Transdermal System USP, 0.05 mg/day (Twice-Weekly) -** each 5.0 cm^2 system contains 0.82 mg of estradiol, USP for nominal* delivery of 0.05 mg of estradiol per day. Patient Calendar Pack of 8 Systems .....NDC 0378-4642-26 **Estradiol Transdermal System USP, 0.075 mg/day (Twice-Weekly) -** each 7.5 cm^2 system contains 1.23 mg of estradiol, USP for nominal* delivery of 0.075 mg of estradiol per day. Patient Calendar Pack of 8 Systems…….....NDC 0378-4641-26 **Estradiol Transdermal System USP, 0.1 mg/day (Twice-Weekly) -** each 10.0 cm^2 system contains 1.64 mg of estradiol, USP for nominal* delivery of 0.1 mg of estradiol per day. Patient Calendar Pack of 8 Systems.....NDC 0378-4640-26 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period 24 months **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data YESYES 2. Batch numbers on stability records the same as the test batch **YES**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available) NO** **3.2.R.2.S Comparability Protocols NO** **3.2.R.3.S Methods Validation Package YES** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation YES **Yield and Reconciliation of the Packaging Process for the Exhibit Lots** (b) (4) [redacted] **3.2.R.1.P.2 Information on Components** YES **3.2.R.2.P Comparability Protocols** NO **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒

5.3.1 (complete study data)

Bioavailability/Bioequivalence

1. Formulation data same? ☒

a. Comparison of all Strengths (check proportionality of multiple strengths)

Composition and Pharmaceutical Function of Adhesive Matrix Components of Mylan's Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice-Weekly)

Components	Pharmaceutical Function	% w/w	mg per system				
			0.025 mg/ day	0.0375 mg/ day	0.05 mg/ day	0.075 mg/ day	0.1 mg/ day
Active Ingredient							
Estradiol (b) (4) USP,	Active Ingredient	(b) (4)	0.41	0.62	0.82	1.23	1.64
Inactive Ingredients							
Oleyl Alcohol, (b) (4) (b) (4)							
Dipropylene Glycol (b) (4)							
Povidone (b) (4) (b) (4)							
Silicone Adhesive (b) (4)	Adhesive						
Acrylic Adhesive (b) (4)	Adhesive						
(b) (4)							
Theoretical Total Matrix[5]							
Components of the Delivery and Packaging System							
Polyolefin Film (b) (4)	Backing						
Brown Ink (b) (4)	Imprinting Ink						
(b) (4) Polyester Film (b) (4)	Oversized Release Liner						

b. Parenterals, Ophthalmics, Otics and Topicals

per 21 CFR 314.94 (a)(9)(iii)-(v) NA

2. Lot Numbers of Products used in BE Study(ies): ANDA: R6A0030, RLD: 38967

3. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)

5.3.1.2 Comparative BA/BE Study Reports ☒

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)

ESTRADIOL TRANSDERMAL SYSTEM, USP (TWICE-WEEKLY)

0.025 MG/DAY, 0.0375 MG/DAY, 0.05 MG/DAY, 0.075 MG/DAY AND 0.1 MG/DAY

ESTRADIOL TRANSDERMAL SYSTEM, 0.1 MG/DAY Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
EDOT-0922 Baseline-corrected estradiol				
Parameter	Test	Reference	Ratio*	90% C.I.**
AUC0-t	7805	7294	1.07	101% – 113%
AUC∞	8026	7398	1.08	102% – 115%
C_{max}	134.0	116.9	1.15	107% – 122%
EDOT-0922 Baseline-uncorrected estradiol				
Parameter	Test	Reference	Ratio*	90% C.I.**
AUC0-t	8228	7529	1.09	104% – 115%
AUC∞	8422	7711	1.09	103% – 115%
C_{max}	137.8	119.1	1.16	108% – 124%

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

**Used Natural Log Transformed Parameter

2. Summary Bioequivalence tables:
   - Table 10. Study Information YES
   - Table 12. Dropout Information YES
   - Table 13. Protocol Deviations YES

5.3.1.3
In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables:
   - Table 11. Product Information YES
   - Table 16. Composition of Meal Used in Fed Bioequivalence Study NA

5.3.1.4
Reports of Bioanalytical and Analytical Methods for Human Studies

1. Summary Bioequivalence table:
   - Table 9. Reanalysis of Study Samples YES
   - Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES
   - Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES

5.3.7
Case Report Forms and Individual Patient Listing YES

5.4 **Literature References** ☐

Possible Study Types:

Study Type

IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle) NA ☐

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)
2. EDR Email: Data Files Submitted: NA
3. In-Vitro Dissolution: NA

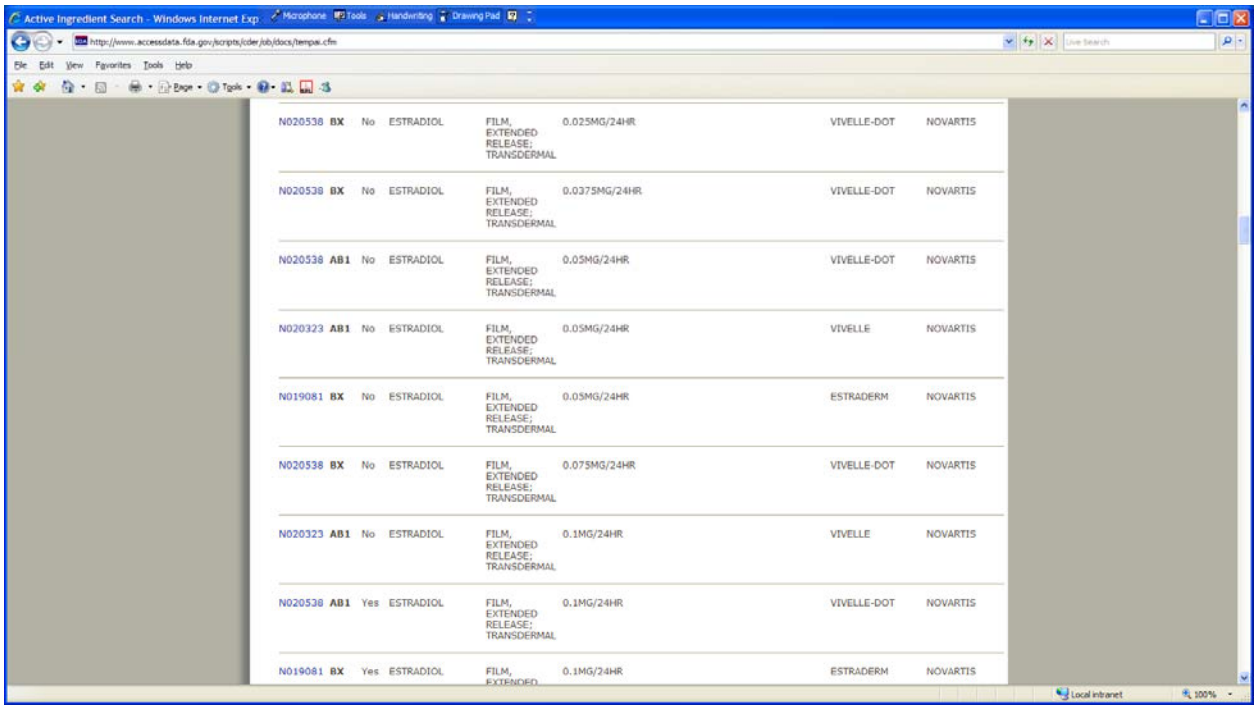
Study Type

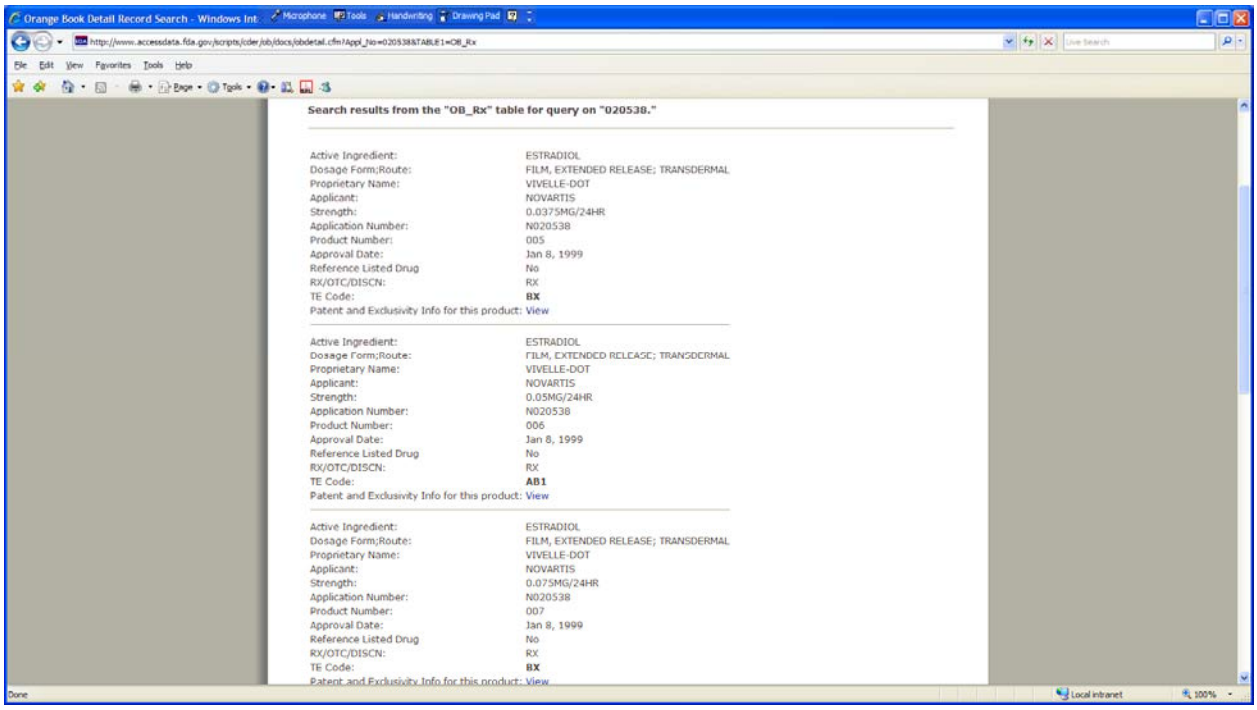
IN-VIVO BE STUDY with CLINICAL ENDPOINTS NO ☐

1. Properly defined BE endpoints (eval. by Clinical Team)
2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25).
3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team)
4. EDR Email: Data Files Submitted

Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** YES STU/BIO (FASTING ON 0.1 MG/DAY) YES Clinical filing review is AC. 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution YES SEE SECTION 2.7.1.2 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☒

Updated 10/19/2009


Active Ingredient Search - Windows Internet Exp
http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
File Edit View Favorites Tools Help
N020538 BX No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.025MG/24HR VIVELLE-DOT NOVARTIS
N020538 BX No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.0375MG/24HR VIVELLE-DOT NOVARTIS
N020538 AB1 No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.05MG/24HR VIVELLE-DOT NOVARTIS
N020323 AB1 No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.05MG/24HR VIVELLE NOVARTIS
N019081 BX No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.05MG/24HR ESTRADERM NOVARTIS
N020538 BX No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.075MG/24HR VIVELLE-DOT NOVARTIS
N020323 AB1 No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.1MG/24HR VIVELLE NOVARTIS
N020538 AB1 Yes ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.1MG/24HR VIVELLE-DOT NOVARTIS
N019081 BX Yes ESTRADIOL FILM, EXTENDED 0.1MG/24HR ESTRADERM NOVARTIS
Local intranet
100%


Orange Book Detail Record Search - Windows Int
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File Edit View Favorites Tools Help
Search results from the "OB_Rx" table for query on "020538."
Active Ingredient: ESTRADIOL
Dosage Form;Route: FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name: VIVELLE-DOT
Applicant: NOVARTIS
Strength: 0.0375MG/24HR
Application Number: N020538
Product Number: 005
Approval Date: Jan 8, 1999
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code: BX
Patent and Exclusivity Info for this product: View
Active Ingredient: ESTRADIOL
Dosage Form;Route: FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name: VIVELLE-DOT
Applicant: NOVARTIS
Strength: 0.05MG/24HR
Application Number: N020538
Product Number: 006
Approval Date: Jan 8, 1999
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code: AB1
Patent and Exclusivity Info for this product: View
Active Ingredient: ESTRADIOL
Dosage Form;Route: FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name: VIVELLE-DOT
Applicant: NOVARTIS
Strength: 0.075MG/24HR
Application Number: N020538
Product Number: 007
Approval Date: Jan 8, 1999
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code: BX
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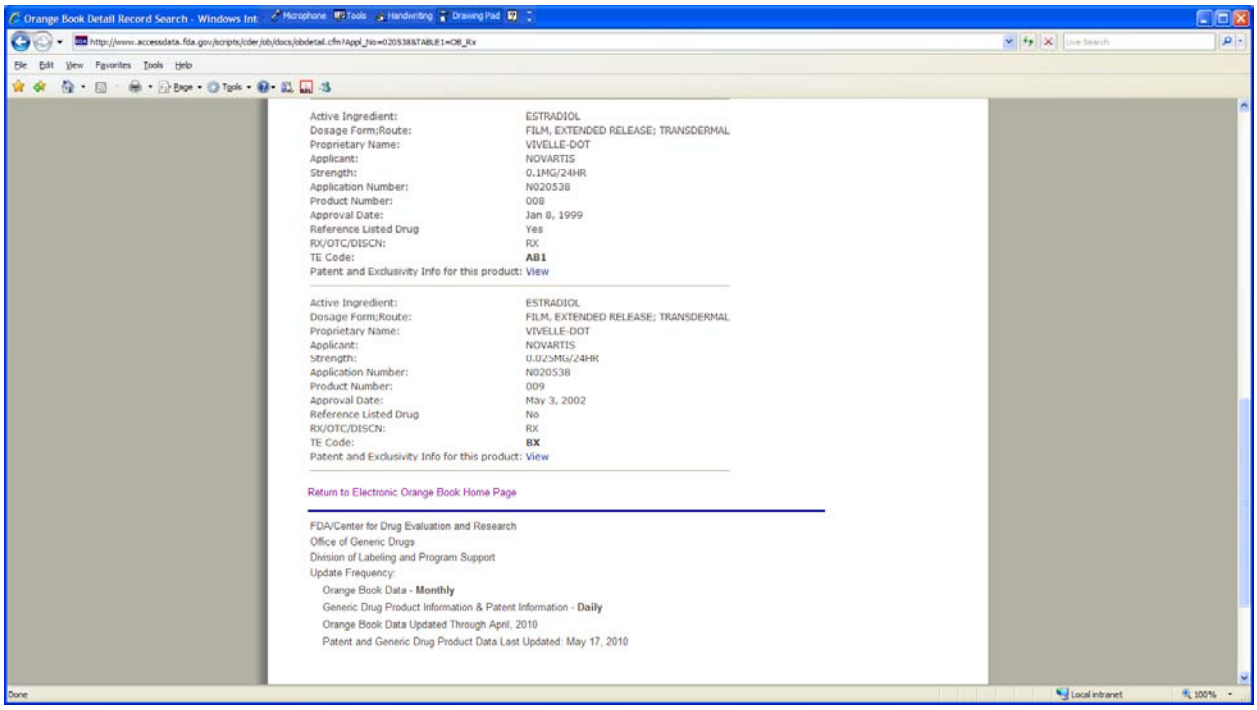
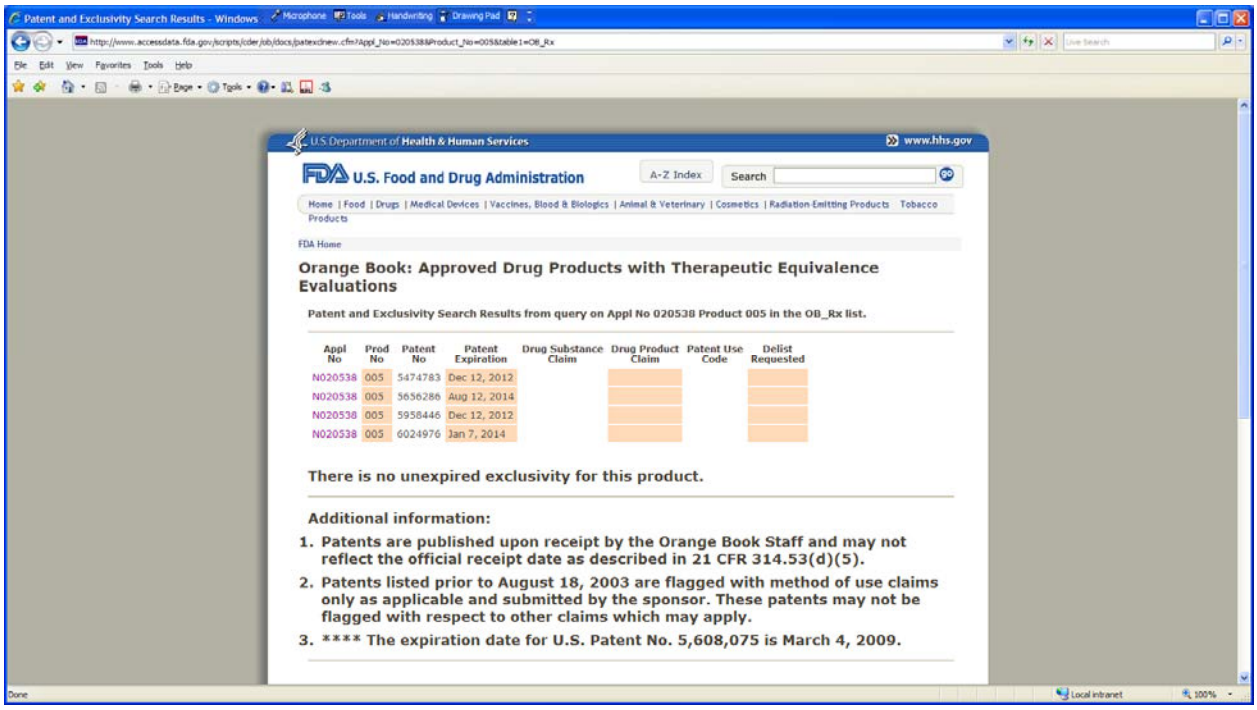
Local intranet
100%


