CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 200910

Name: Xulane (Norelgestromin and Ethinyl Estradiol Transdermal System), 150 mcg/35 mcg per day

Sponsor: Mylan Technologies, Inc.

Approval Date: April 16, 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200910

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Labeling Review(s)	**X**
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Pharm/Tox Review(s)	**X**
Statistical Review(s)	**X**
Microbiology Review(s)	
Bioequivalence Review(s)	**X**
Other Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200910

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 200910

Mylan Technologies, Inc.
Attention: S. Wayne Talton
Vice President, Global Regulatory Affairs Operations
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 31, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Xulane (Norelgestromin and Ethinyl Estradiol Transdermal System), 150 mcg/35 mcg per day.

Reference is also made to the Complete Response letter issued by this office on June 13, 2013, and to your amendments dated August 20, September 18, October 11 (two submissions), and November 27, 2013; and April 15, 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 Xulane (Norelgestromin and Ethinyl Estradiol Transdermal System), 150 mcg/35 mcg per day, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Ortho Evra® Transdermal System, 150 mcg/35 mcg per day, of Janssen Pharmaceuticals, Inc. (Janssen). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The RLD upon which you have based your ANDA, Janssen's Ortho Evra Transdermal System, is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations

(the "Orange Book"), U.S. Patent Nos. 5,876,746 (the '746 patent) and 5,972,377 (the '377 patent) are scheduled to expire on November 20, 2015, and June 7, 2015, respectively.

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Xulane (Norelgestromin and Ethinyl Estradiol Transdermal System) 150 mcg/35 mcg per day, under this ANDA. You have notified the agency that Mylan Technologies Inc. (Mylan) complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against Mylan within the statutory 45-day period.

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.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. You should advise the Office of Generic Drugs 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,

{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

04/16/2014

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200910

LABELING

6.609DPLATE:R6

Place these stickers on your **calendar.**

Patch Change Reminder Stickers

Place the top row of these stickers on your calendar and the bottom row on your patch pouches to help you remember when to change each patch.

Place these stickers on your **pouches.**

M3340STK:R1

090401

Mylan®

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

XULANE™
(norelgestromin and ethinyl estradiol transdermal system)

PIC:NEETS:R3
050903

Instructions for XULANE™ Patch Application

Please read Detailed Patient Labeling provided in this package for additional important information about this product.

HOW TO START USING YOUR XULANE™ PATCH FOR THE FIRST TIME

You have two options for starting the patch. Choose which option is right for you:

- **First Day Start**-Apply your first patch during the first 24 hours of your menstrual period.
- **Sunday Start**-Wait until the first Sunday after your menstrual period begins. With this option, a non-hormonal backup method of birth control, such as a condom or diaphragm and spermicide, is needed for the first 7 days of the first cycle only. If your period starts on a Sunday, the first patch should be applied that day, and no backup contraception is needed.
- **When Switching From the Pill or Vaginal Contraceptive Ring to the Patch**-If you are switching from the pill or vaginal contraceptive ring to XULANE™, complete your current pill cycle or vaginal ring cycle and apply the first XULANE™ patch on the day you would normally start your next pill or insert your next vaginal ring. If you do not get your period within a week after taking the last active pill or removing the last vaginal ring, you may still start the XULANE™ patch. Check with your healthcare professional to be sure that you are not pregnant. If the patch is applied more than a week after taking the last active pill or removal of the last vaginal ring, a non-hormonal method of birth control should be used at the same time as the patch for the first 7 days of patch use.

CHOOSE A PLACE ON YOUR BODY TO PUT THE PATCH

- The patch may be placed on your upper outer arm, abdomen, buttock or back in a place where it won't be rubbed by tight clothing. For example, do not place it under the waistband of clothing.
- Do not put the patch on your breasts, on cut or irritated skin, or on the same location as the previous patch.

Before you apply the patch:

- Make sure your skin is clean and dry.
- Do not use lotions, creams, oils, powders, or make-up at the patch site. It may cause the patch to fail to stick properly or to become loose.