Orange Book Detail Record Search - Windows Int
Active Ingredient: ESTRADIOL
Dosage Form;Route: FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name: VIVELLE-DOT
Applicant: NOVARTIS
Strength: 0.1MG/24HR
Application Number: N020538
Product Number: 008
Approval Date: Jan 8, 1999
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code: AB1
Patent and Exclusivity Info for this product: View
Active Ingredient: ESTRADIOL
Dosage Form;Route: FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name: VIVELLE-DOT
Applicant: NOVARTIS
Strength: 0.025MG/24HR
Application Number: N020538
Product Number: 009
Approval Date: May 3, 2002
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code: AB
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through April, 2010
Patent and Generic Drug Product Data Last Updated: May 17, 2010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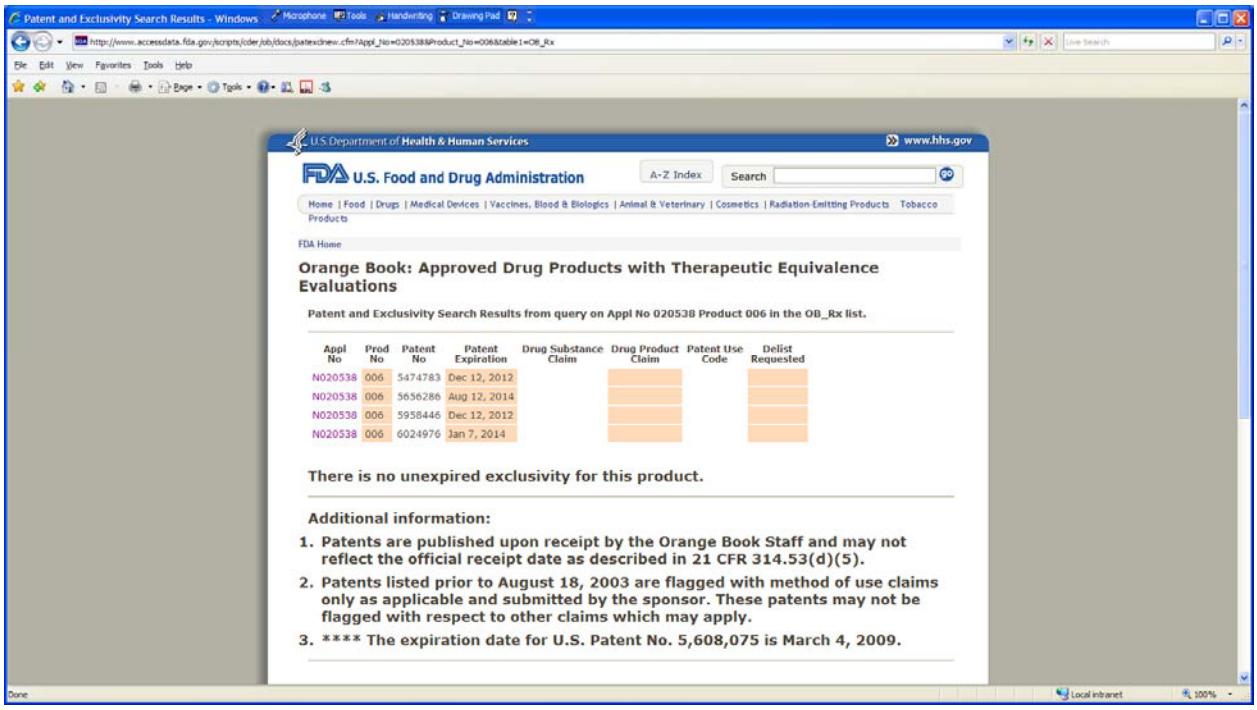
Patent and Exclusivity Search Results from query on Appl No 020538 Product 005 in the OB_Rx list.
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
N020538 | 005 | 5474783 | Dec 12, 2012
N020538 | 005 | 5656286 | Aug 12, 2014
N020538 | 005 | 5958446 | Dec 12, 2012
N020538 | 005 | 6024976 | Jan 7, 2014
There is no unexpired exclusivity for this product.
Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Patent and Exclusivity Search Results from query on Appl No 020538 Product 006 in the OB_Rx list.
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
N020538 | 006 | 5474783 | Dec 12, 2012
N020538 | 006 | 5656286 | Aug 12, 2014
N020538 | 006 | 5958446 | Dec 12, 2012
N020538 | 006 | 6024976 | Jan 7, 2014
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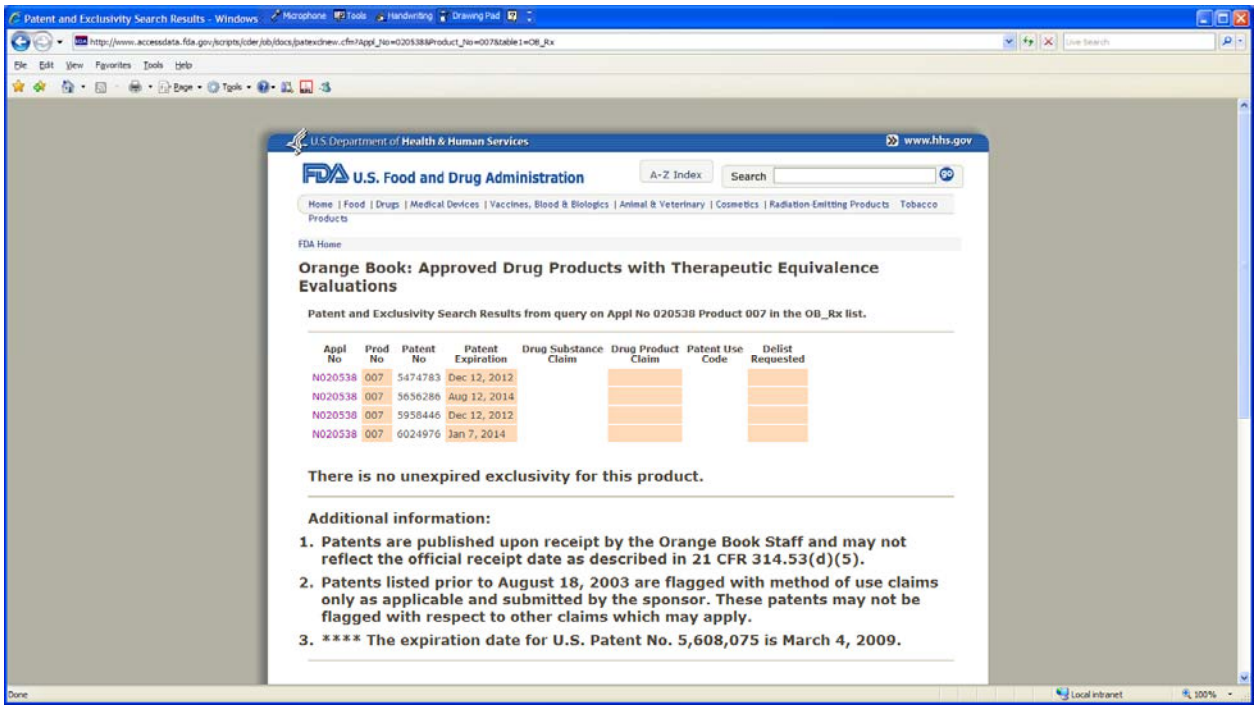
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Patent and Exclusivity Search Results from query on Appl No 020538 Product 007 in the OB_Rx list.
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
N020538 | 007 | 5474783 | Dec 12, 2012
N020538 | 007 | 5656286 | Aug 12, 2014
N020538 | 007 | 5958446 | Dec 12, 2012
N020538 | 007 | 6024976 | Jan 7, 2014
There is no unexpired exclusivity for this product.
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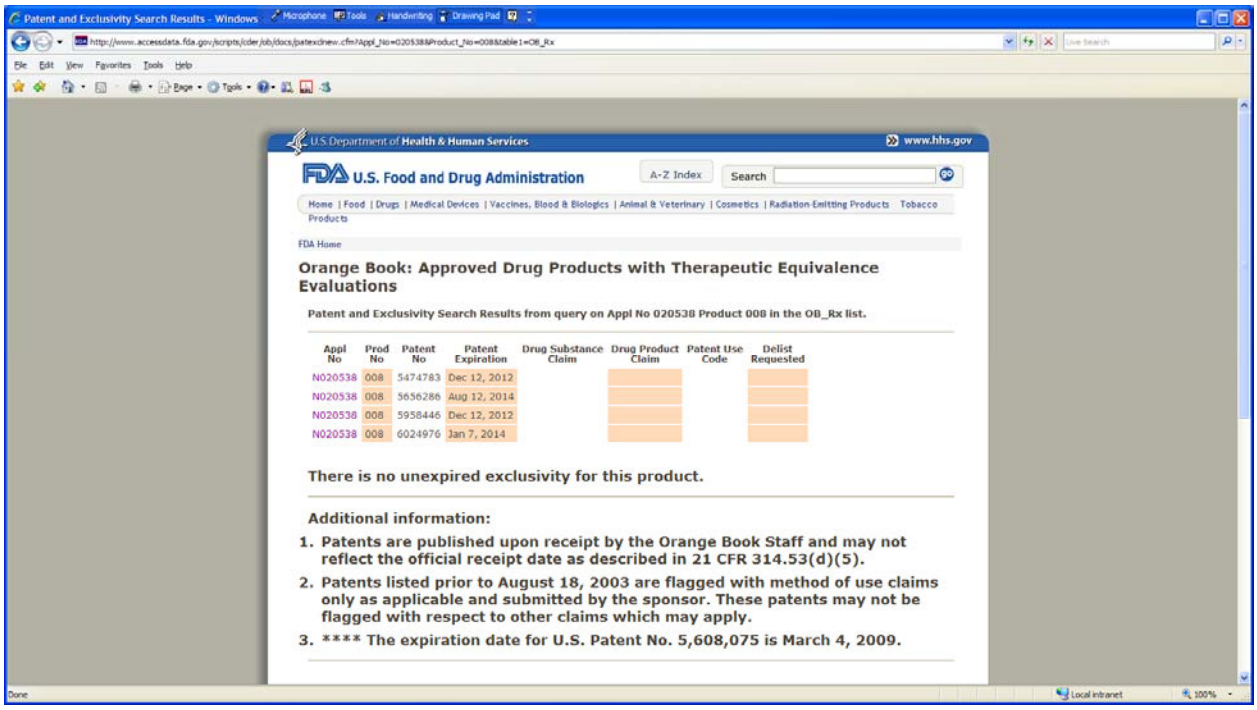
3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.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Patent and Exclusivity Search Results from query on Appl No 020538 Product 008 in the OB_Rx list.
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
N020538 | 008 | 5474783 | Dec 12, 2012
N020538 | 008 | 5656286 | Aug 12, 2014
N020538 | 008 | 5958446 | Dec 12, 2012
N020538 | 008 | 6024976 | Jan 7, 2014
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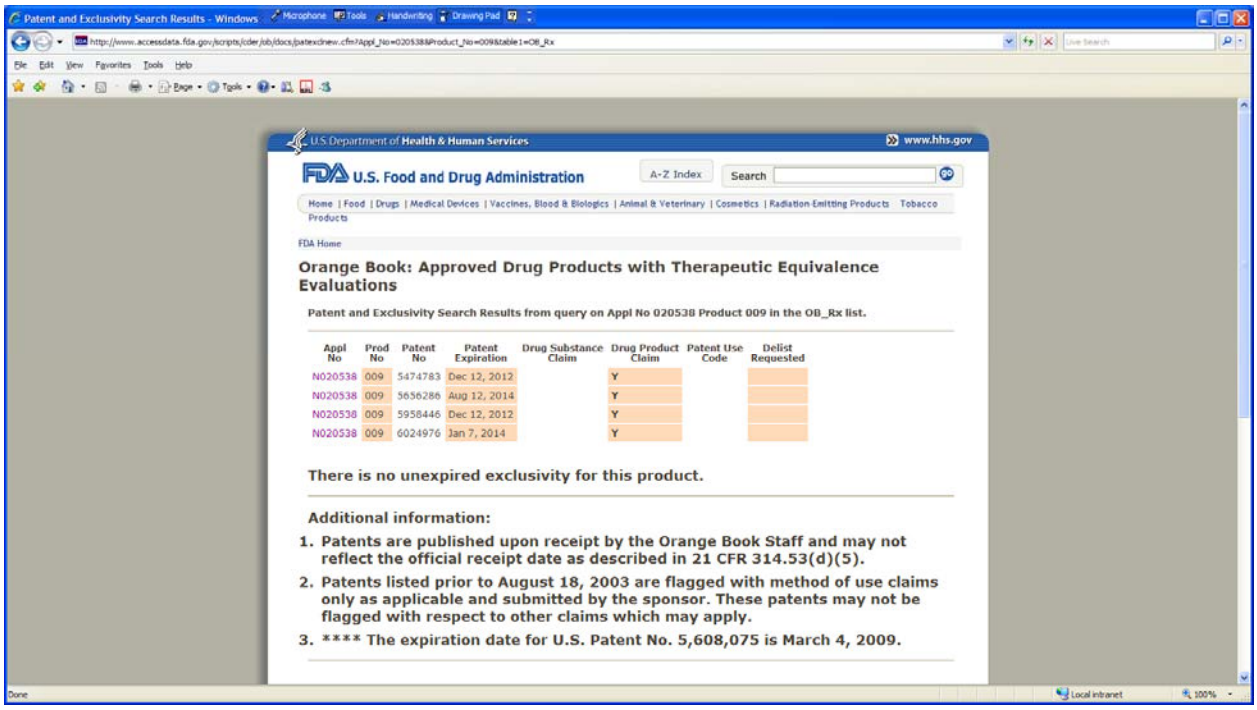
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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Patent and Exclusivity Search Results from query on Appl No 020538 Product 009 in the OB_Rx list.
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
N020538 | 009 | 5474783 | Dec 12, 2012 | | Y | |
N020538 | 009 | 5656286 | Aug 12, 2014 | | Y | |
N020538 | 009 | 5958446 | Dec 12, 2012 | | Y | |
N020538 | 009 | 6024976 | Jan 7, 2014 | | Y | |
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3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.

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/s/

TED C PALAT
12/22/2010

MARTIN H Shimer
12/23/2010

AMENDMENT
CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# 201675_____ **FIRM NAME**_Mylan Technologies Inc. _____

DRUG NAME _Estradiol Transdermal System, USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day_____

DOSAGE FORM __Transdermal System_____

REFERENCE LISTED DRUG (RLD)__Vivelle-Dot® (estradiol transdermal system), NDA 020538_____

Requested by: __Eda Howard_____ Date: _9/16/10_____
Regulatory Support Team, (HFD-615)

	Summary of Findings by Clinical Review Team
X	**Study meets statutory requirements** **Please see Comments to be conveyed to the sponsor for details.**
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: _X__COMPLETE __INCOMPLETE

Reviewed by:

_____ Date: _____
Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

_____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

Response to sponsor's amendment dated 9/10/2010

Comments not to be conveyed to the sponsor

On September 10, 2010, Mylan submitted an amendment in response to our deficiency letter provided on August 6, 2010. The Clinical Review Team refused to file this application because the sponsor did not submit the statistical results using the OGD recommended statistical method to show that the skin irritation potential and adhesion performance of their product are at least as good as those of the reference product. We requested that the sponsor provide the one-sided 95% CI for the mean cumulative irritation score of the test product minus 1.25 X mean cumulative irritation score of the reference product in the PP population and combine dermal response and "other effects" scores for the irritation analysis. The frequency distribution of the irritation scores provided by the sponsor in the original submission based on the greater of the dermal response and "other effects" scores showed considerably more scores of 3 or higher for the test product than the reference product. The one-sided 95% CI for the mean adhesion score of the test product minus 1.25 X mean adhesion score of the reference product in the PP population was also requested.

Reviewer's Comment: *Although the Clinical Review Team wanted to ask the above additional information prior to making a decision about filing of their application, we were informed by the regulatory branch team that a deficiency letter should be issued to request that information.*

Skin irritation

In this submission, Mylan provided the summary of frequencies for the combined dermal response and other effects scores as shown below.

Table 4A - Summary of Frequencies for Summed Dermal Response and Other Effects Scores, for Test

HOUR(Study Hour)	SCORE							
Frequency	0	1	2	3	4	5	6	10	Total
84	200	8	5	0	0	0	0	0	213
168	193	18	2	0	0	0	0	0	213
252	190	16	7	0	0	0	0	0	213
336	192	12	5	0	0	1	2	1	213
420	178	21	10	0	0	1	2	1	213
504	184	21	3	0	0	2	2	1	213
Total	1137	96	32	0	0	4	6	3	1278

Table 4B - Summary of Frequencies of Summed Dermal Response and Other Effects Scores, for Reference

HOUR(Study Hour)	SCORE							
Frequency	0	1	2	3	4	5	6	10	Total
84	198	15	0	0	0	0	0	0	213
168	195	16	2	0	0	0	0	0	213
252	187	25	1	0	0	0	0	0	213
336	190	18	3	0	2	0	0	0	213
420	167	36	7	1	2	0	0	0	213
504	184	22	4	1	2	0	0	0	213
Total	1121	132	17	2	6	0	0	0	1278

Table 5A - Summary of Irritation Scores of 3 or higher, by observations (1278 total), based on Sum of Dermal Response and Other Effects Scores

Summary by Observations		Test – Mylan		
		< 3	≥ 3	
Reference – Vivelle Dot®	< 3	1265	5	Ref. Tot. ≥ 3
	≥ 3	0	8	8
		Test Tot ≥ 3	13	

Table 5B - Summary of Irritation Scores of 3 or higher, by subjects (213 total), based on Sum of Dermal Response and Other Effects Scores

Summary by Subjects		Test – Mylan		
		< 3	≥ 3	
Reference – Vivelle Dot®	< 3	208	2	Ref. Tot. ≥ 3
	≥ 3	0	3	3
		Test Tot. ≥ 3	5	

The sponsor provided the one-sided 95% CI for the mean cumulative irritation score using the OGD's recommended method as shown below.

Table 6: Assessment of Mean Cumulative Irritation Scores based upon Mylan and FDA Statistical Models for EDOT-0908

Method	Parameter	Upper 95% CI	Criteria	Pass/Fail
FDA	Test - 1.25*Ref	0.050	<0	Fail
Mylan	Test – Ref	0.082	<0.25	Pass

treat	score LSMEAN
A	0.19255482
B	0.15329808

The sponsor stated that based on discrete scores ≥3, evaluated as a summed score of dermal response and other effects score, the distributions are 13 for the test versus 8 for the reference. The sponsor also stated that there were 5 more clinically meaningful scores observed for the test than for the reference from a total of 1278 observations for each test article. Only 2 subjects were observed to have summed scores ≥3 for the test who did not also have corresponding observations ≥3 for the reference from a total of 213 subjects.

Reviewer's comment: *Averaging scores over the total of all observations obscures any significant individual scores. The observations in tables 5B and 5A above provide a better demonstration of the irritation potential than the mean scores.*

The sponsor also provided additional frequency tables for skin irritation analysis, separating dermal response score of at least 3, combined dermal and other effects score of at least 3, and other effects score of at least 3, for each treatment group as shown below.

Dermal response score of at least 3

treat=A

SUBJID	treat	studyday	hour	IRDR	IROE	iroen	score
157	A	15	336	3	H	3	6
157	A	18	420	3	H	3	6
157	A	22	504	3	H	3	6
162	A	15	336	3	H	3	6
162	A	18	420	3	H	3	6
162	A	22	504	3	H	3	6
192	A	15	336	7	H	3	10
192	A	18	420	7	H	3	10
192	A	22	504	7	H	3	10
203	A	15	336	3	C	2	5
203	A	18	420	3	C	2	5
203	A	22	504	3	C	2	5

Note:
IRDR: Dermal response
IROR: Other effect
IROEN: Numerical correspondence of other effect
SCORE: Sum of dermal response and other effect

Treatment A: Estradiol Transdermal System, 0.025 mg/day x (6 + 1), Mylan
Treatment B: Vivelle-Dot Transdermal System, 0.025 mg/day x (6 + 1), Novartis

Reviewer's Comment: *No subject had dermal response score of at least 3 with the RLD.*

Combined dermal response and other effects score of at least 3

treat=A

SUBJID	treat	studyday	hour	IRDR	IROE	iroen	score
5	A	22	504	2	H	3	5
157	A	15	336	3	H	3	6
157	A	18	420	3	H	3	6
157	A	22	504	3	H	3	6
162	A	15	336	3	H	3	6
162	A	18	420	3	H	3	6
162	A	22	504	3	H	3	6
192	A	15	336	7	H	3	10
192	A	18	420	7	H	3	10
192	A	22	504	7	H	3	10
203	A	15	336	3	C	2	5
203	A	18	420	3	C	2	5
203	A	22	504	3	C	2	5

treat=B

SUBJID	treat	studyday	hour	IRDR	IROE	iroen	score
157	B	18	420	1	C	2	3
157	B	22	504	1	C	2	3
162	B	15	336	2	C	2	4
162	B	18	420	2	C	2	4
162	B	22	504	2	C	2	4
203	B	15	336	2	C	2	4
203	B	18	420	2	C	2	4
203	B	22	504	2	C	2	4

Other effects score of at least 3

treat=A

SUBJID	treat	studyday	hour	IRDR	IROE	iroen	score
5	A	22	504	2	H	3	5
157	A	15	336	3	H	3	6
157	A	18	420	3	H	3	6
157	A	22	504	3	H	3	6
162	A	15	336	3	H	3	6
162	A	18	420	3	H	3	6
162	A	22	504	3	H	3	6
192	A	15	336	7	H	3	10
192	A	18	420	7	H	3	10
192	A	22	504	7	H	3	10
203	A	15	336	3	C	2	5
203	A	18	420	3	C	2	5
203	A	22	504	3	C	2	5

treat=B

SUBJID	treat	studyday	hour	IRDR	IROE	iroen	score
157	B	18	420	1	C	2	3
157	B	22	504	1	C	2	3
162	B	15	336	2	C	2	4
162	B	18	420	2	C	2	4
162	B	22	504	2	C	2	4
203	B	15	336	2	C	2	4
203	B	18	420	2	C	2	4
203	B	22	504	2	C	2	4

Overall dermal response score only

Table 1 of hour by IRDR

Controlling for treat=A

hour(Study Hour)	IRDR(Dermal Response)					Total
	0	1	2	3	7	
84	200	8	5	0	0	213
168	193	18	2	0	0	213
252	190	16	7	0	0	213
336	192	12	5	3	1	213
420	178	21	10	3	1	213
504	184	21	4	3	1	213
Total	1137	96	33	9	3	1278

Table 2 of hour by IRDR

Controlling for treat=B

hour(Study Hour)	IRDR(Dermal Response)					Total
	0	1	2	3	7	
84	198	15	0	0	0	213
168	195	16	2	0	0	213
252	187	25	1	0	0	213
336	190	18	5	0	0	213
420	167	37	9	0	0	213
504	184	23	6	0	0	213
Total	1121	134	23	0	0	1278

Overall other effects score only

Table 1 of hour by IROE

Controlling for treat=A

hour(Study Hour)	IROE(Other Effects)		Total
	C	H	
84	0	0	0
168	0	0	0
252	0	0	0
336	1	3	4
420	1	3	4
504	1	4	5
Total	3	10	13

Frequency Missing = 1265

Table 2 of hour by IROE

Controlling for treat=B

hour(Study Hour)	IROE(Other Effects)		Total
	C	H	
84	0	0	0
168	0	0	0
252	0	0	0
336	2	0	2
420	3	0	3
504	3	0	3
Total	8	0	8

Frequency Missing = 1270

Reviewer's Comment: *According to the above frequency table for a dermal response score only, 6 observations had a dermal response score of 3 (erythema and papules) and 3 observations had a dermal response score of 7 (strong reaction spreading beyond application site) in the test group. No dermal response score of 3 or 7 was observed in the reference group. For other effects scores only, 10 observations had other effects score of H (small petechial erosions and or scabs=equals to a dermal score of 3) in the test group but none in the reference group. Three observations had other effects score of C (glazing with peeling and cracking=equals to a dermal score of 2) in the test group and 8 observations had other effects score of C in the reference group.*

Furthermore, four subjects (5, 157, 162, and 192) in the test group had other effects score of H but none in the reference group. Four subjects (157, 162, 192, and 203) in the test group had a dermal response of 3 but none in the reference group.

Although cumulative mean irritation scores are less than 1 in both treatment groups (0.192 in the test vs. 0.153 in the reference), more subjects or observations had clinically meaningful unacceptable skin irritation score in the test group compared to that in the reference group. Further detailed review is needed to determine whether these differences between products would be clinically significant, showing more skin irritation potential for the test product than for the reference product.

Skin Adhesion

By converting Mylan's adhesion scores to the OGD's recommended scale (a score of 0=100% adherence and a score of 0=detached), the upper bound of the one-sided 95% CI for the mean adhesion score was provided by the sponsor as shown below.

Table 12 - Assessment of Mean Adhesion Scores, Based on FDA Recommended Scale, and Analyzed According to Mylan and FDA Statistical Models

Method	Parameter	Upper 95% CI	Criteria	Pass/Fail
FDA	Test - 1.25*Ref	0.016	<0	Fail
Mylan	Test – Ref	0.020	<0.25	Pass

The sponsor also provided a new frequency table for skin adhesion scores as shown below.

Frequency	Table 1 of HOUR by SCORE					
	Controlling for TREAT=A					
	SCORE					
HOUR	0	1	2	3	4	Total
24	228	0	0	0	0	228
48	227	1	0	0	0	228
72	224	4	0	0	0	228
84	219	5	0	1	3	228
Total	898	10	0	1	3	912

Frequency	Table 2 of HOUR by SCORE					
	Controlling for TREAT=B					
	SCORE					
HOUR	0	1	2	3	4	Total
24	228	0	0	0	0	228
48	228	0	0	0	0	228
72	227	1	0	0	0	228
84	218	6	1	1	2	228
Total	901	7	1	1	2	912

Adhesion Evaluation Scoring System:
0, >= 90% adhered (essentially no lift off from the skin)
1, >= 75% to < 90% adhered (some edges only lifting off the skin)
2, >= 50% to < 75% adhered (less than half of the system lifting off the skin)
3, < 50% adhered but not detached (more than half lifting off the skin)
4, patch detached (patch completely off the skin)

Treatment A: Estradiol Transdermal System, 0.025 mg/day x (6 + 1), Mylan
Treatment B: Vivelle-Dot Transdermal System, 0.025 mg/day x (6 + 1), Novartis

Since both test and reference products' mean cumulative irritation scores are approaching zero due to low irritation, the sponsor states that the OGD's current statistical approach for evaluating skin irritation potential is overly sensitive to very small differences between the test and reference products. Mylan proposes to evaluate the one-sided 95% CI for the mean cumulative irritation based on Test-Reference <0.25 rather than the OGD's recommended method of Test-1.25 X Reference <0 if the mean cumulative irritation scores are <1. Mylan states that the FDA recommended method could be considered generally applicable to data for which more definite responses are noted (i.e., mean cumulative irritation scores $\geq$ 1). The sponsor also provided their ad hoc analysis outcome using Bootstrap Simulation for justifying their proposal for both skin irritation and adhesion analyses.

Comments to be conveyed to the sponsor

The data submitted to your application are sufficient for receiving your ANDA for review. However, acceptability of your statistical proposal has not been determined and will be addressed during the review cycle.

1. **Although your analysis using the OGD's recommended statistical method for the upper bound of one-sided 95% CI for the mean adhesion score was greater than zero, your new frequency table for the adhesion scores suggests that the adhesion performance of your product is similar to that of the reference product.**

2. **Based on your statistical analysis using the OGD's recommended method, the upper bound of one-sided 95% CI for the mean cumulative irritation score was greater than zero. Your new frequency tables for the skin irritation scores show that more subjects in the test group had consistently higher unacceptable dermal response scores (dermal response only, combined, or other effects scores only) compared to the reference group. Although the cumulative mean irritation scores are less than 1 in both treatment groups, a detailed review is warranted to evaluate the clinical significance of these differences between products.**

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/s/

CAROL Y KIM
11/29/2010

DENA R HIXON
11/30/2010
I concur.

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 201675 **FIRM NAME**: MYLAN TECHNOLOGIES

PIV: YES **Electronic or Paper Submission:** ELECTRONIC (GATEWAY)

RELATED APPLICATION(S): SEE (b) (4) **FROM** MYLAN TECHNOLOGIES RFR 5/18/09 (RLD VIVELLE DOT)

First Generic Product Received? NO

DRUG NAME: ESTRADIOL
DOSAGE FORM: TRANSDERMAL SYSTEM USP, 0.25 MG/DAY, 0.0375 MG/DAY, 0.05 MG/DAY, 0.075 MG/DAY AND 0.1 MG/DAY

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC1 Team 5 ☒ ***Activity***	***Bio Team 10: April Braddy*** ☒ ***Activity***
ANDA/Quality RPM: Ben Danso ☒ ***FYI***	Bio PM: Diana Solana ☐ ***FYI***
Quality Team Leader: Bykadi, Raj No assignment needed in DARRTS	***Clinical Endpoint Team Assignment:*** ☒ ***Activity***
Labeling Reviewer: Ruby Wu ☒ ***Activity***	***Micro Review (No)*** ☐ ***Activity***

*****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). *****

Letter Date: APRIL 26, 2010 **Received Date**: APRIL 27, 2010

Comments: EC - 5 YES **On Cards:** YES
Therapeutic Code: 3011000 ESTROGENS

Archival copy: ELECTRONIC (GATEWAY) **Sections** I
Review copy: NA E-Media Disposition: NA
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST **Ted Palat** **Date 07/29/2010**	**Recommendation:** ☐ **FILE** ☒ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

1. Edit Application Property Type in DARRTS where applicable for
   a. First Generic Received
      ☐ Yes ☒ No
   b. Market Availability
      ☒ Rx ☐ OTC
   c. Pepfar
      ☐ Yes ☒ No
   d. Product Type
      ☐ Small Molecule Drug (usually for most ANDAs except protein drug products)
   e. USP Drug Product (at time of filing review)
      ☒ Yes ☐ No
2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☐ Yes
4. Requested EER
   ☐ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA: 304-599-2595 Wayne Talton
1. failed clinical filing review
2.

BIOEQUIVALENCE CHECKLIST
FOR APPLICATION COMPLETENESS

ANDA# 201675 **FIRM NAME** **Mylan Technologies Inc.**

DRUG NAME Estradiol

DOSAGE FORM Film, extended release - Transdermal; 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

SUBJ: Request for examination of the bioequivalence study submitted with an ANDA 201675 for Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv)

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason: NOTE: The adhesion, skin irritation and sensitization study should be reviewed for completeness by the OGD Clinical Team. Only the BE study with pharmacokinetic (PK) endpoints is reviewed by the Division of Bioequivalence in the current checklist.
☒	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Vipra Kundoor, Ph.D.
Reviewer

_____ Date: _____
April C. Braddy, Ph.D.
Team Leader

BIO_1G_CHKLST.dot v.4/4/2003

CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# 201675_____ **FIRM NAME**_Mylan Technologies Inc. _____

DRUG NAME _Estradiol Transdermal System, USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day_____

DOSAGE FORM __Transdermal System_____

REFERENCE LISTED DRUG (RLD)__Vivelle-Dot® (estradiol transdermal system), NDA 020538_____

Requested by: __Eda Howard_____ Date: _5/19/10_____
Regulatory Support Team, (HFD-615)

	Summary of Findings by Clinical Review Team
	Study meets statutory requirements
X	**Study does NOT meet statutory requirements: The sponsor failed to submit the statistical analysis results using the OGD recommended method to show that skin irritation potential and adhesion performance of their patch are not inferior to those of the RLD. See Comments to be conveyed to the sponsor for details.**
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: ___COMPLETE _X_INCOMPLETE

Reviewed by:

_____ Date: _____
Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

_____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) YES	☒

1.2	**Cover Letter** Dated: APRIL 26, 2010	☒
1.2.1	**Form FDA 3674 (PDF) YES**	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES SEE SECTION 1.3.3 2. List of Convictions statement (original signature) SAME	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES SEE SECTION 1.3.3, form 3454 Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) PIV – '286 and '976, PIII – '783 and '446 **Patent and Exclusivity Search Results from query on Appl No 020538 Product 005 in the OB_Rx list.**	☒

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020538	005	5474783	Dec 12, 2012				
N020538	005	5656286	Aug 12, 2014				
N020538	005	5958446	Dec 12, 2012				
N020538	005	6024976	Jan 7, 2014				

There is no unexpired exclusivity for this product.

2. Paragraph: (Check all certifications that apply)
   MOU ☐ PI ☐ PII ☐ PIII ☒
   PIV ☒ (Statement of Notification) ☒
3. Expiration of Patent(s): 1/7/2014
   a. Pediatric exclusivity submitted?
   b. Expiration of Pediatric Exclusivity?
4. Exclusivity Statement: YES no exclusivity

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES Type II DMF No. (b) (4) b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA	☒
1.12.11	**Basis for Submission OK** NDA# : 20-538 Ref Listed Drug: VIVELLE DOT Firm: NOVARTIS ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients JUSTIFIED 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES SEE SECTION 1.12.14	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): YES ON 0.025 MG/DAY, 0.0375 MG/DAY, 0.050 MG/DAY AND 0.075 MG/DAY SEE SECTION 1.12.15	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** YES **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** YES **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation YES Table 6. Formulation Data YES **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution YES **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies YES Table 3. Statistical Summary of the Comparative BA Data YES **2.7.1.4 Appendix** YES **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study YES **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies YES	☒

3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) **2.3.P.3 Manufacture (Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, 0.1 mg/day (Twice-Weekly))** **Who manufactures the drug product?** Manufacturing, Packaging, Labeling, Quality Control Testing of components, Testing of Finished Dosage Form: **Name and Address** / **Responsibilities** Mylan Technologies 110 Lake Street St. Albans, VT 05478 Manufacturing, Packaging, Labeling, Quality Control Testing of Components and Finished Dosage Form. A cGMP certification letter is provided in Section 3.2.P.3.1. (b) (4) [redacted] 2. CGMP Certification: YES SEE SECTION 3.2.P.3.1 3. Function or Responsibility YES 4. CFN or FEI numbers YES **3.2.P.3.2 Batch Formula** YES **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES (b) (4) [redacted] 3. If sterile product: Aseptic fill / Terminal sterilization NA 4. Reprocessing Statement YES **3.2.P.3.4 Controls of Critical Steps and Intermediates** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation NA 2. Filter validation (if aseptic fill) NA	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA YES	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** YES **3.2.P.5.2 Analytical Procedures** YES **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers R6A0028, 30, 36, 37, 38 **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **3.2.P.5.5 Characterization of Impurities** **3.2.P.5.6 Justification of Specifications**	☒

3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes **HOW SUPPLIED: Estradiol Transdermal System USP, 0.025 mg/day (Twice-Weekly) -** each 2.5 cm^2 system contains 0.41 mg of estradiol, USP for nominal* delivery of 0.025 mg of estradiol per day. Patient Calendar Pack of 8 Systems.....NDC 0378-4644-26 **Estradiol Transdermal System USP, 0.0375 mg/day (Twice-Weekly) -** each 3.75 cm^2 system contains 0.62 mg of estradiol, USP for nominal* delivery of 0.0375 mg of estradiol per day. Patient Calendar Pack of 8 Systems .....NDC 0378-4643-26 **Estradiol Transdermal System USP, 0.05 mg/day (Twice-Weekly) -** each 5.0 cm^2 system contains 0.82 mg of estradiol, USP for nominal* delivery of 0.05 mg of estradiol per day. Patient Calendar Pack of 8 Systems .....NDC 0378-4642-26 **Estradiol Transdermal System USP, 0.075 mg/day (Twice-Weekly) -** each 7.5 cm^2 system contains 1.23 mg of estradiol, USP for nominal* delivery of 0.075 mg of estradiol per day. Patient Calendar Pack of 8 Systems…….....NDC 0378-4641-26 **Estradiol Transdermal System USP, 0.1 mg/day (Twice-Weekly) -** each 10.0 cm^2 system contains 1.64 mg of estradiol, USP for nominal* delivery of 0.1 mg of estradiol per day. Patient Calendar Pack of 8 Systems.....NDC 0378-4640-26 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period 24 months **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data YESYES 2. Batch numbers on stability records the same as the test batch **YES**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available) NO** **3.2.R.2.S Comparability Protocols NO** **3.2.R.3.S Methods Validation Package YES** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation YES **Yield and Reconciliation of the Packaging Process for the Exhibit Lots** (b) (4) [redacted] **3.2.R.1.P.2 Information on Components** YES **3.2.R.2.P Comparability Protocols** NO **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒

5.3.1
(complete study data)

Bioavailability/Bioequivalence

1. Formulation data same? ☒

a. Comparison of all Strengths (check proportionality of multiple strengths)

Composition and Pharmaceutical Function of Adhesive Matrix Components of Mylan's Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice-Weekly)

Components	Pharmaceutical Function	% w/w	mg per system				
			0.025 mg/ day	0.0375 mg/ day	0.05 mg/ day	0.075 mg/ day	0.1 mg/ day
Active Ingredient							
Estradiol (b) (4) USP,	Active Ingredient	(b) (4)	0.41	0.62	0.82	1.23	1.64
Inactive Ingredients							
Oleyl Alcohol, (b) (4) (b) (4)							
Dipropylene Glycol (b) (4)							
Povidone (b) (4)							
Silicone Adhesive (b) (4)	Adhesive						
Acrylic Adhesive (b) (4)	Adhesive						
(b) (4)							
Theoretical Total Matrix[5]							
Components of the Delivery and Packaging System							
Polyolefin Film (b) (4)	Backing						
Brown Ink (b) (4)	Imprinting Ink						
(b) (4) Polyester Film (b) (4)	Oversized Release Liner						

(b) (4)

b. Parenterals, Ophthalmics, Otics and Topicals

per 21 CFR 314.94 (a)(9)(iii)-(v) NA

2. Lot Numbers of Products used in BE Study(ies): ANDA: R6A0030, RLD: 38967

3. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)

5.3.1.2 Comparative BA/BE Study Reports ☒

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)

ESTRADIOL TRANSDERMAL SYSTEM, USP (TWICE-WEEKLY)

0.025 MG/DAY, 0.0375 MG/DAY, 0.05 MG/DAY, 0.075 MG/DAY AND 0.1 MG/DAY

ESTRADIOL TRANSDERMAL SYSTEM, 0.1 MG/DAY Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
EDOT-0922 Baseline-corrected estradiol				
Parameter	**Test**	**Reference**	**Ratio***	**90% C.I.****
AUC0-t	7805	7294	1.07	101% – 113%
AUC∞	8026	7398	1.08	102% – 115%
C_{max}	134.0	116.9	1.15	107% – 122%
EDOT-0922 Baseline-uncorrected estradiol				
Parameter	**Test**	**Reference**	**Ratio***	**90% C.I.****
AUC0-t	8228	7529	1.09	104% – 115%
AUC∞	8422	7711	1.09	103% – 115%
C_{max}	137.8	119.1	1.16	108% – 124%

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

**Used Natural Log Transformed Parameter

2. Summary Bioequivalence tables:
   - Table 10. Study Information YES
   - Table 12. Dropout Information YES
   - Table 13. Protocol Deviations YES

5.3.1.3
In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables:
   - Table 11. Product Information YES
   - Table 16. Composition of Meal Used in Fed Bioequivalence Study NA

5.3.1.4
Reports of Bioanalytical and Analytical Methods for Human Studies

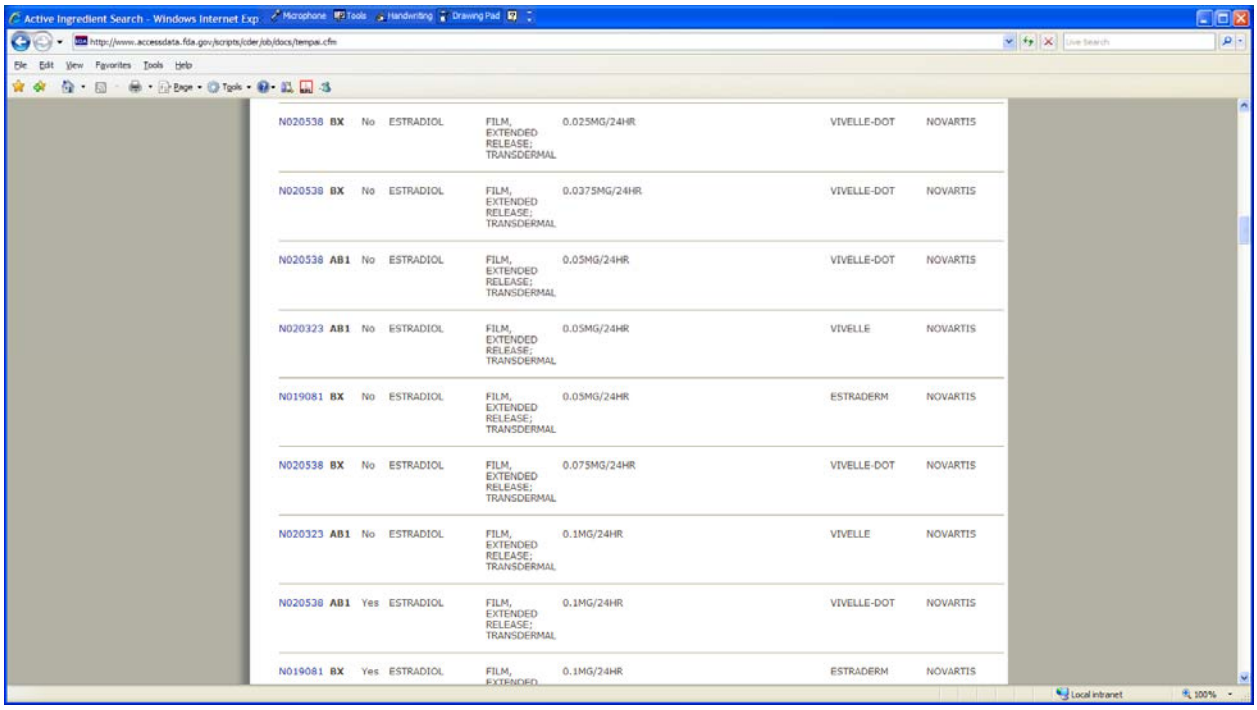
1. Summary Bioequivalence table:
   - Table 9. Reanalysis of Study Samples YES
   - Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES
   - Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES

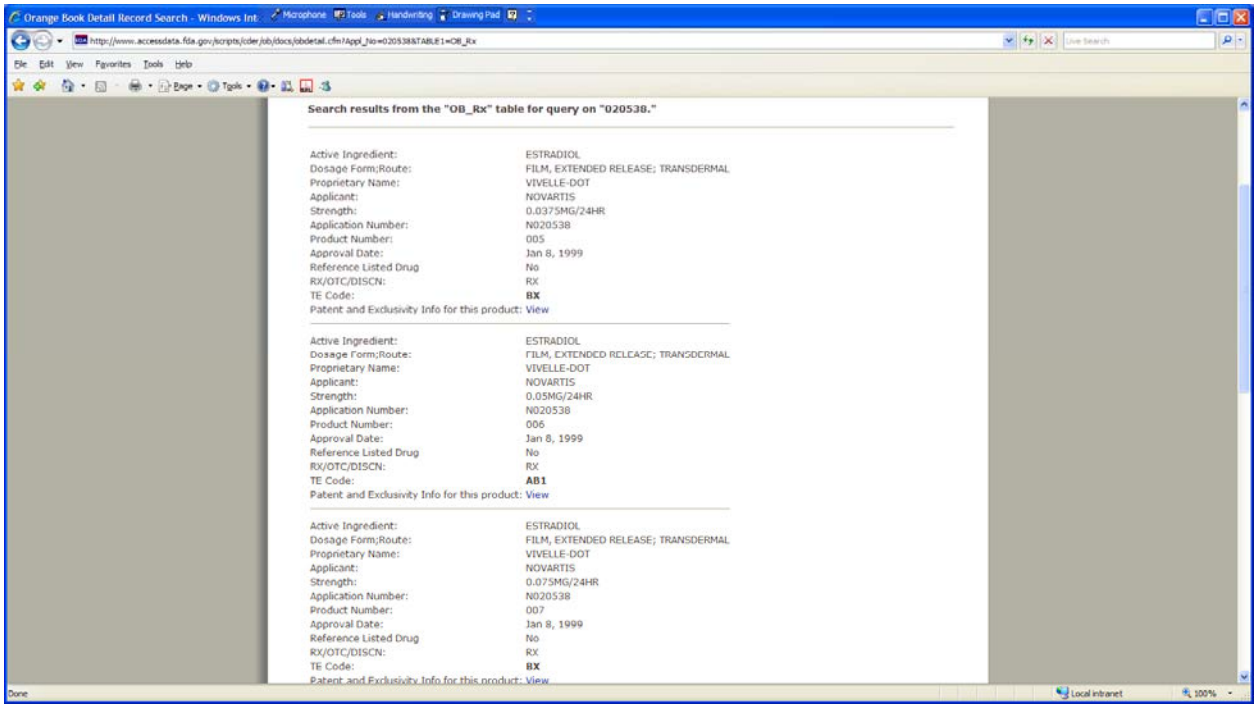
5.3.7
Case Report Forms and Individual Patient Listing YES

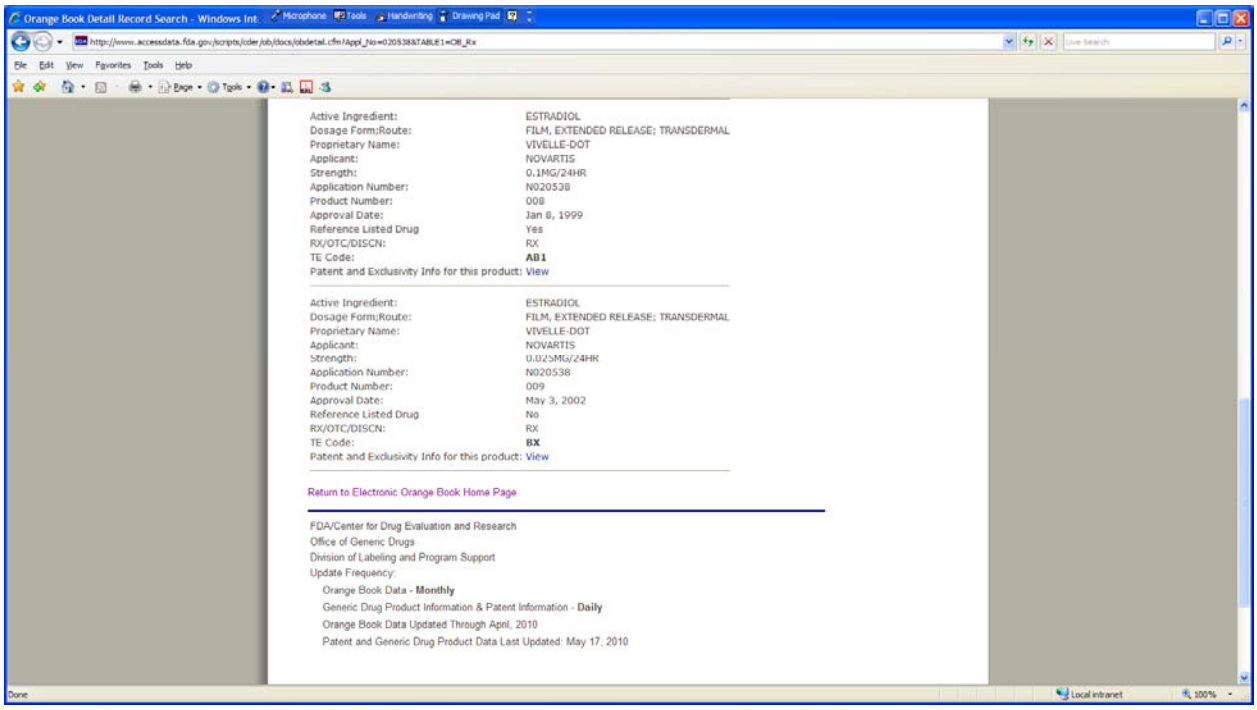
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: NA 3. In-Vitro Dissolution: NA	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐

Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** YES STU/BIO (FASTING ON 0.1 MG/DAY) FAIL 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution YES SEE SECTION 2.7.1.2 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/19/2009


Active Ingredient Search - Windows Internet Exp
http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
File Edit View Favorites Tools Help
N020538 BX No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.025MG/24HR VIVELLE-DOT NOVARTIS
N020538 BX No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.0375MG/24HR VIVELLE-DOT NOVARTIS
N020538 AB1 No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.05MG/24HR VIVELLE-DOT NOVARTIS
N020323 AB1 No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.05MG/24HR VIVELLE NOVARTIS
N019081 BX No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.05MG/24HR ESTRADERM NOVARTIS
N020538 BX No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.075MG/24HR VIVELLE-DOT NOVARTIS
N020323 AB1 No ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.1MG/24HR VIVELLE NOVARTIS
N020538 AB1 Yes ESTRADIOL FILM, EXTENDED RELEASE; TRANSDERMAL 0.1MG/24HR VIVELLE-DOT NOVARTIS
N019081 BX Yes ESTRADIOL FILM, EXTENDED 0.1MG/24HR ESTRADERM NOVARTIS
Local intranet
100%


Orange Book Detail Record Search - Windows Int
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=020538&TABLE1=OB_Rx
File Edit View Favorites Tools Help
Search results from the "OB_Rx" table for query on "020538."
Active Ingredient: ESTRADIOL
Dosage Form;Route: FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name: VIVELLE-DOT
Applicant: NOVARTIS
Strength: 0.0375MG/24HR
Application Number: N020538
Product Number: 005
Approval Date: Jan 8, 1999
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code: BX
Patent and Exclusivity Info for this product: View
Active Ingredient: ESTRADIOL
Dosage Form;Route: FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name: VIVELLE-DOT
Applicant: NOVARTIS
Strength: 0.05MG/24HR
Application Number: N020538
Product Number: 006
Approval Date: Jan 8, 1999
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code: AB1
Patent and Exclusivity Info for this product: View
Active Ingredient: ESTRADIOL
Dosage Form;Route: FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name: VIVELLE-DOT
Applicant: NOVARTIS
Strength: 0.075MG/24HR
Application Number: N020538
Product Number: 007
Approval Date: Jan 8, 1999
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code: BX
Done
Local intranet
100%