HOW TO APPLY THE PATCH

	• Tear open the pouch at the top edge **and** one side edge. Peel open the foil pouch. Gently remove the contents of the foil pouch and discard the additional pieces of film above and below the patch.
	• Peel away half of the clear plastic. Avoid touching the sticky surface with your fingers.
	• Apply the sticky side of the patch on the skin you have cleaned and dried. Remove the other half of the clear plastic and attach the entire patch to your skin.
	• Press firmly on the patch with the palm of your hand for 10 seconds, making sure that the whole patch adheres to your skin. • Run your fingers over the entire surface area to smooth out any "wrinkles" around the outer edges of the patch.

- Check your patch every day to make sure all edges are sticking correctly.

  Never cut, damage or alter the patch in any way.

  Refer to the Detailed Patient Labeling provided within this package for complete instructions.

WHEN DO I CHANGE MY XULANE™ PATCH?

- The patch works for 7 days (one week). Apply a new patch on the same day each week (your Patch Change Day) for 3 weeks in a row. Make sure you have removed your old patch prior to applying the new patch.
- During week 4, **DO NOT** wear a patch. Make sure you removed your old patch. (Your period should begin during this week.)
- Following week 4, repeat the cycle of three weekly applications followed by a patch-free week.

Please see the Detailed Patient Labeling for important information about what to do if you forget to change your patch and how to dispose of used patches.

WHAT IF MY PATCH BECOMES LOOSE OR FALLS OFF?

The patch must stick securely to your skin to work properly.

If a patch edge lifts up:

- Press down firmly on the patch with the palm of your hand for 10 seconds, making sure that the whole patch adheres to your skin. Run your fingers over the entire surface area to smooth out any “wrinkles” around the edges of the patch.
- If your patch does not stick completely, remove it and apply a new patch.
- Do not tape or wrap the patch to your skin or reapply a patch that is partially adhered to clothing.

If your patch has been off or partially off:

- **For less than 1 Day**, try to reapply it. If the patch does not adhere completely, apply a new patch immediately. (No backup contraception is needed and your Patch Change Day will stay the same.)
- **For more than 1 Day or if you are not sure for how long**, you may become pregnant. To reduce this risk, apply a new patch and start a new 4-week cycle. You will now have a new Patch Change Day and **MUST USE NON-HORMONAL BACKUP CONTRACEPTION** (such as a condom or diaphragm and spermicide) for the first week of your new cycle.

Please see the Detailed Patient Labeling section of the full Prescribing Information within this package.

Special Precautions for Storage

Store at 20° to 25°C (68° to 77°F).

Store patches in their protective pouches. Apply immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

Mylan®

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

REVISED AUGUST 2012
PIC:NEETS:R3

NDC 0378-3340-16

3340: 8RX1

1 Week Therapy | Rx only

Xulane™

(norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day

Each 14 cm^2 system contains 4.86 mg norelgestromin and 0.53 mg ethinyl estradiol, USP. The inactive components are polyisobutene adhesive, crospovidone, mineral oil, non-woven polyester fabric, oleyl alcohol, dipropylene glycol, polyester backing film laminate and polyester release liner.

This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Mylan®

For Transdermal Use Only

3340:8RX1

See patient instructions. Apply immediately upon removal from pouch.
Each transdermal system is intended to be worn 7 days as prescribed.

Keep out of reach of children. Package not child-resistant.

Do not store unpouched. Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

USED PATCHES SHOULD NOT BE FLUSHED DOWN THE TOILET.

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

Mylan®
Mylan.com

(N3) 0378-3340-16 (6)

Pharmacode
Area

Xulane™

(norelgestromin and ethinyl estradiol transdermal system)
150/35 mcg per day

Note your Patch Change Day here

- Sunday ☐
- Monday ☐
- Tuesday ☐
- Wednesday ☐
- Thursday ☐
- Friday ☐
- Saturday ☐

See patient instructions. Apply immediately upon removal from pouch. Each transdermal system is intended to be worn 7 days as prescribed.

Package not child-resistant. Keep out of reach of children.