Orange Book Detail Record Search - Windows Int
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=020538&TABLE1=OB_Rx
File Edit View Favorites Tools Help
Active Ingredient: ESTRADIOL
Dosage Form;Route: FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name: VIVELLE-DOT
Applicant: NOVARTIS
Strength: 0.1MG/24HR
Application Number: N020538
Product Number: 008
Approval Date: Jan 8, 1999
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code: AB1
Patent and Exclusivity Info for this product: View
Active Ingredient: ESTRADIOL
Dosage Form;Route: FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name: VIVELLE-DOT
Applicant: NOVARTIS
Strength: 0.025MG/24HR
Application Number: N020538
Product Number: 009
Approval Date: May 3, 2002
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code: BX
Patent and Exclusivity Info for this product: View
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Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through April, 2010
Patent and Generic Drug Product Data Last Updated: May 17, 2010
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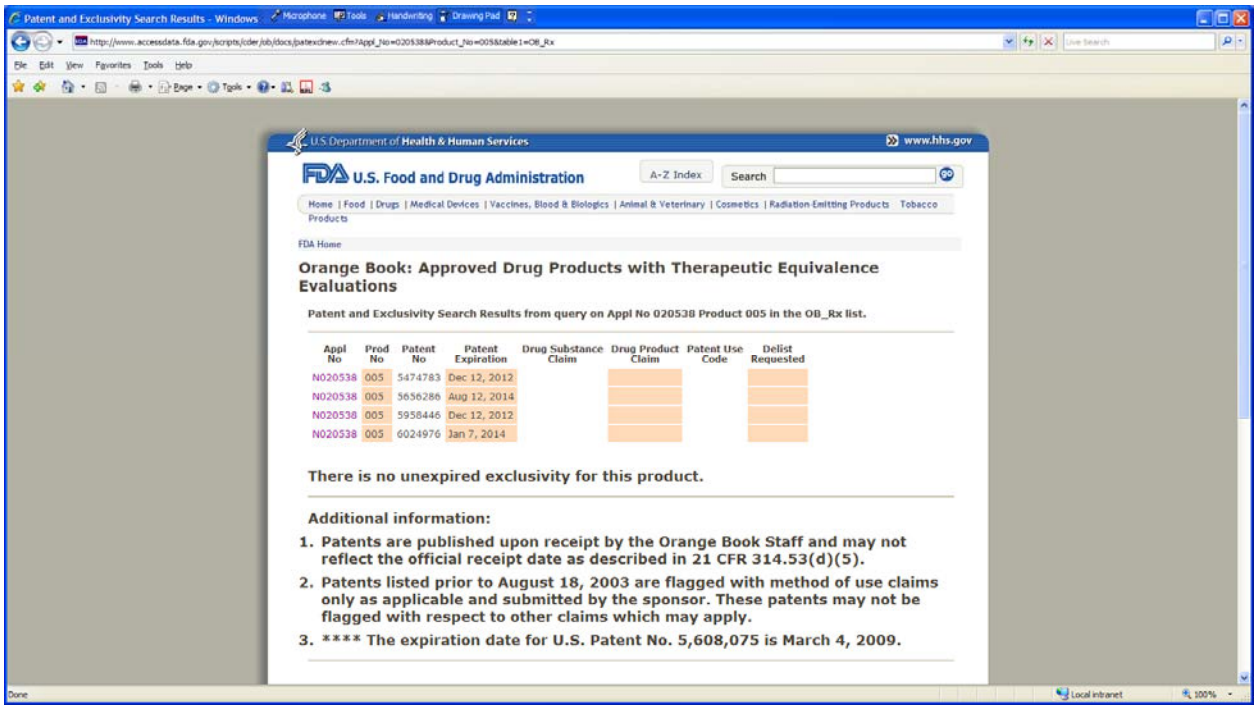
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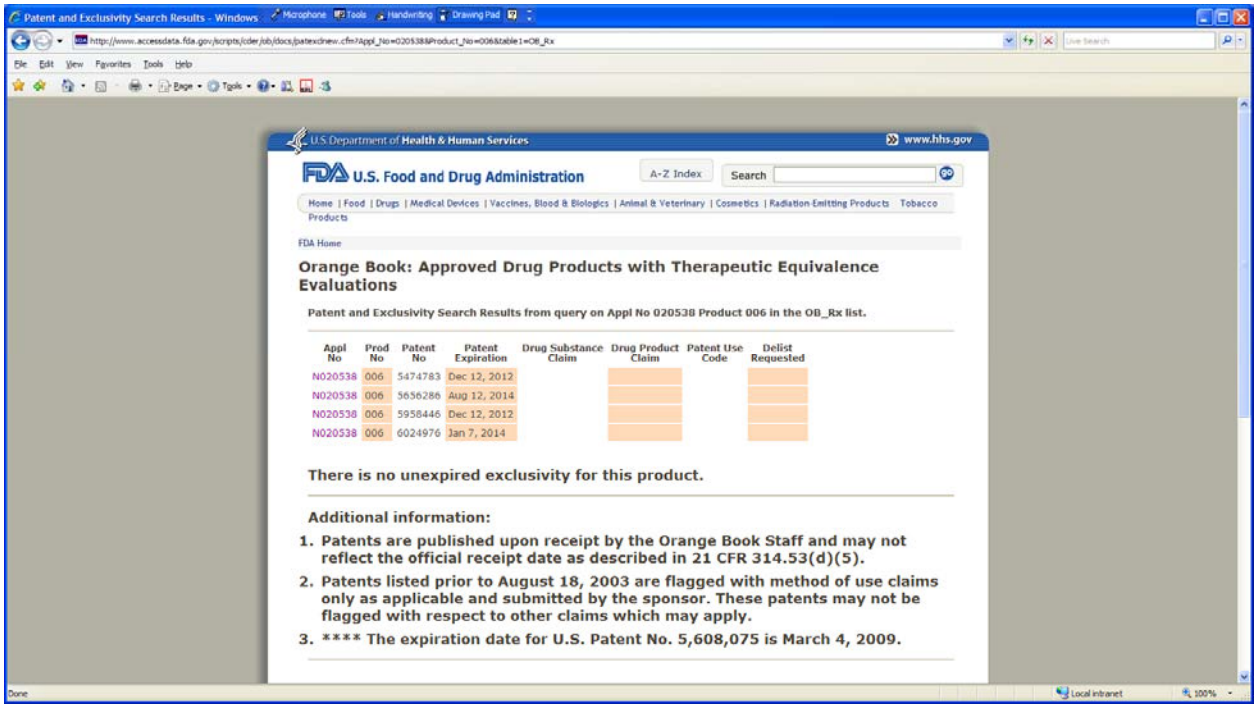
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
N020538 | 005 | 5474783 | Dec 12, 2012
N020538 | 005 | 5656286 | Aug 12, 2014
N020538 | 005 | 5958446 | Dec 12, 2012
N020538 | 005 | 6024976 | Jan 7, 2014
There is no unexpired exclusivity for this product.
Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.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Patent and Exclusivity Search Results from query on Appl No 020538 Product 006 in the OB_Rx list.
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
N020538 | 006 | 5474783 | Dec 12, 2012
N020538 | 006 | 5656286 | Aug 12, 2014
N020538 | 006 | 5958446 | Dec 12, 2012
N020538 | 006 | 6024976 | Jan 7, 2014
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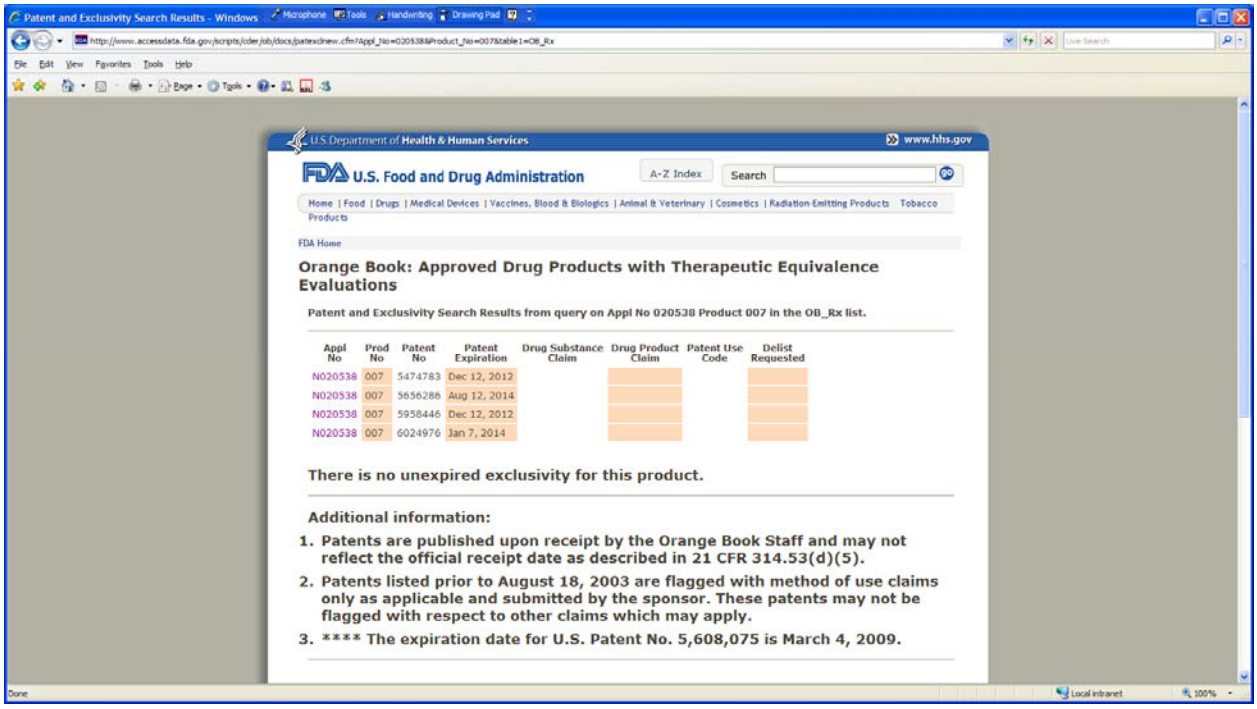
Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.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Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
N020538 | 007 | 5474783 | Dec 12, 2012
N020538 | 007 | 5656286 | Aug 12, 2014
N020538 | 007 | 5958446 | Dec 12, 2012
N020538 | 007 | 6024976 | Jan 7, 2014
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2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.
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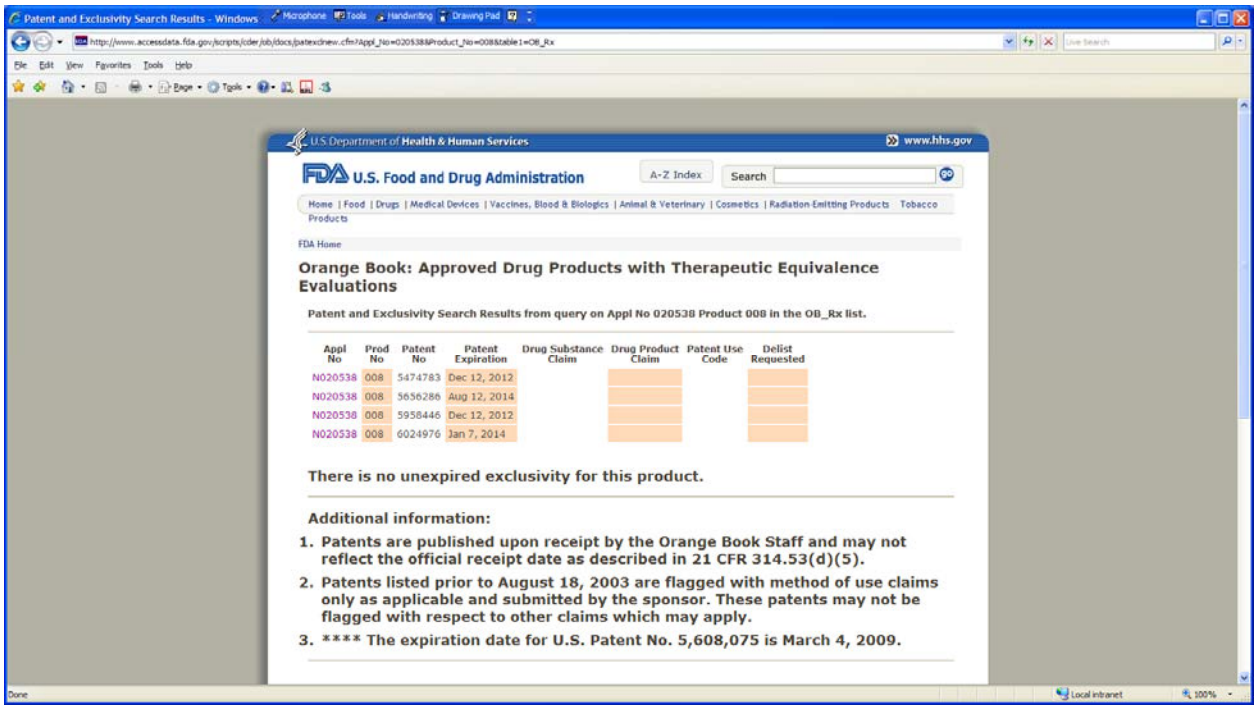
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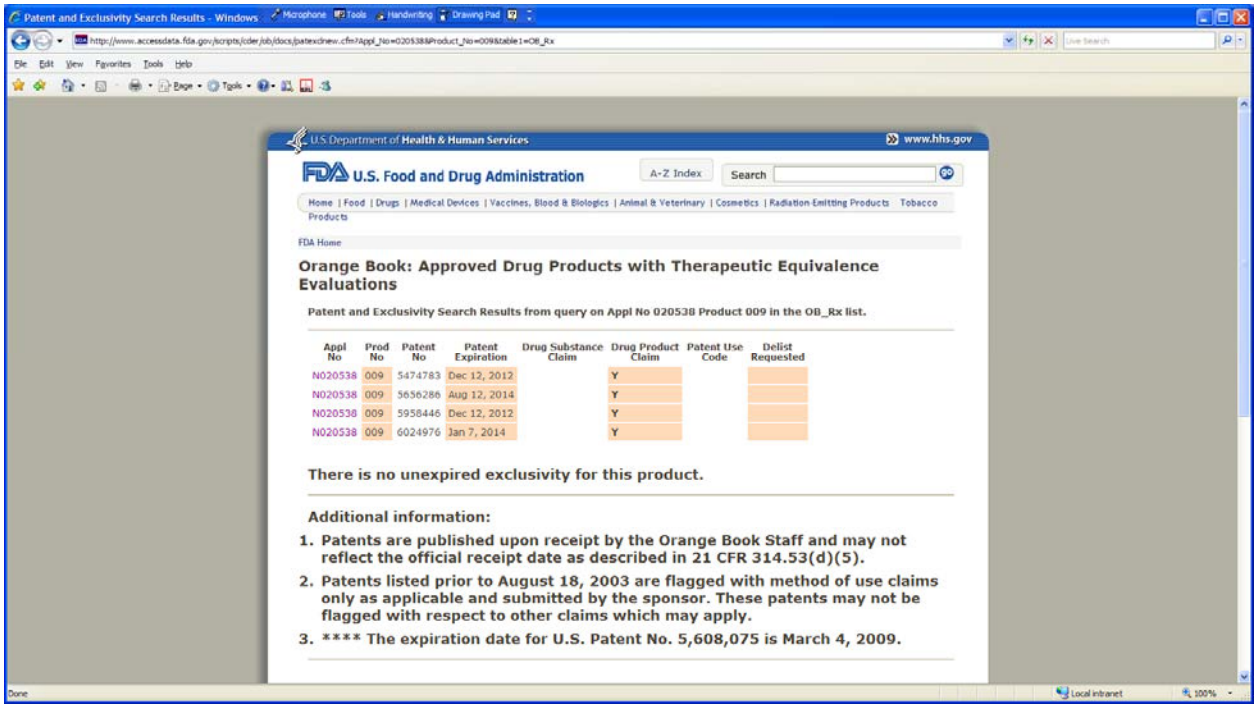
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
N020538 | 008 | 5474783 | Dec 12, 2012
N020538 | 008 | 5656286 | Aug 12, 2014
N020538 | 008 | 5958446 | Dec 12, 2012
N020538 | 008 | 6024976 | Jan 7, 2014
There is no unexpired exclusivity for this product.
Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.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Patent and Exclusivity Search Results from query on Appl No 020538 Product 009 in the OB_Rx list.
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
N020538 | 009 | 5474783 | Dec 12, 2012 | | Y | |
N020538 | 009 | 5656286 | Aug 12, 2014 | | Y | |
N020538 | 009 | 5958446 | Dec 12, 2012 | | Y | |
N020538 | 009 | 6024976 | Jan 7, 2014 | | Y | |
There is no unexpired exclusivity for this product.
Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
3. **** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201675	ORIG-1	MYLAN TECHNOLOGIES INC	ESTRADIOL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TED C PALAT
08/03/2010

MARTIN H Shimer
08/06/2010

CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# 201675_____ **FIRM NAME**_Mylan Technologies Inc. _____

DRUG NAME _Estradiol Transdermal System, USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day_____

DOSAGE FORM __Transdermal System_____

REFERENCE LISTED DRUG (RLD)__Vivelle-Dot® (estradiol transdermal system), NDA 020538_____

Requested by: __Eda Howard_____ Date: _5/19/10_____
Regulatory Support Team, (HFD-615)

	Summary of Findings by Clinical Review Team
	Study meets statutory requirements
X	**Study does NOT meet statutory requirements: The sponsor failed to submit the statistical analysis results using the OGD recommended method to show that skin irritation potential and adhesion performance of their patch are not inferior to those of the RLD. See Comments to be conveyed to the sponsor for details.**
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: **___COMPLETE** **_X_INCOMPLETE**

Reviewed by:

_____ Date: _____
Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

_____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	X				A combined skin irritation, adhesion, and sensitization study using Mylan's Estradiol TDS, 0.025 mg/day and Novartis' Vivelle-Dot® 0.025 mg/day was submitted. (Mylan#EDOT-0908)
Summary of Study	X				
Clinical Site (s)	X				A single site in Russian Federation
Study Investigator (s)	X				
List of subjects included in PP/ (M)ITT populations per treatments	X				
List of subjects excluded/ from PP/ (M)ITT per treatments	X				
Reasons for discontinuation from the study if discontinued	X				
Adverse Events	X				
Concomitant Medications	X				
Individual subject's scores/data per visit	X				
Pre-screening of Patients	X				
IRB Approval	X				
Consent Forms	X				
Randomization Schedule	X				
Protocol Deviations	X				
Case Report Forms	X				
PD Data Disk (or Elec Subm)	X				
Study Results	X				

Clinical Raw Data/ Medical Records	X				
Financial Disclosure	X				
Composition	X				
BioStudy Lot Numbers	X				
Date of Manufacture	X				
Exp. Date of RLD	X				
Statistical Reports	X				
Summary results provided by the firm indicate no worse skin irritation and sensitization potential and adhesion performance of the test product compared to those of the RLD		X			See comments below.
Waiver requests for other strengths / supporting data		X			N/A

Comments <u>NOT</u> to be conveyed to the sponsor:

The sponsor evaluated the skin irritation and sensitization potential and adhesion performance of the test product (0.025 mg/day) and reference product (0.025 mg/day) in healthy post-menopausal female subjects. Both patches were placed on the abdomen simultaneously for a total of 6 sequential applications of 3.5 days (84 hours) duration, giving a total induction phase of 21 days of continuous same-site exposure to each product. Following a 14-day rest phase, a challenge application of each product was applied to a naïve skin site followed by 3 days of observation and irritation evaluation.

For the skin irritation analysis, the sponsor did not provide the upper bound of the one-sided 95% CI of the mean irritation score of the test product minus 1.25 X mean irritation score of the reference product. Instead, the sponsor modified the statistical criteria such that the upper bound of the reference mean irritation score was based on the reference mean irritation score +0.25, where the absolute value of 0.25 represents 25% of the sensitivity limit of irritation scoring (e.g., a score of one). The sponsor used the greater of the dermal response and other effect scores (e.g., skin irritation response of 2 + other effects of 1=actual score of 2) for their analysis instead of a combined score. The sponsor's summary of cumulative mean irritation analysis is shown below.

Table 11.5 Primary Efficacy Analysis of Cumulative Irritation Scores

Number of Subjects	Least-Squares Mean: Mylan Estradiol Transdermal System, 0.025 mg/day (2.5 cm^2)	Least-Squares Mean: Vivelle-Dot® (Estradiol Transdermal System), 0.025 mg/day (2.5 cm^2)	$\mu_1-\mu_2$	One-sided 95% Confidence bounds [1]: Lower Bound	One-sided 95% Confidence bounds [1]: Upper Bound
213	0.165	0.142	0.023	-0.008	0.053

[1] Upper one-sided 95% confidence bound on $\mu_1-\mu_2$ is < 0.25, which indicates Mylan estradiol TDS is non-inferior to Vivelle-Dot® TDS

Table 11.6 Frequency Distribution of Irritation Scores (Per Protocol Population Only)

Treatment A[1]

Study Hour / Frequency	Irritation Score 0	1	2	3	7	Total
84	200	8	5	0	0	213
168	193	18	2	0	0	213
252	190	16	7	0	0	213
336	192	12	5	3	1	213
420	178	21	10	3	1	213
504	184	21	3	4	1	213
Total	1137	96	32	10	3	1278
Total %	**89%**	**7.5%**	**2.5%**	**0.8%**	**0.2%**	**100%**

Treatment B[1]

Study Hour / Frequency	Irritation Score 0	1	2	3	7	Total
84	198	15	0	0	0	213
168	195	16	2	0	0	213
252	187	25	1	0	0	213
336	190	18	5	0	0	213
420	167	37	9	0	0	213
504	184	22	6	1	0	213
Total	1121	133	23	1	0	1278
Total %	**88%**	**10%**	**1.8%**	**0.1%**	**0.0%**	**100%**

[1]Treatment A: Estradiol Transdermal System, 0.025 mg/day x (6), Mylan

[1]Treatment B: Vivelle-Dot Transdermal System, 0.025 mg/day x (6), Novartis

Table 11.7 Frequency Distribution of Mean Cumulative Irritation Scores

Treatment[1] / Frequency	Irritation Score = 0	0 < & < = 1	1< & < = 2	> 3	Total
A	144	61	7	1	213
B	130	80	3	0	213
Total	274	141	10	1	426
Cum. % Total	**64.3%**	**97.4%**	**99.8%**	**100%**	**100%**

[1]Treatment A: Estradiol Transdermal System, 0.025 mg/day x (6), Mylan

[1]Treatment B: Vivelle-Dot Transdermal System, 0.025 mg/day x (6), Novartis

For skin adhesion analysis, the sponsor did not provide the upper bound of the one-sided 95% CI of the mean adhesion score of the test product minus 1.25 X mean adhesion score of the reference product. Instead, the sponsor modified the statistical criteria such that the lower one-sided 95% confidence bound on μT-0.8μR was calculated and assessed relative to zero. The sponsor included only average adhesion scores from the induction application #1. Subjects were instructed to apply gentle pressure to smooth out the system when lifted. In the case of missing adhesion scores, the last observation carried forward method was applied. The sponsor's summary of adhesion analysis is shown below.

Table 11.3 Primary Efficacy Analysis of Adhesion Scores

	Least-Squares Mean				
Number of Subjects	Mylan Estradiol Transdermal System, 0.025 mg/day (2.5 cm^2)	Vivelle-Dot® (Estradiol Transdermal System), 0.025 mg/day (2.5 cm^2)	$\mu_T-0.8\mu_R$[1]	Lower Bound of 95% Confidence Region[2]	P-Value[3]
228	98.87	98.93	19.73	19.40	<0.0001

[1] Estimated as Estradiol TDS least-squares mean – 0.8 x Vivelle-Dot® least-squares mean.

[2] Lower one-sided 95% confidence bound on $\mu_1-0.8\mu_2$. A value > 0 indicates Estradiol TDS is non-inferior to Vivelle-Dot® TDS

[3] P-value for Ho: $\mu_1-0.8\mu_2 = 0$, from two-way analysis of variance with factors of treatment and patch site. If the estimate of $\mu_1-0.8\ \mu_2 > 0$, a p-value ≤ 0.1000 indicates estradiol TDS is non-inferior to Vivelle-Dot® TDS.

Table 11.4 Frequency Distribution of Adhesion Scores

		Treatment A[1]									
Patch	**Study Hour**	**Adhesion Score[2]**									
	Frequency	0	15	45	55	65	75	85	95	100	Total
1	24 hr	0	0	0	0	0	0	0	0	228	228
1	48 hr	0	0	0	0	0	0	1	5	222	228
1	72 hr	0	0	0	0	0	1	3	33	191	228
1	84 hr	3	1	0	0	0	1	4	57	162	228
2	168 hr	1	0	0	0	0	1	15	58	153	228
3	252 hr	0	0	0	0	1	2	7	44	174	228
4	336 hr	2	0	0	0	0	4	10	70	140	226
5	420 hr	1	0	1	0	0	1	7	45	168	223
6	504 hr	0	0	0	0	0	0	13	58	152	223
Challenge	888 hr	2	0	0	0	0	0	2	41	178	223
	Total	**9**	**1**	**1**	**0**	**1**	**10**	**62**	**411**	**1768**	**2263**

Patch	Study Hour	Treatment B[1] Adhesion Score[2]									
	Frequency	0	15	45	55	65	75	85	95	100	Total
1	24 hr	0	0	0	0	0	0	0	1	227	228
1	48 hr	0	0	0	0	0	0	0	4	224	228
1	72 hr	0	0	0	0	0	0	1	42	185	228
1	84 hr	2	0	1	1	0	0	6	67	151	228
2	168 hr	2	0	0	0	0	6	20	55	145	228
3	252 hr	2	0	0	0	0	2	6	49	169	228
4	336 hr	0	0	0	0	0	5	10	79	132	226
5	420 hr	0	0	0	0	0	2	13	49	159	223
6	504 hr	0	0	0	0	0	4	14	53	152	223
Challenge	888 hr	0	1	0	0	0	0	8	41	173	223
	Total	**6**	**1**	**1**	**1**	**0**	**19**	**78**	**440**	**1717**	**2263**

[1]Treatment A: Estradiol Transdermal System, 0.025 mg/day x (6 + 1), Mylan

[1]Treatment B: Vivelle-Dot Transdermal System, 0.025 mg/day x (6 + 1), Novartis

[2]Score: 100, Adhesion: 100%; Score: 95, Adhesion: >90% to <100%;

[2]Score: 85, Adhesion: >80% to 90%; Score: 75, Adhesion: >70% to 80%;

[2]Score: 65, Adhesion: >60% to 70%; Score: 55, Adhesion: >50% to 60%;

[2]Score: 45, Adhesion: >40% to 50%; Score: 35, Adhesion: >30% to 40%;

[2]Score: 25, Adhesion: >20% to 30%; Score: 15, Adhesion: >10% to 20%;

[2]Score: 5, Adhesion: >0 to 10%; Score: 0, Adhesion: Fell-off

According to the sponsor, no skin sensitization reaction was observed during the challenge phase. No subject received a dermal response score greater than zero either in the test group or reference group during the challenge phase.

The composition of the test product is shown below.

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Comments to be conveyed to the sponsor:

1. **The data submitted to your application are not sufficient for receiving your ANDA. Your frequency distribution table of irritation scores shows considerably more scores of 3 or higher for the test product than for the reference product (13 vs. 1). You have failed to submit the statistical analysis results using the OGD recommended method to show that the skin irritation potential and adhesion performance of your product are at least as good as those of the reference product.**

2. **The one-sided 95% CI for the mean cumulative irritation score of the test product minus 1.25 X mean cumulative irritation score of the reference product in the per protocol population should be provided. The cumulative mean irritation score analysis should include "other effect" scores. For example, if the dermal response score is 2 and other effects score is H(3), then the actual irritation score is 5 (2+3). If a patch is moved to an alternate site due to an unacceptable irritation, the last score on the original site is to be carried forward as the score for all subsequent irritation scores for the patch.**

3. **In addition to cumulative irritation scores, it is necessary to also evaluate the proportion of subjects with a meaningful degree of irritation for each product. The proportion of subjects with a meaningful degree of irritation should be no higher for the test product than for the reference product, and irritation should not occur earlier in the application period for the test than for the reference product. Therefore, the study report should include a frequency table for skin irritation scores, other effect scores, and combination of skin irritation and other effect scores in the per protocol population during the induction period for each patch type on each evaluation day.**

4. **The one-sided 95% CI for the mean adhesion score of the test product minus 1.25 X mean adhesion score of the reference product in the per protocol population should be provided.**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201675	ORIG-1	MYLAN TECHNOLOGIES INC	ESTRADIOL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL Y KIM
07/29/2010

DENA R HIXON
07/29/2010
I concur.

BIOEQUIVALENCE CHECKLIST
FOR APPLICATION COMPLETENESS

ANDA# 201675 **FIRM NAME** **Mylan Technologies Inc.**

DRUG NAME Estradiol

DOSAGE FORM Film, extended release - Transdermal; 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

SUBJ: Request for examination of the bioequivalence study submitted with an ANDA 201675 for Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv)

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason: NOTE: The adhesion, skin irritation and sensitization study should be reviewed for completeness by the OGD Clinical Team. Only the BE study with pharmacokinetic (PK) endpoints is reviewed by the Division of Bioequivalence in the current checklist.
☒	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Vipra Kundoor, Ph.D.
Reviewer

_____ Date: _____
April C. Braddy, Ph.D.
Team Leader

_____ Date: _____

Hoainhon N. Caramenico
Acting Deputy Director

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			Module 5.3.1.2.4
Assay Methodology	☒	☐			Module 5.3.1.4.3
Procedure SOP	☒	☐			Module 5.3.1.4.3
Methods Validation	☒	☐			Module 5.3.1.4
Study Results Ln/Lin	☒	☐			Study Report Body, Module 5.3.1.2.3
Adverse Events	☒	☐			Module 5.3.1.2.22
IRB Approval	☒	☐			Study Report Body, Module 5.3.1.2.3 (Appendix 16.1.3)
Dissolution Data	☒	☐			Module 2.7
Pre-screening of Patients	☒	☐			See Clinical reports for each study in module 5.3.1.2.3
Chromatograms	☒	☐			Module 5.3.1.4.3
Consent Forms	☒	☐			Study Report Body, Module 5.3.1.2.3 (Appendix 16.1.3)
Composition	☒	☐			Module 3.2.P.1
Summary of Study	☒	☐			Module 5.3.1.2.2
Individual Data & Graphs, Linear & Ln	☒	☐			Study Report Body, Module 5.3.1.2.3
PK/PD Data Disk Submitted)	☒	☐			.xpt files (Module 5.3.1.2.25.3.1
Randomization Schedule	☒	☐			Module 5.3.1.2.10

Protocol Deviations	☒	☐			Module 5.3.1.2.17
Clinical Site	☒	☐			Cetero Research – Miami, 1405 NW 167 Street, Miami Gardens, FL 33169
Analytical Site	☒	☐			(b) (4)
Study Investigators	☒	☐			Lawrence A. Galitz, M.D. (b) (6)
Medical Records	☒	☐			Part of CRF (Module 5.3.1.2.24)
Clinical Raw Data	☒	☐			Module 5.3.1.2.23
Test Article Inventory	☒	☐			Study Report Body, Module 5.3.1.2.3 (Appendix 16.2.5)
BIO Batch Size	☒	☐			(b) (4), Module 5.3.1.3
Assay of Active Content Drug	☒	☐			Test: 101.7%, Lot # R6A0030 Reference: 101.1%, Lot # 38967 Module 5.3.1.3
Content Uniformity	☒	☐			(b) (4) (2.2%), Lot # R6A0030, Module 5.3.1.3
Date of Manufacture	☒	☐			08/2009, Lot # R6A0030, Module 5.3.1.3
Exp. Date of RLD	☒	☐			02/2011, Module 5.3.1.3
BioStudy Lot Numbers	☒	☐			Test: R6A0030 Reference: 38967 Module 5.3.1.3
Statistics	☒	☐			Module 5.3.1.2.3
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			Module 5.3.1.2.2

Waiver requests for other strengths / supporting data	☒	☐			Module 2.7

Additional Comments regarding the ANDA:

1. This is an electronic submission.

2. The reference listed drug (RLD) is Vivelle-Dot® (estradiol transdermal system), 0.1 mg/24hr from Novartis (NDA # 020538, approved on July 31, 1996)[1].

3. Vivelle-Dot® Transdermal System is indicated for the following[2]:
   - Treatment of moderate to severe vasomotor symptoms associated with the menopause.
   - Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.
   - Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
   - Prevention of postmenopausal osteoporosis.

4. There are bioequivalence (BE) recommendations for Estradiol film, extended-release / transdermal, systems located in the internal control correspondence database (# 07-0511-Mylan Technologies, Inc.)[3]. The Division of Bioequivalence (DBE) recommends the following studies:

   - A single-dose, two way crossover *in vivo* bioequivalence study comparing Estradiol Transdermal System, 0.1 mg/24 hr, to the reference listed drug (RLD), Vivelle-Dot® (estradiol transdermal system), 0.1 mg/24 hr in healthy postmenopausal women. The test and RLD products should be applied to the abdomen for 3.5 days

   - A skin irritation/sensitization study comparing Estradiol Transdermal System 0.025 mg/24 hr to the RLD, Vivelle-Dot®. In addition, the study should also evaluate adhesion properties.

   - Estradiol Transdermal Systems, 0.0375 mg/24 hr, 0.05 mg/24 hr and 0.075 mg/24 hr, may be considered for a waiver of in-vivo bioequivalence testing based on (1) acceptable bioequivalence studies on 0.1 mg/24 hr and 0.025 mg/24 hr strength, (2) acceptable dissolution testing of the 0.025 mg/24 hr, 0.0375 mg/24 hr, 0.05 mg/24 hr, 0.075 mg/24 hr and 0.1 mg/24 hr strengths, and (#) proportional similarity in the formulations of all strengths.

   - Please also submit the results of an "apparent dose delivered" study based on an *in-vitro* study for each patch used in the bioequivalence study by subtracting the "total amounts of

[1] Drugs@FDA, Last accessed date: 06/02/2010
[2] RLD Label approved on 08/06/2004. Last accessed date: 06/02/2010.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/20538s024lbl.pdf
[3] Control Correspondence # 07-0511, Applicant: Mylan. Submission date: 03/22/2007. Letter date (response to applicant): 05/16/2007.. Last accessed date: 06/02/2010.

drug remaining in the patch and on the skin" from the "dose (assayed potency)".

5. The firm conducted and submitted the following[4]:

   A BE study with pharmacokinetic (PK) endpoints (Study # EDOT-0922)

   - This was a Single-Dose Fasting Bioequivalence Study of Estradiol Transdermal System, USP (Twice Weekly) (0.1 mg/day; Mylan) and Vivelle-Dot® (0.1 mg/day; Novartis) in Healthy Post-Menopausal Women

   - The 90% Confidence Intervals for the PK parameters in the BE study passed the 80-125% BE criterion.

Pharmacokinetic Results (N = 47):

Baseline-corrected Estradiol				
Parameter	**Arithmetic Mean A = Mylan**	**Arithmetic Mean B = Vivelle-Dot®**	**LSMEANS Ratio (A/B)**	**90% Confidence Interval**
AUCL (pg•hr/mL)	8264 (33.36)	7742 (35.75)	1.07	101% – 113%
AUCI (pg•hr/mL)	8420 (33.10)^	7913 (35.09)^	1.08†	102% – 115%
CPEAK (pg/mL)	144.9 (41.58)	126.2 (40.66)	1.15	107% – 122%
KEL (hr^{-1})	0.0681 (81.52)^	0.0702 (58.06)^		
HALF (hr)	14.61 (63.90)^	13.18 (49.62)^		
TPEAK (hr)	22.64 (30.94)	30.13 (48.50)		

^N = 46; †N = 45

Baseline-uncorrected Estradiol				
Parameter	**Arithmetic Mean A = Mylan**	**Arithmetic Mean B = Vivelle-Dot®**	**LSMEANS Ratio (A/B)**	**90% Confidence Interval**
AUCL (pg•hr/mL)	8722 (34.66)	7998 (35.86)	1.09	104% – 115%
AUCI (pg•hr/mL)	8726 (31.43)^	8243 (36.07)^	1.09†	103% – 115%
CPEAK (pg/mL)	148.7 (40.91)	128.4 (40.10)	1.16	108% – 124%
KEL (hr^{-1})	0.0527 (66.68)^	0.0618 (68.09)^		
HALF (hr)	18.22 (58.02)^	16.33 (60.36)^		
TPEAK (hr)	22.64 (30.94)	30.13 (48.50)		

^N = 46; †N = 45

An adhesion, skin irritation and sensitization study (Study # EDOT-0908)

- This was a comparative evaluation of the adhesion, cumulative irritation and contact sensitization potential of Mylan' Estradiol Transdermal System, USP (Twice-Weekly) (0.025 mg/day) to Vivelle-Dot® (Estradiol Transdermal System) (Novartis; 0.025 mg/day) in Healthy Post Menopausal Women.

6. The firm did not submit the results of an "apparent dose delivered" study for each patch of

[4] ANDA 201675 submission, Module 5.3.1.2.3

drug remaining in the patch and on the skin" from the "dose (assayed potency)". – *as per the recommendations of controlled correspondence # 07-0511.*

7. There is no USP or FDA recommended dissolution method available for this drug product. The firm submitted dissolution testing data using their method and specifications. The firm's method and specifications are as follows[5]:

8. From a bioequivalence standpoint the application is acceptable for filing.

9. *The completeness of adhesion, skin irritation and sensitization study (Study # EDOT-0908) should be reviewed by the clinical team.*

Additional Information Requested From the Applicant:

As requested in controlled correspondence, # 07-0511, the firm, Mylan Technologies, Inc., (Letter date: 05/16/2007) is requested to submit an *in vitro* study report for an "apparent dose delivered" study for each patch used in the bioequivalence study by subtracting the "total amounts of drug remaining in the patch and on the skin" from the "dose (assayed potency)".

[5] ANDA 201675 submission, Module 2.7.

Outcome Page

ANDA: 201675

Completed Assignment for 201675 ID: 11328

Reviewer: Kundoor, Vipra **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
11328	4/26/2010	Paragraph 4	Paragraph 4 Checklist	1	1
				Bean Total:	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201675	ORIG-1	MYLAN TECHNOLOGIES INC	ESTRADIOL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VIPRA R KUNDOOR
06/08/2010

APRIL C BRADDY
06/09/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
06/09/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 201675Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	**Author:** Heather Strandberg	

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)**

RPM: AP Team: **Approval Date:** 12/19/2014

☐ **PI** ☐ **PII** ☒ **PIII** ☐ **PIV** (*eligible for 180 day exclusivity* ☐ **Yes** ☒ **No)** ☐ **MOU** ☒ **RX or** ☐ **OTC**

ANDA #: 201675 Applicant: Mylan Technologies Inc. Established Product Name: Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice Weekly).

Basis of Submission (RLD): Vivelle-Dot
(Is ANDA based on an approved Suitability Petition? ☐ *Yes* ☒ *No)*

Does the ANDA contain REMS? ☒ **Yes** ☐ **No** *(If YES, initiate approval action 6 weeks prior to target action date)*

Regulatory Project Manager Evaluation:		**Date: 12/5/2014**
☒ Date last Complete Response (CR) letter was issued -- Date 4/4/2014 ☐ Previously reviewed and tentatively approved (if applicable) --- Date _____		
Date of Application 4/26/2010	Original Received Date 4/27/2010	Date Acceptable for Filing 4/27/2010

YES	NO		
☒	☐	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)	
		Date of Acceptable Quality 9/24/2014 Date of Acceptable Dissolution 1/20/2012 Date of Acceptable Bioequivalence 1/20/2012 Date of Acceptable Labeling 10/31/2013	If applicable: Date of Acceptable Microbiology N/A Date of Acceptable Clinical Review 12/5/2014 Date of Acceptable REMS _____
☐	☒	Are consults pending for any discipline?	
☐	☒	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES→Verify a second filing review was completed and that all disciplines completed new reviews ☐	
☐	☒	Is there a pending Citizen Petition (CP)?	
☒	☐	Overall OC Recommendation is acceptable (EES is acceptable) Date Acceptable: _____ Re-evaluation Date: _____	
☒	☐	OSI Clinical Endpoint and Bioequivalence Site Inspections are acceptable	
☐	☐	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff (OGDREQUEST) 30 to 60 days prior to approval, Date emailed _____	
Draft Approval/Tentative Approval Letter			
☒	☐	Approval/Tentative Approval letter is drafted and uploaded to the Final Decision task	
Review Discipline/Division Endorsements			
☒	☐	Division of Legal and Regulatory Support Endorsement completed, Date 12/12/14	
☐	☒	Paragraph IV Evaluation completed (if applicable), Date N/A	
☒	☐	Quality Endorsement completed, Date 12/18/14	
☒	☐	Bioequivalence Endorsement completed, Date 12/17/14	
☒	☐	Labeling Endorsement completed, Date 12/15/14	
☐	☒	REMS Endorsement (if applicable), Date N/A	
RPM Team Leader Endorsement and Action Package Verification			
☒	☐	RPM Team Leader Endorsement completed, Date 12/19/2014	
Final Decision and Letter Sign-off			
☒	☐	Final Decision recommending approval/tentative approval completed, Date 12/19/2014	
☒	☐	Approval/Tentative Approval letter electronically signed, Date: 12/19/2014	
Project Close-Out			
☒	☐	Notify applicant of approval and provide a courtesy copy of the electronically signed letter	
☐	☒	Is there a Post Marketing Agreement (PMA)? IF YES → Send email to PMA coordinator, Date emailed _____	
☒	☐	Email OGD Approval distribution list (CDER-OGDAPPROVALS) with approval information	

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

This page to be completed by the RPM

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 12/12/2014
Name/Title: **IM for MHShimer**

Contains GDEA certification: Yes ☒ No ☐	
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Vivelle-Dot NDA# 20-538 Date Checked N/A Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days: Yes ☒ No ☐ Has case been settled: Yes ☒ No ☐ Date settled: Is applicant eligible for 180 day No Is a forfeiture memo needed: Yes ☐ No ☒ If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒☐	
Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER:	

Comments:

BOS = Vivelle Dot (NDA 20-538) Application submission 4/27/2010 with a PIV certification to the '286 and '976 patents and PIII certifications to the '783 and '446 patents. Application received an RTR 8/6/2010. ANDA was subsequently acknowledged (LO 12/23/2010) with a receipt date of 4/27/2010.

Patent amendment 1/11/2011 stating RR had been sent. Amendment dated 2/2/2011 with copies of the PIV RR sent via (b) (4) 1/11/2011 to Novartis (FL, NJ) and rc'd 1/12/2011.

Amendment 3/8/2011 stating litigation was filed 2/22/2011 in USDC of NY, CA# 11-cv-1187, and 2/24/2011 in USDC of VT, CA#5:11-cv-00050-cr , both on the '286 and '976 patents.

Amendment containing copies of Complaint Dismissals for both cases, entered 6/27/2011 in USDC of VT and 12/23/2011 in USDC of NY. Mylan also states they reached a settlement agreement with Novartis which allows them to go to market prior to the expiration '286 and '976 patents.

The '286 patent expired 8/12/2014 and the '976 patent expired 1/7/2014. There are no unexpired patents or exclusivities remaining in the OB for the RLD. Of note, the Mylan application was the first-to-file a PIV citing NDA 20538 as their BOS, but there are no remaining patents on which to grant the 180-day. This application is eligible for Immediate Full Approval.

2. ***Paragraph IV Evaluation (for ANDAs with PIV certifications or other controversial regulatory issues)***
Date: 12/19/14 **Name/Title:** RLWest **Comments:** N/A. There are no paragraph IV certifications currently associated with this ANDA.

Or see corresponding endorsement task under the ANDA project within the platform

3. ***Quality Endorsement by the Office of Pharmaceutical Science***
Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

4. ***Bioequivalence Endorsement***
Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

5. ***Labeling Endorsement***
Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

6. ***REMS Endorsement***
Date: 12/19/14 **Name/Title:** RLWest **Comments:** N/A. No REMS is required.

Or see corresponding endorsement task under the ANDA project within the platform

7. ***RPM Team Leader Endorsement***
Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

8. Final Decision

Date: 12/19/14
Name/Title: **RLWest**

Para.IV Patent Cert: Yes ☐ ☐ ☐ No ☒
Pending Legal Action: Yes ☐ ☐ No ☒
Petition: Yes ☐ No ☒
Entered to APTrack database ☒
GDUFA User Fee Obligation Status Met ☒ Unmet ☐
Press Release Acceptable ☐
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐

Date PETS checked for first generic drug _____

Comments:
CDER's Office of Compliance has provided an overall "Acceptable" recommendation for this ANDA. The reevaluation date associated with this recommendation will expire on 4/30/15.

I have reviewed the final recommendations provided by each of the review disciplines (Chemistry, Bioequivalence, Clinical, Statistics, Labeling, Policy) and I concur.

Mylan Technologies submitted a fasting PK study on the 0.1 mg strength of their drug product. This study, along with appropriate in-vitro dissolution data for all 5 product strengths, was reviewed by the Division of Bioequivalence and found acceptable. Based upon the PK data, acceptable in-vitro dissolution data and the dose-proportionality of the individual formulations, waivers were granted to the 0.025 mg, 0.0375 mg, 0.05 mg and 0.075 mg strengths under 21 CFR 320.24(b)(6). The bio study sites have acceptable OSI inspection histories. In addition, OGD's Clinical Team reviewed the skin irritation, sensitization and adhesion attributes of the Mylan product and found them to be acceptable for approval. The statistical review supported the clinical team's conclusions. No REMS is required for approval of Estradiol Transdermal System, USP. A patient information leaflet intended to be dispensed to the patient at the time of dispensing, is part of the approved labeling for this drug product. At present, there are no unexpired patents or exclusivity currently listed in the "Orange Book" for this drug product.

This ANDA is recommended for approval.

EES DATA:

Click here to enter text.

Application History:

Click here to enter text.

Orange Book Report:

Click here to enter text.

REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form

EASILY CORRECTABLE DEFICIENCY - FAX

ANDA 201675

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Mylan Technologies Inc. TEL: (304) 599-2595 x 6429

ATTN: Joseph J. Sobecki FAX: (304) 285-6407

FROM: Brijet Burton Coachman FDA CONTACT PHONE: (240) 402-4878

Dear Sir:

This communication is in reference to your abbreviated new drug application (ANDA) dated April 26, 2010 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Estradiol Transdermal System, USP (Twice-Weekly); 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**EASILY CORRECTABLE DEFICIENCY-
CHEMISTRY**

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Andrew Potter, at (240) 402-9266.

We have completed our review and have the following comments:

PRODUCT QUALITY

A. Deficiencies

In accordance with the Residual Drug Guidance, ANDA product should have a residual drug load equal to or less than that in RLD. Please provide comparative residual drug data for your product and the RLD at the completion of the delivery period.

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

Based on the current information, it's hard to understand the root cause for the higher shear strength observed for your estradiol product (b) (4) . Therefore, you are requested to provide commitment that you will investigate into these issues based on additional data generated through validation batches and commercial batches.