Do not store unpouched. Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Place Rx Label Here

Mylan® | **Mylan Pharmaceuticals Inc.**
Morgantown, WV 26505 U.S.A.

Mylan.com **M3340-53-3C:R11RX1**

3 Transdermal Systems

Mylan®

Xulane™
(norelgestromin and enthinyl estradiol transdermal system)
150/35 mcg per day

Xulane™
(norelgestromin and ethinyl estradiol transdermal system)
150/35 mcg per day

NDC 0378-3340-53

Mylan®

NDC 0378-3340-53

Contents: 3 Transdermal Systems | Rx only

Xulane™
(norelgestromin and ethinyl estradiol transdermal system)
150/35 mcg per day

Each 14 cm^2 system contains 4.86 mg norelgestromin and 0.53 mg ethinyl estradiol, USP. The inactive components are polyisobutene adhesive, crospovidone, mineral oil, non-woven polyester fabric, oleyl alcohol, dipropylene glycol, polyester backing film laminate and polyester release liner.

This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Mylan®

For Transdermal Use Only

(N3) 0378-3340-53 (1)

3 Transdermal Systems

Mylan®

Xulane™
(norelgestromin and enthinyl estradiol transdermal system)
150/35 mcg per day

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XULANE™ safely and effectively. See full prescribing information for XULANE.

XULANE™ (norelgestromin and ethinyl estradiol transdermal system)
Initial U.S. Approval: 2001

WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING, RISK OF VENOUS THROMBOEMBOLISM, AND PHARMACOKINETIC PROFILE OF ETHINYL ESTRADIOL
See full prescribing information for complete boxed warning.
Women over 35 years old who smoke should not use Xulane. (4)
Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptives (CHC) use. (4)
There may be an increased risk of venous thromboembolism (VTE) among women who use the Xulane patch compared to women who use certain oral contraceptives. (5.1)
The pharmacokinetic (PK) profile of ethinyl estradiol (EE) for the Xulane patch is different from the PK profile for oral contraceptives in that it has higher area under the time-concentration curve, steady state concentrations and lower peak concentrations. (5.2)

---------- INDICATIONS AND USAGE ----------
Xulane is an estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women who elect to use a transdermal patch. (1)
Limitation of Use: Xulane may be less effective in preventing pregnancy in women at or above 198 lbs (90 kg). (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Xulane uses a 28-day (4-week) cycle. Apply a new patch to the upper outer arm, abdomen, buttock or back each week for 3 weeks (21 total days). Week 4 is patch-free. (2.1, 2.3)
- Apply each new patch on the same day of the week. Wear only one patch at a time. (2.1)
- Do not cut or alter the patch in any way. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Transdermal system: 150 mcg/day norelgestromin and 35 mcg/day ethinyl estradiol. (3)

---------- CONTRAINDICATIONS ----------
- A high risk of arterial or venous thrombotic diseases (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Vascular risks: Stop Xulane if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Liver disease: Discontinue Xulane if jaundice occurs. (5.3)
- High blood pressure: Do not prescribe Xulane for women with uncontrolled hypertension or hypertension with vascular disease. (5.4)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Xulane. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.6)
- Headache: Evaluate significant change in headaches and discontinue Xulane if indicated. (5.7)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.8)

---------- ADVERSE REACTIONS ----------
The most frequent adverse reactions reported during clinical trials (≥ 5%) were breast symptoms, nausea/vomiting, headache, application site disorder, abdominal pain, dysmenorrhea, vaginal bleeding and menstrual disorders, and mood, affect and anxiety disorders. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

---------- DRUG INTERACTIONS ----------
Drugs or herbal products that induce certain enzymes (for example CYP3A4) may decrease the effectiveness of CHCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with CHCs. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------
- Nursing mothers: Not recommended; can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2014
NEETS:R8RX1/PL:NEETS:R8

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING, RISK OF VENOUS THROMBOEMBOLISM, AND PHARMACOKINETIC PROFILE OF ETHINYL ESTRADIOL

Cigarette Smoking and Serious Cardiovascular Risks

Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, hormonal contraceptives, including Xulane, should not be used by women who are over 35 years of age and smoke.