Sincerely yours,

{See appended electronic signature page}

Bhagwant Rege, Ph.D.
Supervisor, Chemistry V
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DHAVAL GAGLANI
09/17/2014

Dempsey, Mary

From: Dempsey, Mary
Sent: Sunday, February 23, 2014 11:21 AM
To: [redacted (b) (6)]; rajiv.malik@mylanlabs.com; marcie.mcclintic@mylanlabls.com
Cc: Dempsey, Mary
Subject: OGD reply to Mylan

Dear [redacted (b) (6)] Rajiv, and Marcie,

Thank you for your e-mail. Unfortunately, due to the number of email requests Dr. Uhl receives, she is unable to respond to you directly.
I am responding on her behalf.

I have researched your inquiries regarding the following: 1) Norelgestromin and Ethinyl Estradiol Transdermal System and Estradiol Transdermal System USP, 2) [redacted (b) (4)] [redacted (b) (4)].

My research confirms that the basis for our determinations outlined in previous meetings with Mylan in unchanged. "The Agency will not use clinical judgment to override a guidance. Scientific evidence will be considered in the clinical context of use and serve as supportive evidence for modification of current guidances if satisfactorily validated."

The Agency additionally conveyed to Mylan the following: "…The Agency supports Mylan's efforts to provide and explanation for the outliers. One acceptable way of doing this would be to conduct a restudy of the outliers against a number of controls from the original irritation study, The Agency recommends using four controls for each outlier."

The guidance in place requires review among various disciplines within the Agency and may require public comments before any revisions will be considered or endorsed and this may take a considerable amount of time. Until such time, Mylan can conduct a restudy of outliers and submit the data for FDA review.

Regards,

Mary Dempsey
Associate Director for Regulatory Affairs
Office of Generic Drugs
Center for Drug Evaluation & Research, FDA
MPN 1, Room 255
7520 Standish Place
Rockville, MD 20855
New Phone: (240) 276-8173
mary.dempsey@fda hhs.gov

From: [redacted (b) (6)] **On Behalf Of** Rajiv.Malik@mylanlabs.com
Sent: Monday, February 03, 2014 4:38 PM
To: Uhl, Kathleen (CDER)

Cc: Rajiv.Malik@mylanlabs.com; Marcie.McClintic@mylanlabs.com
Subject: Follow-Up from Mylan

Dear Dr. Uhl,

I am writing to request an opportunity to discuss an issue of common concern. Specifically, I would like to convey our concern, which I believe is mirrored by the generic industry more generally, over recent delays in resolving straight forward scientific issues, which in turn has the potential to further delay the availability of affordable generic alternatives.

Mylan has been working with OGD for months to resolve an outstanding issue common to certain pending transdermal applications. The issue involves an overly sensitive methodology in FDA's guidance which generates a non-passing result for products that demonstrate excellent adhesion and/or low irritation profiles for four proposed transdermal products. In two of four applications, this longstanding issue is the only remaining barrier to approval which is further described below. If these products did not demonstrate such good performance and thus trigger the non-passing result under the overly sensitive guidance, these products would otherwise be in the hands of patients who today continue to pay more than $80 and $100 per prescription each month.

As explained further below, there are scientifically sound alternative methodologies by which to assess these products and resolve the overly sensitive guidance issue which is currently blocking action on these applications. The resolution remains pending with FDA. This creates an unnecessary barrier because no generic product with very good adhesion and irritation profiles similar to the RLD could pass the study outlined in the guidance (in fact, Mylan has provided evidence to FDA to show that the brand itself would routinely fail FDA's stated criteria if tested against itself). This issue also creates the perverse result of penalizing products which have really good product performance.

Norelgestromin and Ethinyl Estradiol Transdermal System and Estradiol Transdermal System USP

Mylan's ANDA for Norelgestromin and Ethinyl Estradiol Transdermal (NEETS) System, 0.15 mg/24 hr and 0.02 mg/24 hr was originally submitted on December 31, 2009 and our ANDA for Estradiol Transdermal System USP (Twice Weekly), 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day was submitted on April 26, 2010.

OGD initially refused to accept Mylan's NEETS because of its uncertainty regarding the appropriate statistical methodology for demonstrating adhesion and lack of irritation in these products. After Mylan provided a detailed scientific rationale for its statistical methodology, in September 2010, OGD determined that the ANDA should be accepted. The Agency thus has been aware of this issue ***for more than three years***. FDA nonetheless has not settled on an appropriate statistical methodology for these products although it is clear that FDA's product-specific Bioequivalence Guidance does not identify an appropriate methodology by which to assess these products. Mylan has diligently reached out to OGD in an attempt to resolve this issue in a timely manner, but so far to no avail.

On July 1, 2013, Mylan participated in a teleconference with Agency officials to seek clarification on comments contained in OGD's Complete Response letter for ANDA No. 201675. When OGD asked Mylan to request a formal meeting to address this issue in further detail, Mylan promptly did so—and a Type A meeting at which both ANDAs were discussed was held on September 24th with members of both OGD and OND in attendance .

At the Type A Scientific Discussion meeting with FDA on September 24, 2013 Mylan discussed the following salient points:

- OGD's method for assessing non-inferiority becomes progressively overly sensitive when both the test product and the RLD have good adhesion and/or low irritation scores progressing to the best possible adhesion and/or irritation scores. This has led to the inability to demonstrate non-inferiority and discriminates against exactly those ANDAs for which both test and RLD products have superior adhesion and/or irritation profiles.

- Simulations were provided that demonstrate an assessment of the RLD against itself, using OGD's method, would likely fail.

- This current methodology imposes an unnecessary barrier to generic entry for products with essentially equal (favorable) performance.

- Mylan provided threshold considerations and suggested alternatives, and believes the OGD should use science

based criterion to apply a more rational metric that both avoids the progressive reduction of the margin as irritation and adhesion scores approach perfect outcomes, and yet continues to satisfy the requirements of the applicable statutes and regulations for demonstration of therapeutic equivalence.

- Mylan's studies and analyses demonstrate that there are no clinically meaningful adhesion or irritation concerns with Mylan's products.

- These products present very good performance with respect to adhesion and/or irritation, with the scores of both Test and RLD that approach zero. Using OGD's current guidance, statistical metrics approaching responses of zero are overly sensitive.

- Both clinical and statistical interpretation of Mylan's data should allow OGD to find such products as therapeutically equivalent, when there is essentially no evidence of inferior product performance with respect to adhesion or irritation.

It is our current understanding that the Division of Clinical Review is reconsidering the statistical model that should be applied when both test and reference products perform well. Mylan has been in launch readiness position in anticipation of approval in December 2013 for both products. Mylan's Estradiol Transdermal System became eligible for approval on the date of its patent license December 16th and Norelgestromin and Ethinyl Estradiol Transdermal System ("NEETS") does not have any blocking legal exclusivities.

Mylan has now exhausted all avenues within the Office of Generic Drugs to escalate and resolve this matter involving these important medications for which US patients do not have affordable, approved generic alternatives.

(b) (4)

(b) (4)

I would like the opportunity to talk to you about the general situation and propose to call your office to set up a time to call to discuss how we can move forward with this common issue based on the sound science available. Please understand that I do appreciate the challenges you are facing in restructuring OGD and my purpose is to try to be constructive to reach timely resolution based on the scientific merits.

I will call your office to find a time to discuss.

All my best,

Rajiv

--

Rajiv Malik
President
Mylan
1000 Mylan Blvd.
Canonsburg, PA 15317

rajiv.malik@mylan.com

Direct: 724.514.1475
Fax: 724 514 1881
(b) (6)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY J DEMPSEY
03/03/2014

DATE: 2/9/2014

TO: MYLAN TECHNOLOGIES INC

ATTN: S. Wayne Talton

E-Mail: wayne.Talton@mylan.com

FAX: 304-285-6407

RE: Update summary of filed and pending original ANDA(s)

Dear Sir or Madam:

The Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is providing you with this one-time communication on the status of your filed and pending original abbreviated new drug application(s) (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act. OGD is providing these updates as an interim measure to help applicants assess the status of their current submissions as we transition towards predictable goal times pursuant to the Generic Drug User Fee Amendments of 2012 (GDUFA).

Your status update is limited to available review information as of January 29, 2014. Any additional information regarding your ANDA collected after this date is neither considered nor provided. Furthermore, your ANDA status is subsequently subject to revision pending additional information or concerns raised by any of the discipline reviews (bioequivalence, clinical, chemistry, microbiology, labeling, facility), other unforeseen legal, scientific or regulatory issues, or inspectional results, which can also impact the status or ability to issue a complete response. Any applicable fees can also affect the status of your ANDA.

OGD is providing your ANDA status update in the attached chart with a list of applicable acronyms. The chart only contains current information regarding discipline review and does not forecast if and when OGD will issue a complete response, tentative approval, or final approval letter.

Please do not respond to this communication by asking FDA or your Regulatory Project Manager for additional or more detailed information. This is a one-time communication intended to assist you to ascertain the current status of submissions. It is not feasible for us to respond to a high volume of follow up inquiries.

Sincerely yours,

CAPT Aaron W. Sigler, USPHS
Chief, Review Support Branch

ANDA	DRUG NAME	CHEM	BIO	MICRO	LABEL	CLINICAL	FACILITY
200910	ETHINYL ESTRADIOL;NORELGESTROMIN	AQ	UR	NA	UR	UR	AC
201675	ESTRADIOL	UR	AQ	NA	AQ	UR	AC
202346	LIDOCAINE	UR	UR	NA	AQ	AQ	AC

CHART ACRONYMS

Column Headings

ANDA - The application number for your Abbreviated New Drug Application
DRUG NAME - The official filed name of the drug associated with the ANDA number
CHEM - Product Quality Chemistry Review
BIO - Bioequivalence Review, typically including OSI, if applicable
MICRO - Microbiology Review
LABEL - Labeling Review
CLINICAL - Clinical Review
FACILITY - Overall Facility inspections summary. All facilities must be acceptable at the time of 29 JAN 14 in order to warrant an adequate notation. If one of more facility is not acceptable then the FACILITY column will be marked as such. OSI information is not considered.

Discipline Notations

IQ	- Inadequate. This particular discipline is currently found to be inadequate.
AQ	- Adequate. This particular discipline was found to be adequate when the information was gathered for this communication.
UR	- Under Review. This particular discipline is currently assigned OR under review with the discipline team.
NR	-Not Reviewed. This particular discipline is either currently not under review or assigned.
NA	- Not applicable. This particular discipline is not required for the approval of this ANDA.

Facility Notations

PN	- Pending, i.e., one or more facilities have been inspected and are pending an outcome.
AC	- All facilities are acceptable at the time of this publication.

*Please note that you may receive your updates in multiple communications over time, based on the number of ANDAs pending in OGD.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SIMON S ENG on behalf of AARON W SIGLER
02/12/2014

From: Uhl, Kathleen (CDER)
Sent: Tuesday, February 04, 2014 10:00 AM
To: Sigler, Aaron; Margand, Iain
Cc: Dempsey, Mary
Subject: FW: Follow-Up from Mylan

Aaron and Iain,
Can you please be sure that this letter gets filed to the various ANDAs mentioned in this email?
The ANDA numbers are not included but this letter should be sent to the administrative file for each of these applications.
Thanks,
Cook

From: (b) (6) **On Behalf Of** Rajiv.Malik@mylanlabs.com
Sent: Monday, February 03, 2014 4:38 PM
To: Uhl, Kathleen (CDER)
Cc: Rajiv.Malik@mylanlabs.com; Marcie.McClintic@mylanlabs.com
Subject: Follow-Up from Mylan

Dear Dr. Uhl,

I am writing to request an opportunity to discuss an issue of common concern. Specifically, I would like to convey our concern, which I believe is mirrored by the generic industry more generally, over recent delays in resolving straight forward scientific issues, which in turn has the potential to further delay the availability of affordable generic alternatives.

Mylan has been working with OGD for months to resolve an outstanding issue common to certain pending transdermal applications. The issue involves an overly sensitive methodology in FDA's guidance which generates a non-passing result for products that demonstrate excellent adhesion and/or low irritation profiles for four proposed transdermal products. In two of four applications, this longstanding issue is the only remaining barrier to approval which is further described below. If these products did not demonstrate such good performance and thus trigger the non-passing result under the overly sensitive guidance, these products would otherwise be in the hands of patients who today continue to pay more than $80 and $100 per prescription each month.

As explained further below, there are scientifically sound alternative methodologies by which to assess these products and resolve the overly sensitive guidance issue which is currently blocking action on these applications. The resolution remains pending with FDA. This creates an unnecessary barrier because no generic product with very good adhesion and irritation profiles similar to the RLD could pass the study outlined in the guidance (in fact, Mylan has provided evidence to FDA to show that the brand itself would routinely fail FDA's stated criteria if tested against itself). This issue also creates the perverse result of penalizing products which have really good product performance.

Norelgestromin and Ethinyl Estradiol Transdermal System and Estradiol Transdermal System USP

Mylan's ANDA for Norelgestromin and Ethinyl Estradiol Transdermal (NEETS) System, 0.15 mg/24 hr and 0.02 mg/24 hr was originally submitted on December 31, 2009 and our ANDA for Estradiol Transdermal System USP (Twice Weekly), 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day was submitted on April 26, 2010.

OGD initially refused to accept Mylan's NEETS because of its uncertainty regarding the appropriate statistical methodology for demonstrating adhesion and lack of irritation in these products. After Mylan provided a detailed scientific rationale for its statistical methodology, in September 2010, OGD determined that the ANDA should be accepted. The Agency thus has been aware of this issue ***for more than three years***. FDA nonetheless has not settled on an appropriate statistical methodology for these products although it is clear that FDA's product-specific Bioequivalence Guidance does not identify an appropriate methodology by which to assess these products. Mylan has diligently reached out to OGD in an attempt to resolve this issue in a timely manner, but so far to no avail.

On July 1, 2013, Mylan participated in a teleconference with Agency officials to seek clarification on comments contained in OGD's Complete Response letter for ANDA No. 201675. When OGD asked Mylan to request a formal meeting to address this issue in further detail, Mylan promptly did so—and a Type A meeting at which both ANDAs were discussed was held on September 24th with members of both OGD and OND in attendance .

At the Type A Scientific Discussion meeting with FDA on September 24, 2013 Mylan discussed the following salient points:

- OGD's method for assessing non-inferiority becomes progressively overly sensitive when both the test product and the RLD have good adhesion and/or low irritation scores progressing to the best possible adhesion and/or irritation scores. This has led to the inability to demonstrate non-inferiority and discriminates against exactly those ANDAs for which both test and RLD products have superior adhesion and/or irritation profiles.

- Simulations were provided that demonstrate an assessment of the RLD against itself, using OGD's method, would likely fail.

- This current methodology imposes an unnecessary barrier to generic entry for products with essentially equal (favorable) performance.

- Mylan provided threshold considerations and suggested alternatives, and believes the OGD should use science based criterion to apply a more rational metric that both avoids the progressive reduction of the margin as irritation and adhesion scores approach perfect outcomes, and yet continues to satisfy the requirements of the applicable statutes and regulations for demonstration of therapeutic equivalence.

- Mylan's studies and analyses demonstrate that there are no clinically meaningful adhesion or irritation concerns with Mylan's products.

- These products present very good performance with respect to adhesion and/or irritation, with the scores of both Test and RLD that approach zero. Using OGD's current guidance, statistical metrics approaching responses of zero are overly sensitive.

- Both clinical and statistical interpretation of Mylan's data should allow OGD to find such products as therapeutically equivalent, when there is essentially no evidence of inferior product performance with respect to adhesion or irritation.

It is our current understanding that the Division of Clinical Review is reconsidering the statistical model that should be applied when both test and reference products perform well. Mylan has been in launch readiness position in anticipation of approval in December 2013 for both products. Mylan's Estradiol Transdermal System became eligible for approval on the date of its patent license December 16th and Norelgestromin and Ethinyl Estradiol Transdermal System ("NEETS") does not have any blocking legal exclusivities.

Mylan has now exhausted all avenues within the Office of Generic Drugs to escalate and resolve this matter involving these important medications for which US patients do not have affordable, approved generic alternatives.

I would like the opportunity to talk to you about the general situation and propose to call your office to set up a time to call to discuss how we can move forward with this common issue based on the sound science available. Please understand that I do appreciate the challenges you are facing in restructuring OGD and my purpose is to try to be constructive to reach timely resolution based on the scientific merits.

I will call your office to find a time to discuss.

All my best,

Rajiv

--
Rajiv Malik
President
Mylan
1000 Mylan Blvd.
Canonsburg, PA 15317

rajiv.malik@mylan.com

Direct: 724.514.1475
Fax: 724.514.1881
(b) (6)

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/s/

IAIN MARGAND
02/04/2014

Memo to File

From: Chuh, Esther
Sent: Friday, December 20, 2013 1:02 PM
To: Juliane.Foley@mylanlabs.com
Subject: ANDA 201675/ Estradiol TDS - follow up to Type A meeting

Hello Juliane,

Please refer the attachment regarding our inquiry on ANDA 201675 from Type A meeting held on 9/24/13. We would like to know if you plan to submit further explanation of the outliers. Please let me know of a planned timeframe in submitting this information.

In addition, please notify me when you submit the information to your ANDA.

Thank you,

Esther

Attachment to the Email

ANDA 201675

At the Type A Meeting of September 24, 2013, the Agency provided the following response regarding the irritation study results for ANDA 201675:

> Yes, the Agency acknowledges that Mylan's product demonstrated a very low degree of irritation on average, but it failed in the final analysis. The Agency supports Mylan's efforts to provide an explanation for the outliers. One acceptable way of doing this would be to conduct a restudy of the outliers against a number of controls from the original irritation study. The Agency recommends using four controls for each outlier.

Since that meeting, you have not provided any further explanation for the outliers, other than the post meeting footnote provided in your official copy of the meeting minutes, dated October 18, 2013. In that footnote, you provided some information about Subject 192.

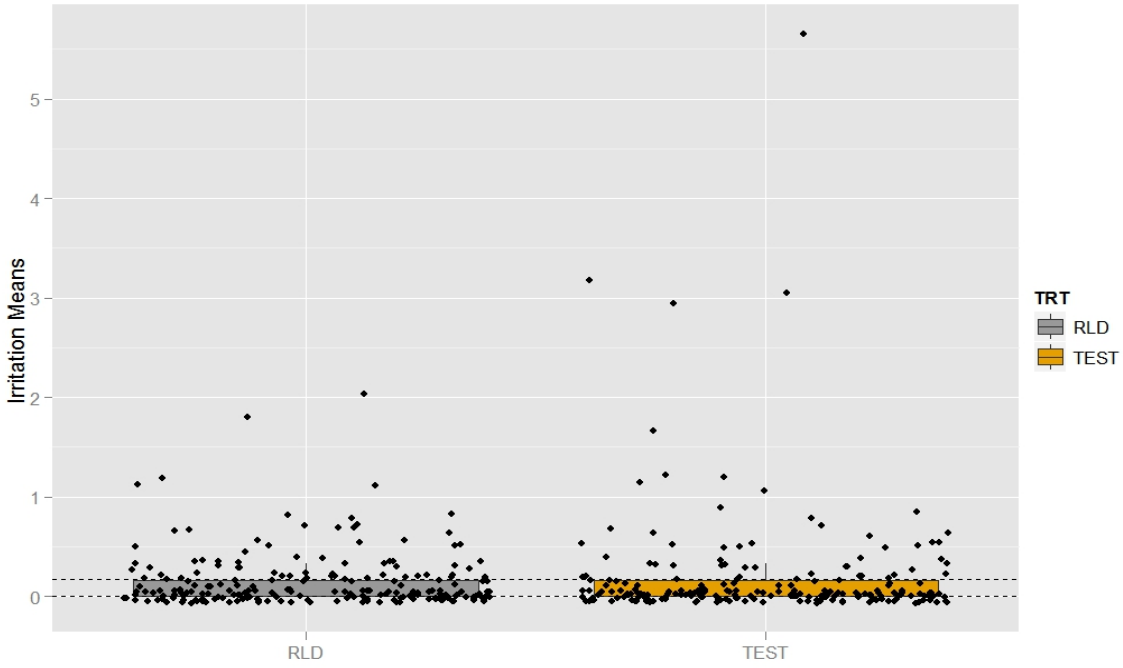
Our Statistical Review Team is providing the following information about the other three outliers, so that you can address the Agency's response provided above:

In additional to non-normality, it appears the TEST distribution includes outliers (outliers are defined as values outside the main body of the data). Whether these outliers are gross errors (bad data such reading, copying, transmission errors, etc.) or "true" observations is yet to be determined. Unfortunately these four outliers are "influential values;" if they are removed from the analyses the inference one draws from the analysis changes. A list of subjects with a combined irritation score ≥ 4 for a visit is provided in Table 1. The Irritation Mean Box Plots are provided in Figure 1.

Table 1. Outlying Irritation Scores

ID (Mean)	Visit	Trmt	Value
157 (3.17)	8	TEST	3H = 6
157	9	TEST	3H = 6
157	10	TEST	3H = 6
157 (1.17)	9	RLD	1C = 4
203 (3.00)	8	TEST	3C = 6
203	9	TEST	3C = 6
203	10	TEST	3C = 6
203 (1.83)	8	RLD	2C = 5
162 (3.00)	8	TEST	3H = 6
162	9	TEST	3H = 6
162	10	TEST	3H = 6
162 (2.00)	8	RLD	2C = 5
162	9	RLD	2C = 5
162	10	RLD	2C = 5
192 (5.67)	8	TEST	7H = 10
192	9	TEST	7H = 10
192	10	TEST	7H = 10

Figure 1. Irritation Mean Box Plots for TEST and RLD (dashed lines at Overall Median=0 and Overall Mean=0.17)



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/s/

EUNJUNG E CHUH
12/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDAs 200910 and 201675

TYPE A MEETING MINUTES

Mylan Technologies Inc.
Attention: Joseph J. Sobecki
Vice President, Regulatory Affairs
110 Lake St.
St. Albans, VT

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) 200910 dated December 31, 2009, received December 31, 2009, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15mg/24hr and 0.02mg/24hr.

Please also refer to your ANDA 201675 dated April 26, 2010, received April 27, 2010, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Estradiol Transdermal System USP (Twice-Weekly), 0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg and 0.1 mg/day.

We also refer to the Type A meeting between representatives of your firm and the FDA on September 24, 2013. The purpose of the requested meeting was to give your firm an opportunity to present your findings, methodology, and conclusions to FDA participants who are most aware of the issue, and who will be able to review this information and recommend a path forward.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Esther Chuh, Regulatory Project Manager at (240) 276-8530.

Sincerely,

{See appended electronic signature page}

Eunjung Esther Chuh, Pharm.D.
Regulatory Project Manager
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A Meeting
Meeting Category: End of Review
Meeting Date and Time: September 24, 2013 12pm – 2pm

Application Numbers and Product Names:
ANDA 200910; Norelgestromin and Ethinyl Estradiol Transdermal System 0.15 mg/24 hr and 0.02 mg/24 hr
ANDA 201675; Estradiol Transdermal System, USP (Twice Weekly) 0.025, 0.0375, 0.05, 0.075 and 0.1 mg/day

Applicant Name: Mylan Technologies, Inc. (Mylan)

Meeting Recorder: Nitin K. Patel, PharmD

FDA ATTENDEES

John R. Peters, MD, Director, Division of Clinical Review
Dale Conner, PharmD., Director, Division of Bioequivalence I
Robert A. Lionberger, PhD., Acting Deputy Director for Science
Yih-Chain Huang, PhD., Science Staff
Caroline Strasinger, PhD, Chemistry Reviewer, Division of New Drug Quality Assessment II
Bing Cai, PhD., Deputy Division Director, Division of Chemistry I
Stella C. Grosser, PhD, Statistical Team Leader, DB6, Office of Biostatistics
Donald J. Schuirmann, MS, Expert Statistical Reviewer, DB6, Office of Biostatistics
Huaixiang (Helen) Li, PhD, Statistical Reviewer, DB6, Office of Biostatistics
Mohamed Nagem PhD, Statistical Reviewer, DB6, Office of Biostatistics
Vicki Lancaster, PhD, Statistical Reviewer, DB6, Office of Biostatistics
Sarah H. Seung, PharmD, Clinical Reviewer, Division of Clinical Review
Esther Chuh, PharmD., Regulatory Project Manager
Nitin K. Patel, PharmD, Medical Affairs Coordinator, Division of Clinical Review
Martin Yoon, PharmD., Project Manager, Team 8, Division of Bioequivalence I
Diana Solana-Sodeinde, PharmD., Project Manager, Team 10, DB I

APPLICANT ATTENDEES

Walt Owens, PhD., Senior Vice President, Global Research and Development, Mylan
Andrea Miller, R.PH., Esq., Senior Vice President, Specialty Products Operations, Mylan
Wayne Talton, M.S., Vice President, Global Regulatory Affairs Operations, Mylan
Joseph Sobecki, MBA, Vice President, US Regulatory Affairs, Mylan
Juliane Foley, MSA, Director, Regulatory Affairs, Mylan Technologies
Russ Rackley, PhD., Vice President, Pharmacokinetics and Drug Metabolism, Mylan
Michael E Houghton, BA, Vice President, R&D, Mylan Technologies
(b) (4), MD, Consultant
(b) (4)., Consultant (by phone)

Gloria McHenry, MPM, Project Manager, Global Regulatory
Alison Pangilinan, MBA, Program Director, R&D
Raymond Urbanski, MD, Chief Medical Officer
Marcie McClintic-Coates, JD, MBA, Global Regulatory Affairs
Mark Liu, M.S., Senior Director of Biostatistics

BACKGROUND

- For ANDA 201675 (Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day), the Agency's Complete Response (CR) letter dated May 28, 2013, communicated the following deficiency from the OGD Division of Clinical Review (DCR):

  > In the skin irritation, sensitization and adhesion study (EDOT-0908), your product was statistically significantly less adhesive than the reference product and failed to show that it is no more irritating than the RLD.

- For ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 hour and 0.02 mg/24 hour), the Agency's CR letter dated June 13, 2013, communicated the following deficiency from the OGD DCR:

  > In the adhesion study (ORTH-09198), your product was statistically significantly less adhesive than the reference product.

Subsequently, for ANDA 201675, Mylan requested a post-CR teleconference which was held on July 1, 2013. At that teleconference, Mylan inquired if it would be possible for the Agency to accept alternate statistical methodology. DCR indicated that this teleconference was not the correct forum for a scientific discussion on this topic and clarified that a Type C meeting request would be more appropriate. The framework for a Type C meeting would allow for (a) DCR to gather appropriate experts from within OGD and CDER; (b) the submission and review of Mylan's proposal(s) through pre-meeting materials; and (c) adequate time to present and discuss this issue. Mylan indicated that they would like to have a meeting to further discuss this issue, and will submit a Type C meeting request.

On August 15, 2013 Mylan requested a Type A meeting for ANDA 201675, and on August 20, 2013 Mylan also requested a Type A meeting for ANDA 200910. Given the similarity in the subject matter, Mylan requested that these meetings be combined into a single meeting. The Agency granted the combined Type A meeting on August 20, 2013.

Mylan started the meeting and outlined that the primary objectives of this meeting are two fold:

1. Short term - to discuss very specific issues relating to the pending ANDAs. Mylan would like to address whatever issues are remaining so that unnecessary barriers to patient access caused by the current methodology are removed, leading to approval for these products.
2. Long term – Mylan would like to work closely with the Agency to develop what Mylan believes are long term fixes to the current guidance

Mylan then gave a presentation (see attached slides) to frame the discussion points for this meeting and to list the questions for the Agency.

Following the presentation, Mylan and FDA covered a number of discussion items which are summarized below. Following the discussion, FDA provided their responses to Mylan's questions.

DISCUSSION

FDA stated that from a patient perspective they are pleased with improved transdermal product performance but recognize that the industry has a much higher bar to pass to demonstrate equivalence. This becomes challenging as the FDA is looking for a statistical methodology that is not based on clinical acceptability or effectiveness but is rather based on equivalence.

FDA asked at what point in Mylan's development did they recognize the need to use a threshold or alternate scale. Mylan indicated that for irritation, they recognized the issue when reviewing the irritation study data for ANDA 201675, Estradiol Transdermal System. For adhesion, they had recognized this issue several years ago and therefore, the scaling proposals for adhesion were predefined in the study protocols.

FDA asked for clarification about the alternatives that Mylan has proposed to the current guidance. In the presentation, FDA heard two different proposals; one is to replace the scoring scale with a 100% scoring scale, and a different proposal was to use the established scoring scale, but when the RLD's average score is less than 1, the limit is fixed at 0.25. Mylan clarified that these are both alternatives, but Mylan's preference is the method which uses the 100% scale.

FDA expressed concern regarding the granularity of the 0 – 100% scale and the ability of clinical experts to make judgments to that level of detail. FDA indicated that both the irritation and adhesion scales are subjective scales. The judging of that scale is going to be specifically based on the training of the observer. FDA would have to see in the protocols, either that the same observer is making the observation on each subject at the same time, or there is some inter-rater reliability test. In terms of developing a long term solution to modifying the guidance, whatever methodology we come to agree on, we will have to have this discussion about how we are going to verify and validate the observer. Mylan acknowledged that the 0-100% scale essentially becomes a
10 point scale, and expressed willingness to provide further information on practical considerations for assuring consistency of scoring in the clinic.

Mylan expressed concern with OGD's utility of the irritation method being very different than the utility of the cumulative irritancy method employed by the Office of New Drugs (OND), which is a provocative test to detect the mildest of irritation potential and that the idea of these irritation studies is to provoke a reaction, not demonstrate sameness. Mylan expressed concern about using an overly sensitive criteria for equivalency when the test is a provocative test performed under extreme conditions compared to labeled clinical use.

OGD acknowledged that there is an inherent problem with using a clinical study to come to a bioequivalence endpoint, and OGD has no disagreement with Mylan's concern, and that is why we are having this type of a meeting. However, OGD emphasized that part of their responsibility is to make sure that they are consistent with what OND does for the same issue, so with that in mind, any of the guidances that OGD has posted, particularly with respect to irritation, have been vetted through the OND Division of Dermatology and Dental Products (DDDP) and any changes that OGD will be making in the future, would likewise have to be vetted through DDDP. The FDA has to operate consistently throughout, much as within OGD.

Mylan questioned whether during the guidance development process, FDA understood that as the scores approach 0, how the margins also approach 0, and that there is a limit function that is inherent in the methodology.

FDA stated again, that this is the reason why we are having this discussion now, so that we can get a better understanding of the limitations.

Mylan stated that one objective that they wanted to discuss at this meeting is the guidance, but the other objective is that Mylan has provided information in these two applications, which is above and beyond what was requested in the draft guidance, that leads Mylan to conclude that there are no issues with respect to adhesion and irritation. Mylan requested FDA to consider these two objectives separately.

FDA indicated that Mylan's proposals would be brought back and discussed within OGD's group, as well as with their colleagues in OND and then FDA will have to reach some conclusion as to what would be the most effective way for FDA to demonstrate either differences or similarities with the products.

Mylan's consultant, (b) (4) commented that the way forward is to identify an alternate criterion to the current guidance criterion by using one of the methods that Mylan has proposed. There would be two ways of being successful. One would be maintaining the criterion in the current guidance, (e.g. when the mean of reference is one or bigger), and have the availability of the alternative criterion which could be used in cases when it would be unduly stringent. We would have two potential ways of achieving success.

FDA addressed Mylan's mixed scaling proposal for irritation data evaluation, and questioned why the cut off point was drawn at 1. Mylan explained that a score of 1 was selected since the Agency defines a score of 1 as "not clinically significant" in the Agency guidance and that is the level of sensitivity for irritation, for example when irritation response becomes discernible.

FDA asked Mylan if they know how the RLD is going to perform before they start the studies, and if they know that the adhesion is likely to be almost perfect in the RLD.

Mylan indicated that they try to get an idea of what to expect by looking at the summary basis of approval, and sometimes by conducting pilot studies. "But there are cases where you don't know

for sure. Therefore, it is best to have a method that will allow for a broad spectrum of possible responses."

FDA indicated that "our purpose today is to gather information which will help us, because we are willing to consider variations in the way we do things for the long term. We appreciate that Mylan has given us a fairly good amount of information. Then as far as the shorter term question for these specific applications, we try to be very consistent, and we would like to hear your thoughts on how we should move forward."

Mylan indicated that they would like to be consistent with an OND assessment of safety and effectiveness. The only issue is the methodology used to make this assessment. When you look at the totality of the data that has been presented in these two applications it is safe and effective with the given dose and patient population.

FDA asked Mylan if they were familiar with recent European Medicines Agency (EMA) guidance on transdermal products, since this may have relevance in terms of the adhesion scoring scale. A draft guidance was issued a few months ago by the EMA, and OND is recognizing the value of this guidance and is looking into its application.

FDA asked how Mylan decides how to power a study not knowing for sure how the RLD will perform? Mylan acknowledged that this can be challenging. FDA also asked if Mylan has any thoughts about evaluating adhesion over time (eg. from time of application to first lifting of patch) and if Mylan's datasets have enough granularity over time to be able to analyze these events. Mylan shared that they do look at adhesion over time much like a pharmacokinetic profile. FDA stressed the importance of understanding irritation and adhesion events because these are the things the patient sees and understands; therefore, it is important to consider them closely before making any significant changes to the guidance.

FDA inquired if Mylan was aware of the skewness in the data and suggested that perhaps a nonparametric inferential method using the median or a quartile might be more appropriate since the data are not normally distributed, a requirement of the current method recommended in the FDA guidance. FDA is aware the current method is not appropriate for Mylan's data. FDA also wondered what level of adhesion is acceptable to the patient, what is the cut off of importance for the patient, and when is adhesion or lack thereof considered a failure to the patient? OGD indicated if OND suggests something would be considered a failure under an NDA, OGD also considers this a failure in an ANDA. Regardless, it was acknowledged that for a generic, the standard control would be based on demonstrating non-inferiority to the RLD.

Mylan asked a procedural question about what should their expectation be for the two pending ANDAs, and if Mylan needed to engage with further discussions, how FDA would contact Mylan.

FDA indicated that we should address the meeting list of questions at this time, and that might provide a partial answer to Mylan's procedural question. Beyond that, FDA indicated that with

the information that was obtained today, FDA's group would need to get together and make some decision and move forward with different ways to approach any of these products. FDA indicated that they do not know how long this process would take.

FDA discussed one alternative to Mylan's proposal for adhesion in which to use a scale as implemented, but if the average score for the RLD was 1 or less, to hold the limit at 0.25 (difference between the averages of the two products could not exceed 0.25). In this alternative proposal, no matter what the average performance of the RLD is, the two products would have to be within 0.25. This would allow for relief on the low end, but would force a more stringent criterion on the higher end. Both Mylan and OGD participants questioned why the criterion could not be scaled and agreed that a constant does not seem appropriate. Mylan shared that there is precedence in current guidance where changes in scaling are allowed, for example with scaled bioequivalence.

FDA also discussed another proposal. If the RLD has poor performance, you could design your product to be better and the current approach would allow a reasonable size study to demonstrate equivalence. If the RLD performance was good, equivalence would be concluded if both the generic and RLD meet a predefined quality standard.

FDA provided answers to the questions that Mylan posed in the meeting packages as listed below. Mylan's original questions are incorporated below in *italics* followed by FDA responses in **bold** font.

ANDA 200910

1. *Does the Agency agree that science based discretion should be used to apply a more appropriate metric that continues to satisfy the requirements of the applicable statutes and regulations for demonstration of therapeutic equivalence rather than being bound by published draft guidance?*

   No, the Agency will not use clinical judgment to override a guidance. Scientific evidence will be considered in the clinical context of use and serve as supportive evidence for modification of current guidances if satisfactorily validated.

2. *Does the Agency acknowledge that the Mylan patch demonstrated perfect adhesion and that the RLD demonstrated less than perfect adhesion? Could the Agency please explain how it is possible to reach the conclusion that the Mylan product failed to demonstrate non-inferiority to the RLD given the perfect adhesion demonstrated by the Mylan patch?*

   The Agency agrees that the adhesion appears to be very good for both products and does not show significant difference. We will consider the information that has been provided today, however, acceptability will depend on further discussions at FDA.

3. *Does the Agency agree that the FDA statistical assessment methodology is excessively stringent in cases where both products have very good adhesion? If so, does the Agency accept Mylan's proposed statistical assessment criteria as demonstrating non-inferiority of Mylan's Norelgestromin and Ethinyl Estradiol Transdermal System product?*

   No, the Agency does not agree that the FDA statistical methodology is excessively stringent. The Agency agrees that adhesion is very good for both products and acknowledges Mylan's proposal, and will discuss it further internally.

ANDA 201675

1. *Does the Agency agree that science based discretion should be used to apply a more appropriate metric that continues to satisfy the requirements of the applicable statutes and regulations for demonstration of therapeutic equivalence rather than being bound by published draft guidance?*

   No, the Agency does not use clinical judgment to override a guidance since both clinical and scientific judgment were intrinsic to the development of the guidance. Scientific evidence will be considered in the clinical context of use and serve as supportive evidence for modification of current guidances if satisfactorily validated.

2. *Does the Agency acknowledge that both the RLD and Mylan's product have demonstrated very good adhesion? Does the Agency agree that the differences between the scores of the two products are not clinically meaningful?*

   a) Yes, the Agency acknowledges that both the RLD and Mylan's product have demonstrated very good adhesion.
   b) No, because such use of clinical discretion is not within our authority. Generic products must be interchangeable with the RLD and so must be equivalent. Consistent decision making based on published guidance, specific methodology, and statistical evidence is necessary.
   The Agency will look at what was discussed today and will assess and decide what the Agency can do. Guidance is guidance and the Agency can use flexibility when scientific alternate approaches are provided. Changes to the current guidance will require review among various disciplines within the Agency and may require the solicitation of public comments, which can take some time.

3. *Does the Agency acknowledge that both the RLD and Mylan's product have demonstrated a very low degree of irritation? Does the Agency agree that the differences between the scores of the two products are not clinically meaningful?*

   As explained in the previous question, The Agency is very cautious in using the term 'not clinically meaningful.' OGD cannot use clinical judgment to make a regulatory approval decision when comparing a proposed generic product to a reference product. We emphasize that the responsibilty of the OGD is to approve equivalent drug products not simply products that are clinically acceptable.

Yes, the Agency acknowledges that Mylan's product demonstrated a very low degree of irritation on average, but it failed in the final analysis. The Agency supports Mylan's efforts to provide an explanation for the outliers. One acceptable way of doing this would be to conduct a restudy of the outliers against a number of controls from the original irritation study. The Agency recommends using four controls for each outlier.

4. *Does the Agency agree that there should be a high probability of the study meeting the established acceptance criteria when the RLD is tested against itself?*

   Yes, the Agency agrees. The Agency will consider Mylan's proposed modeling and will need to look at the methodology in more detail internally and with our OND colleagues.

5. *Does the Agency agree that the FDA statistical assessment methodology is excessively stringent in cases where both products have very good adhesion and/or a very low degree of irritation? If so, does the Agency accept Mylan's proposed statistical assessment criteria as demonstrating non-inferiority of Mylan's Estradiol Transdermal System product?*

   No, the Agency does not agree that the FDA statistical methodology is excessively stringent, but the Agency agrees that there is room for methodology improvement. As indicated in today's discussion, the Agency is looking into alternate methodologies.

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
None

ATTACHMENTS AND HANDOUTS
See Mylan's slide presentation attached below

35 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

EUNJUNG E CHUH
12/06/2013

JOHN R PETERS
12/16/2013

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA# 201675 Estradiol TDS
ANDA 200910 NEE TDS

APPLICANT: Mylan Tech
DATE OF SUBMISSION:10/18/2013

The Office of Generic Drugs may grant expedited review status to either an Original or Supplemental abbreviated new drug application for the following reasons (MaPP 5240.1,MaPP 5240.3 & GDUFA). At least one of the criteria must be met to receive Expedited Review Status:

1. ☐ **PUBLIC HEALTH NEED.** Events that affect the availability of a drug for which there is no alternative

2. ☐ **EXTRAORDINARY HARDSHIP ON THE APPLICANT.**

   a) Catastrophic events such as explosion, fire storms damage.

   b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:

      - ♦ Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
      - ♦ Relocation of a facility or change in an existing facility because of a catastrophic event(see item 2.a)

3. **AGENCY NEED.**
   a) ☐ Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
   b) ☐ Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
   c) ☐ Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
   d) ☐ Request for approval of a strength that was previously tentatively approved (To be used in those cases where 180-day generic drug exclusivity prevented full approval of all strengths).
   e) ☐ MaPP 5240.3 conditions.

4. ☐ **GDUFA.** Year one and year two cohort PIV 180-day eligibility (First Generic)

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant x Deny ☐	E. Chuh 10/30/13 re-evaluated on 12/11/13
Chemistry Team Leader (sign as needed)	Grant☐ Deny☐	
Micro Team Leader (sign as needed)	Grant☐ Deny☐	
Labeling Team Leader (sign as needed)	Grant☐ Deny☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant☐ Deny☐	
Office Director/Deputy Director (email concurrence) (Original ANDAs)	Grant x Deny ☐	RLW 11/12/13; re-evaluated 12/11/13

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: CMC Team 12

ENTER FORM INTO DAARTS DATE EC/12/11/13

Paste Email Copy Below:

From: West, Robert L
Sent: Wednesday, December 11, 2013 12:35 PM
To: Chuh, Esther
Subject: RE: Expedited Review Request - 201675 Estradiol TDS

I concur.

Thank you,

Bob

> **From:** Chuh, Esther
> **Sent:** Wednesday, December 11, 2013 9:46 AM
> **To:** West, Robert L
> **Subject:** Expedited Review Request - 201675 Estradiol TDS
>
> Hello Bob,
>
> Mylan is requesting for Expedited review of their ANDA 201675 and states that there is no blocking patent/exclusivity and this allows for immediate approval of the ANDA. My finding is that there is no approved generic in the market for this ANDA and the patents no longer block the ANDA from being approved, however there still exist patents in OB. Therefore this ANDA does not qualify for an expedited review under MaPP 5240.3.
>
> However, they do qualify for an expedited review on the basis that the ANDA is a P-IV First to File applicant. Please let me know if you agree with this Grant decision.
>
> Mylan is also requesting for expedited review of ANDA 200910/NEET. I will prepare a separate form for this ANDA as different criteria may need to be addressed for this ANDA.
>
> Thank you,
> Esther

Re: ANDA 200910

From: West, Robert L
Sent: Wednesday, December 11, 2013 12:47 PM
To: Chuh, Esther
Cc: Shimer, Martin; Read, David T; Flanagan, Keith; Sigler, Aaron; Sipes, Grail
Subject: RE: Assessment of P4 status of upcoming Mylan applications

Esther:

I concur with your reasoning with regard to this ANDA. It's clearly a "gray" issue, but I believe that because it represents a first generic and there really are no blocking patents (first filer withdrew their ANDA), it would be appropriate to "expedite" this ANDA.

Thank you,

Bob

From: Chuh, Esther
Sent: Tuesday, December 10, 2013 12:50 PM
To: Flanagan, Keith; West, Robert L
Cc: Shimer, Martin; Read, David T; Sigler, Aaron; Sipes, Grail
Subject: RE: Assessment of P4 status of upcoming Mylan applications

Hi Keith,

ANDA 200910 is a patch and there is no generic in the market. Currently the only active application for this drug product (RLD – Ortho Evra Patch) is Mylan's ANDA 200910. In my opinion, it would be a good public health reason to prioritize this ANDA – as there is no generic on the market and there will not be one for quite some time until another applicant submits an ANDA for the DP. This case may be simple since there is no other active application for the DP, but if there were numerous ANDAs in-house pending review, it would be harder to make the decision as we would need to expedite them all and end up over flooding our priority queue. So, for this single incidence, I think it would be good health reason to expedite but looking into the bigger picture for better management of our priority queue, I say we don't have a good basis to prioritize it at this time.

Thank you,
Esther

From: Flanagan, Keith
Sent: Monday, December 09, 2013 9:59 PM
To: Chuh, Esther; West, Robert L
Cc: Shimer, Martin; Read, David T; Sigler, Aaron; Sipes, Grail
Subject: Re: Assessment of P4 status of upcoming Mylan applications

Thanks, Esther. Do you know how many generics like 2000910 are on the market? In your opinion, is there a good public health reason for prioritizing it?
I'm adding Grail Sipes to this email chain for information purposes. She is leading development of a revised prioritization MaPP, and working on the P4 issues now. OGD policy shop is keenly interested in the policy issue as a categorical matter but defers to Bob, Jason and Aaron re this specific ANDA.

From: Chuh, Esther
Sent: Monday, December 09, 2013 09:41 PM
To: West, Robert L
Cc: Flanagan, Keith; Shimer, Martin; Read, David T; Sigler, Aaron

Subject: FW: Assessment of P4 status of upcoming Mylan applications

Hi Bob,

Attached is the Expedited Review – Denied Form that was pending your signature in DARRTS for Mylan's ANDA 201675 and 2000910. I have retrieved it back to me for reconsideration on the decision.

We determined that Mylan's request for expedited review does not qualify because it did not meet the MaPP 5240.3 or any other criteria. Since our determination, OGD has reprioritized to give priority to the P-IV First Generics submitted Pre-GDUFA. Therefore based on this, ANDA 201675 qualifies for an expedited review. FYI, ANDA 201675 recently forfeited their exclusivity back in August.

Determination need to be made on ANDA 200910 which is a P-IV, however is not a first generic and does not qualify for expedited review under MaPP 5240.3. ANDA 200910 is the only ANDA in OGD for the DP. (b) (4) ased on this, can we provide any support to grant expedited review of ANDA 200910? Can the fact that we only have one active ANDA in OGD be a basis for an expedited review?

Per Jason's recommendation, I have cc'ed Keith, Marty and Dave on this email for their input.

Thank you,
Esther

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/s/

EUNJUNG E CHUH
12/13/2013

ROBERT L WEST
12/13/2013
Deputy Director, Office of Generic Drugs

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2013-0868	
TO *(Division/Office)* Division of Clinical Review: Nitin Patel			FROM: Guohua Li	
DATE: 11/4/2013	IND NO.	ANDA NO. 201675	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 08/15/2013,
NAME OF DRUG Estradiol Transdermal System		PRIORITY CONSIDERATION 30 days	CLASSIFICATION OF DRUG Estrogen derivatives	DESIRED COMPLETION DATE 12/5/2013

NAME OF FIRM Mylan Technologies

REASON FOR REQUEST

I. GENERAL

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

II.BIOMETRICS

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

III.BIOPHARMACEUTICS

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

IV.DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

□ CLINICAL □ PRECLINICAL

COMMENTS:

OGD is requesting a Pharm/Tox Review for the Firm's Toxicology data in Section 3.3 Literature References within the Amendment dated August 15, 2013 (SD 15 in DARRTS) (b) (4) are acceptable or not in Estradiol Transdermal System USP. (b) (4) Please review Firm's Safety Assessment for Residual (b) (4) in Estradiol TDS and provide comment if these levels are safe for human use. Please provide an electronic copy of the review to the requestor by email and cc Steven Yang, HFD-617 (Steven.Yang@FDA.HHS.gov) when it is being checked into DARRTS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* □ MAIL □ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

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/s/

GUOHUA LI
11/07/2013

STEVEN W YANG
11/07/2013

M E M O R A N D U M

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

DATE: February 28, 2011

TO: Associate Director
International Operations Drug Group
Division of Foreign Field Investigations

FROM: Martin K. Yau, Ph.D. Martin K. Yau 3/2/2011
Acting Team Leader—Bioequivalence
GLP and Bioequivalence Investigations Branch
Division of Scientific Investigations

SUBJECT: FY 2011, **CDER ANDA Pre-Approval Data Validation Inspection**, Bioresearch Monitoring, Human Drugs, CP 7348.001.

RE: ANDA 201-675
DRUG: Estradiol Transdermal System USP, 0.025, 0.0375, 0.05, 0.075, and 0.1 mg/day
SPONSOR: Mylan Technologies Inc.
110 Lake Street
Saint Albans, VT 05478
Sponsor's Agent: S. Wayne Talton
Vice President, Regulatory Affairs
TEL: 1-304-599-2595
FAX: 1-304-285-6407

This memo requests an inspection of the clinical portion of the following study. **At the request of the Clinical Review Team, Office of Generic Drugs, this inspection should be completed by July 1, 2011.**

Study EDOT-0908: "Comparative Evaluation of the Adhesion, Cumulative Irritation and Contact Sensitization Potential of Mylan's Estradiol Transdermal System, USP (Twice-Weekly) (0.025 mg/day) to Vivelle-Dot® (Estradiol Transdermal System) (Novartis; 0.025 mg/day) in Healthy Post-Menopausal Women"

Number of Subjects: 228

Clinical Site:

Federal State Enterprise "Scientific Research Center for Preventive Medicine of Federal Agency of High Technology Care"
10 Petroverigsky Str.
Moscow, 101990 Russian Federation
TEL: +7-495-625-38-09
FAX: Not available

Clinical Investigator:

Sergey J. Martsevich, M.D., Ph.D., D. Sc.
Principal Investigator
TEL: +7-495-621-20-49, +7-495-627-03-08
FAX: +7-495-625-37-4
EMAIL: (b) (6)

Please check the batch numbers of the test and reference formulations used in study EDOT-0908 with the descriptions in documents submitted to the Agency. Please have the records of at least 50 subjects in study EDOT-0908 audited. The subject records in the ANDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Please confirm the presence of 100% of the signed and dated informed consent forms, and comment on this informed consent check in the EIR. Please determine if the subjects met the protocol inclusion/exclusion criteria. Also, please verify that the subjects were compliant with the trial regimen.

Headquarters Contact Person: Michael F. Skelly, Ph.D.
(301) 796-3375

cc:
CDER DSI PM TRACK
DSI/Skelly/Dejernett/Bonapace/CF
HFD-600/Nitin K. Patel, Dena R. Hixon
HFC-130/ORA HQ DFFI IOB BIMO
Draft: CB 2/28/11
Edit: MKY 2/28/11
DSI: 6183; O:\BE\Assigns\bio201675.doc
FACTS: 1265620

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/s/

CHARLES R BONAPACE
12/04/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2012-0724	
TO *(Division/Office)* DRUP - HFD-580 Thru: Jennifer Mercier , ODEIII HFD-103			FROM: Xihao Li	
DATE: 10/17/2012	IND NO.	ANDA NO. 201675	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 6/15/2012,
NAME OF DRUG Estradiol Transdermal System		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG Estrogen derivative	DESIRED COMPLETION DATE 12/16/2012

NAME OF FIRM Mylan Technologies

REASON FOR REQUEST

I. GENERAL

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

II.BIOMETRICS

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III.BIOPHARMACEUTICS

DISSOLUTION
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IN--VIVO WAIVER REQUEST
DEFICIENCY LETTER RESPONSE
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PHASE IV STUDIES

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COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
_SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL PRECLINICAL

COMMENTS
OGD is requesting a Pharm/Tox Review. The firm submitted information regarding limits of (b) (4) impurities found in the excipients used in the drug product. They have proposed limits of (b) (4) (b) (4) in the finished drug product of Estradiol Transdermal System. Please review the information and provide comment if these levels are safe for human use. Please provide an electronic copy of the review to the requestor by email and cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) when it is being checked into DARRTS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

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/s/

XIHAO LI
10/17/2012

TRANG Q TRAN
10/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2012-0723	
TO *(Division/Office)* DRUP - HFD-580 Thru: Jennifer Mercier , ODEIII HFD-103			FROM: Xihao Li	
DATE: 10/17/2012	IND NO.	ANDA NO. 201675	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 6/15/2012,
NAME OF DRUG Estradiol Transdermal System		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG Estrogen derivative	DESIRED COMPLETION DATE 12/16/2012

NAME OF FIRM Mylan Technologies

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_SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL | PRECLINICAL

COMMENTS
OGD is requesting a Pharm/Tox Review. One of the excipients (b) (4) used in the drug product 0.10mg/day strength is (b) (4) than the IIG list of 57.14mg. Firm has provided safety assessment in Sectin x.x Literature References of Quality Amendment submitted on 06/15/2012. Please review the information and provide comment if the level of (b) (4) is safe for human use. Please provide an electronic copy of the review to the requestor by email and cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) when it is being checked into DARRTS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
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FORM FDA 3291 (7/83)

cc: ANDA
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/s/

XIHAO LI
10/17/2012

TRANG Q TRAN
10/17/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA See Attached

Date: 8/20/2012

Attention:
Department of Regulatory Affairs
MYLAN TECHNOLOGIES
781 CHESNUT RIDGE RD P.O. 4310
MORGANTOWN, WV 26504

RE: Request to Withdraw Applications from the Generic Drug Backlog to Avoid Incurring Backlog Fee

Dear Sir or Madam:

This letter is in reference to your Abbreviated New Drug Applications (ANDAs), included in the attached list, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III), enacted on July 9, 2012, establish a one-time backlog fee for any ANDA that is pending at the US Food and Drug Administration (FDA) on October 1, 2012 and has not received a tentative approval.

FDA is issuing this letter to encourage applicants who have pending ANDAs for which the applicants no longer wish to seek approval to notify FDA of the request to withdraw those ANDAs (see Federal Register Notice Docket Number FDA-2012-N-0879). **Requests for withdrawal should be submitted in writing individually for each ANDA as a "Request for Withdrawal" to the affected ANDA**. A decision to withdraw the ANDA is without prejudice to refiling.

Any ANDA that is not withdrawn by September 28, 2012 will incur the obligation to pay the backlog fee. Payment of backlog fees will be due no later than 30 calendar days after publication in the Federal Register of a notice (to be issued by October 31, 2012) announcing the amount of the backlog fee. Applicants with original ANDAs that fail to pay the backlog fee by the due date will be placed on a publicly available arrears list, and FDA will not receive new ANDAs or supplements submitted by those applicants, or any affiliates of those applicants, until the outstanding fee is paid.

To avoid incurring the backlog fee for an application, you, the applicant, must submit a request to withdraw the application and that request must be received by the FDA on or before **September 28, 2012**. However, to expedite this process, you are encouraged to submit the request by **September 15, 2012**.

You should submit the request to withdraw your applications by standard application submission methods. If an application was submitted via the FDA electronic gateway, a request for withdrawal should be submitted to the application via the gateway. Alternatively, you should send written notification to the ANDA archival file at the following address: Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Document Control Room, Metro Park North VII, 7620 Standish Pl., Rockville, MD 20855.

In addition, please provide electronic confirmation of all ANDAs you wish to withdraw by sending an email to OGDGDUFA@fda.hhs.gov within the timeframe specified above**.**

For your convenience, a list of pending ANDAs for which we have identified you as the applicant is attached. **However, this list may be incomplete. Therefore, it is important to note that the absence of an ANDA from this list does not exempt that ANDA from incurring a backlog fee. Please verify the list for completeness of all ANDAs you have submitted. Discrepancies should be reported to the email address noted above.**

The GDUFA statute exempts only generic Positron Emission Tomography (PET) products from the user fees. There are no additional exemptions or waivers for GDUFA fees beyond those in the statute.

If you have questions regarding this communication, contact Thomas Hinchliffe at OGDGDUFA@fda.hhs.gov.

Please direct general GDUFA questions to ASKGDUFA@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: Attached List of ANDAs

PENDING ANDAs
(List produced as of 8/20/2012)

ANDA #	Drug Name
201675	ESTRADIOL

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/s/

WILLIAM P RICKMAN
08/22/2012

Please send an email to the labeling reviewer (charles.hoppes@fda.hhs.gov) to confirm that you received the labeling comments

Labeling Comments

ANDA 201675

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8988)

TO: Mylan Technologies

TEL: 304-599-2595

ATTN: S. Wayne Talton

FAX: 304-285-6407

FROM: Charlie Hoppes

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice Weekly)

Pages (including cover and signature page): 3

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

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

ANDA Number: 201675 Date of Submission: 4/26/2010

Applicant's Name: Mylan Technologies

Established Name: Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (Twice Weekly)

Labeling Deficiencies:

A. GENERAL COMMENTS:

We note that you have provided product specific information regarding the adhesion properties of your transdermal system. We have asked the Office of Generic Drugs Clinical Review Team to verify the accuracy of this information and we defer comment on that part of the labeling until the time that their review has been completed.

B. PACKAGE INSERT:

1. See GENERAL COMMENTS above.

2. Improve the resolution of figures appearing in the insert labeling when submitting final print labeling.

C. PATIENT LABELING:

Revise to delete [redacted] (b) (4). Alternatively explain how you believe patients will understand the meaning of [redacted] (b) (4)

Submit final printed labeling (or draft if you prefer) electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with the last approved labeling of the RLD with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

JOHN F GRACE
02/06/2012
for Wm Peter Rickman

QUALITY DEFICIENCY - MINOR

ANDA 201675

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Mylan Technologies Inc

TEL: 802-527-7792

ATTN: S. Wayne Talton

FAX: 802-527-8155

FROM: Esther Chuh

FDA CONTACT PHONE: (240) 276-8530

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated April 26, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Estradiol Transdermal System USP, 0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.075mg/day, and 0.10mg/day.

Reference is also made to your amendment dated January 4, 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	201675
APPLICANT:	Mylan Technologies
DRUG PRODUCT:	Estradiol Transdermal System USP 0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.075mg/day, 0.1mg/day

The deficiencies presented below are minor deficiencies:

A. Deficiencies

1. Please provide the lot number of the USP reference standard that was used for drug substance and drug product. If any commercially available reference standard was used please provide the COA of the reference standard.

2. The amount of silicone adhesive (b) (4) used in 0.1mg/day drug product is (b) (4) than the IIG limit of 57.14mg. Please provide justifications.

3. Please conduct freeze thaw study on the finished product to demonstrate there is no recrystallization in the drug product.

4. Please include microscopic monitoring for crystals in the release and stability specifications.

5. We recommend that viscosity of the blend should be monitored for a robust process since viscosity affects the flow properties which impact the coating process.

6. Please provide study on cold flow of the drug product and comment whether there is any potential drug leakage in cold flow.

7. Please contact the supplier of (b) (4) regarding the (b) (4) impurities (b) (4) (b) (4). Please establish suitable acceptance criteria for (b) (4) in the final drug product specification.

8. Please contact DMF (b) (4) holder regarding the (b) (4) impurities of (b) (4) Please establish suitable acceptance criteria for these (b) (4) impurities in the drug product specification.

9. For the drug product release specifications:
    a. Please include a shear test and limit.
    b. Please tighten the limit for total impurities.
    c. Please include a quantitative test and limit for cold flow.
    d. Please tighten the limits for residual monomers.
    e. Please discuss why (b) (4) is not included as one of the residual monomers.

10. For the drug product stability specifications:
    a. Please include a shear test and limit.
    b. Please tighten the limit for total impurities.
    c. Please include a quantitative test and limit for cold flow.

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

1. Your reply should also address the bio incomplete deficiencies provided to you by facsimile on Nov. 09 2011.

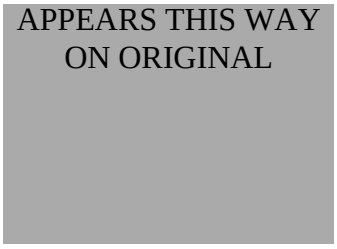
2. Your labeling information is pending review. Deficiencies, if any, will be communicated separately.

3. Please provide any additional long-term stability data that may be available.

Sincerely yours,

{See appended electronic signature page}

Andre Raw, Ph. D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research


APPEARS THIS WAY
ON ORIGINAL

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/s/

BING CAI
12/20/2011

BIOEQUIVALENCE AMENDMENT

ANDA 201675

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Mylan Technologies, Inc

TEL: (304) 599-2595

ATTN: S. Wayne Talton

FAX: (802) 527-8155

FROM: Diana Solana-Sodeinde

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on April 26, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Estradiol Transdermal System, USP (Twice-weekly), 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day.

Reference is also made to your amendment dated May 25, 2010; September 10, 2010 and July 28, 2011.

The Division of Bioequivalence has completed its review of the submissions referenced above and has identified deficiencies which are presented on the attached __2__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request
Bioequivalence Dissolution Acknowledgement

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA: 201675

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Estradiol Transdermal System, USP (Twice-weekly), 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

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

Deficiencies Related to the Fasting BE Study:

1. In the protocol deviation table for the fasting BE study (Report # EDOT-0922 (M1GJ09001), Table 10.3), you stated that "*there were pharmacokinetic (PK) sample processing errors: Period II, 12 hour B samples tubes were out of order at dispensing. It is unknown which subject's samples were in which tube.*" This statement was applied to the Period II, 12-hour samples of subject Nos. 9, 10, 12, 13, 16 (test treatment) and subjects 11, 14 and 15 (reference treatment). Please clarify how the issue was resolved and how you were able to confirm the sample identities.

2. In the protocol deviation table for the fasting BE study (Report # EDOT-0922 (M1GJ09001), Table 10.3), you indicated that there was a deviation in the "*transdermal sample handling*: *the Period 1 Control Sample 1A was found under the freezer*". Please explain how the issue was resolved and whether the found sample was used during the study.

Deficiency Related to Dissolution Testing:

3. You have conducted comparative dissolution testing using the FDA-recommended method. Based on the data you submitted, the DB recommends the specifications below. Please acknowledge your acceptance of the FDA recommended dissolution method and specifications as follows:

Apparatus:	USP VI (cylinder, modified)
Speed:	50 rpm
Medium:	Water
Volume:	500 mL for 0.025 mg/day and 0.0375 mg/day; 900 mL for 0.05 mg/day, 0.075 mg/day and 0.1 mg/day.
Temperature:	32°C ± 0.5°C

The test product should meet the following specifications:

2 hr: (b) (4)
6 hr:
12 hr: 70-90%

Sincerely yours,

{See appended electronic signature page}

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

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/s/

DALE P CONNER
11/09/2011

BIOEQUIVALENCE AMENDMENT

ANDA 201675

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Mylan Technologies

TEL: (802) 527-7792

ATTN: S. Wayne Talton

FAX: (802) 527-8155

FROM: Diana Solana-Sodeinde

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on April 26, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Estradiol Transdermal System, USP (Twice-Weekly), 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day).

The Division of Bioequivalence has completed its review of the submission referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA: 201675

APPLICANT: Mylan Technologies

DRUG PRODUCT: Estradiol Transdermal System, USP, (Twice-Weekly), 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence (BE) study and waiver requests will be conducted later. The following deficiencies have been identified:

1. Please conduct the dissolution test using the following FDA-recommended dissolution method as shown in the current FDA dissolution database at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm.

USP Apparatus :	VI (Cylinder) attach the patch to a disk at the bottom of the cylinder
Speed (rpm) :	50
Medium :	Water
Volume (mL) :	500 mL (0.025 mg/24 hr and 0.0375 mg/24 hr); 900 mL (0.05 mg/24 hr , 0.075 mg/24 hr and 0.1 mg/24 hr)
Temperature :	32°C ± 0.5°C
Sampling Times :	1, 2, 4, 6, 8, 10 and 12 hours

2. In addition, as recommended in the current Bioequivalence Guidance for Estradiol Transdermal System (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234963.pdf), dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatuses for transdermal systems in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be conducted. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The dissolution test should include early sampling times of 0.5, 1, 2, and 4 hours and continue every 2 hours until at

least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

3. Please clarify which of the following two parameters: the delivered dose (i.e, 0.025 mg/day) or the loading amount (i.e. 0.41 mg), was used in your calculation for the percentage of drug release in your dissolution data.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

DALE P CONNER
04/15/2011

MEMORANDUM
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 11, 2011

TO: C.T. Viswanathan, PhD
Associate Director - Bioequivalence, Division of Scientific Investigations
WO51, HFD-48

THROUGH: Dena R. Hixon, MD
Associate Director for Medical Affairs
Office of Generic Drugs
MPNI, HFD-600

FROM: Nitin K. Patel, PharmD
Medical Affairs Coordinator, Clinical Review Team
Office of Generic Drugs
MPNI, HFD-600
240-276-8887

SUBJECT: Compliance Program 7348.001 – In Vivo Bioequivalence

REQUEST FOR INSPECTION

REFERENCES:

ANDA#	201675
Product	Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day
Sponsor: full address	Mylan Technologies Inc. 110 Lake St. St. Albans, VT 05478
Phone	304-599-2595
Fax	802-527-8155
Sponsor Contact	S. Wayne Talton, Vice President, Regulatory Affairs
Phone	304-599-2595
Fax	802-527-8155
Submission Date	April 26, 2010

PRIORITY: C

A (highest) = ready for approval in the office
B = ready for approval, clinical study under review
C = pending clinical review

DUE DATE: May 11, 2011

REASON FOR REQUEST:

	Not inspected in the last three years
	For Cause/Violative History
X	New Sites
	Other

Clinical Study

TITLE:	Comparative Evaluation of the Adhesion, Cumulative Irritation and Contact Sensitization Potential of Mylan's Estradiol Transdermal System, USP (Twice-Weekly) (0.025 mg/day) to Vivelle-Dot® (Estradiol Transdermal System) (Novartis; 0.025 mg/day) in Healthy Post-Menopausal Women
PROTOCOL #:	Mylan EDOT-0908 (b) (4)
NUMBER OF STUDY SITES:	1
CROs/SMO:	Not provided with submission

SITE TO BE INSPECTED	
Site	Federal State Enterprise "Scientific Research Center for Preventive Medicine of Federal Agency of High Technology Medical Care"
Address	10 Petroverigsky str., Moscow, 101990, Russian Federation
Phone	Tel: 7-495-625-3809
Investigator (Name/Contact Info)	Sergey Martsevich, MD, PhD.
# of subjects	228

COMMENTS/ADDITIONAL INFORMATION FOR INSPECTORS:

This ANDA is located in the Electronic Document Room (EDR).

CLINICAL STUDY STATUS:

	Study under review
	Study review completed
	Decision:
X	Other: Review not started.

CLINICAL REVIEWER/CONTACT INFORMATION: Not yet assigned to a clinical reviewer.

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/s/

NITIN K PATEL
02/11/2011

DENA R HIXON
02/11/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 201675

Mylan Technologies, Inc.
Attention: S. Wayne Talton
718 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

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

Reference is made to our "Refuse to Receive" letter dated August 6, 2010 and your amendment dated September 10, 2010.

NAME OF DRUG: Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day.

DATE OF APPLICATION: April 26, 2010

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 27, 2010

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or

judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240) 276-8675.

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

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

Should you have questions concerning this application, contact:

Benjamin Danso
Project Manager
240-276-8527

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

MARTIN H Shimer
12/23/2010
Signing for Wm Peter Rickman

M E M O R A N D U M

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

DATE : May 19, 2010

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 201675 for Estradiol Transdsermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Mylan Technologies Inc. has submitted ANDA 201675 for Estradiol Transdsermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. In order to accept an ANDA, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Mylan Technologies Inc. on April 26, 2010 for its Estradiol product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201675	ORIG-1	MYLAN TECHNOLOGIES INC	ESTRADIOL

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/s/

EDA E HOWARD

09/16/2010

Responsed to RTF Filing 2nd memo requested from Ted Palat. 9/16/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 201675

Mylan Technologies, Inc.
Attention: S. Wayne Talton
718 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated April 26, 2010, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Estradiol Transdermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day.

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

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

1. The data submitted to your application is not sufficient for receiving your ANDA. Your frequency distribution table of irritation scores shows considerably more scores of 3 or higher for the test product than for the reference product (13 vs. 1). You have failed to submit the statistical analysis results using the OGD recommended method to show that the skin irritation potential and adhesion performance of your product are at least as good as those of the reference product.

2. The one-sided 95% CI for the mean cumulative irritation score of the test product minus 1.25 X mean cumulative irritation score of the reference product in the per protocol population should be provided. The cumulative mean irritation score analysis should include "other effect" scores. For example, if the dermal response score is 2 and other effects score is H(3), then the actual irritation score is 5 (2+3). If a patch is moved to an alternate site due to an unacceptable irritation, the last score on the original site is to be carried forward as the score for all subsequent irritation scores for the patch.

3. In addition to cumulative irritation scores, it is necessary to also evaluate the proportion of subjects with a meaningful degree of irritation for each product. The proportion of subjects with a meaningful degree of irritation should be no higher for the test product than for the reference product, and irritation should not occur earlier in the application period for the test than for the reference product. Therefore, the study report should include a frequency table for skin irritation scores, other effect scores, and combination of skin irritation and other effect scores in the per protocol population during the induction period for each patch type on each evaluation day.

4. The one-sided 95% CI for the mean adhesion score of the test product minus 1.25 X mean adhesion score of the reference product in the per protocol population should be provided.

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

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Ted Palat
Project Manager
(240) 276-8982

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201675	ORIG-1	MYLAN TECHNOLOGIES INC	ESTRADIOL

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/s/

MARTIN H Shimer
08/06/2010
Signing for Wm Peter Rickman

M E M O R A N D U M

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

DATE : May 19, 2010

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 201675 for Estradiol Transdsermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Mylan Technologies Inc. has submitted ANDA 201675 for Estradiol Transdsermal System USP, 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. In order to accept an ANDA, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Mylan Technologies Inc. on April 26, 2010 for its Estradiol product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-201675	ORIG-1	MYLAN TECHNOLOGIES INC	ESTRADIOL

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/s/

EDA E HOWARD
05/19/2010