Risk of Venous Thromboembolism

The risk of venous thromboembolism (VTE) among women aged 15 to 44 who used the Xulane patch compared to women who used several different oral contraceptives was assessed in five U.S. epidemiologic studies using electronic healthcare claims data. The relative risk estimates ranged from 1.2 to 2.2; one of the studies found a statistically significant increased relative risk of VTE for current users of Xulane [see *Warnings and Precautions (5.1)*].

Pharmacokinetic (PK) Profile of Ethinyl Estradiol (EE)

The PK profile for the Xulane patch is different from the PK profile for oral contraceptives in that it has a higher steady state concentrations and a lower peak concentration. Area under the time-concentration curve (AUC) and average concentration at steady state (C_{ss}) for EE are approximately 60% higher in women using Xulane compared with women using an oral contraceptive containing 35 mcg of EE. In contrast, the peak concentration (C_{max}) for EE is approximately 25% lower in women using Xulane. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using Xulane compared with women using oral contraceptives containing 30 mcg to 35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including VTE [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].

1 INDICATIONS AND USAGE

Xulane is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.

Limitation of Use:

- Xulane may be less effective in preventing pregnancy in women who weigh 198 lbs (90 kg) or more.

2 DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, Xulane must be used exactly as directed.

Complete instructions to facilitate patient counseling on proper system usage may be found in the FDA-Approved Patient Labeling.

2.1 How to Use Xulane

The Xulane transdermal system uses a 28-day (4-week) cycle. A new patch is applied each week for 3 weeks (21 total days). Week 4 is patch-free. Withdrawal bleeding is expected during this time.

Every new patch should be applied on the same day of the week. This day is known as the "Patch Change Day." For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time.

Do not cut, damage or alter the Xulane patch in any way. If the Xulane patch is cut, damaged or altered in size, contraceptive efficacy may be impaired.

On the day after Week 4 ends, a new 4-week cycle is started by applying a new patch. Under no circumstances should there be more than a 7-day patch-free interval between dosing cycles.

2.2 How to Start Using Xulane

The woman has two options for starting the patch and she should choose the option that is right for her:

- **First Day Start—**The woman should apply her first patch during the first 24 hours of her menstrual period.

- **Sunday Start—**The woman should apply her first patch on the first Sunday after her menstrual period begins. With this option, a non-hormonal backup method of birth control, such as a condom and spermicide or diaphragm and spermicide, is needed for the first 7 days of the first cycle only. If her period starts on a Sunday, the first patch should be applied that day, and no backup contraception is needed.

- **When Switching From the Pill or Vaginal Contraceptive Ring to the Patch—**If the woman is switching from the pill or vaginal contraceptive ring to Xulane, she should complete her current pill cycle or vaginal ring cycle and apply the first Xulane patch on the day she would normally start her next pill or insert her next vaginal ring. If she does not get her period within a week after taking the last active pill or removing the last vaginal ring, she should check with her healthcare professional to be sure that she is not pregnant, but she may go ahead and start Xulane for contraception. If the patch is applied more than a week after taking the last active pill or removal of the last vaginal ring, she should use a non-hormonal contraceptive concurrently for the first 7 days of patch use.

Use after Childbirth

Start contraceptive therapy with Xulane in women who elect not to breastfeed no sooner than 4 weeks after childbirth due to increased risk of thromboembolism. If a woman begins using Xulane postpartum, and has not yet had a period, consider the possibility of ovulation and conception occurring prior to use of Xulane, and instruct her to use an additional method of contraception, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days. *[See Warnings and Precautions (5.1) and Pregnancy (8.1).]*

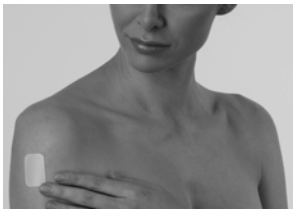
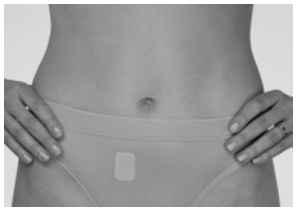
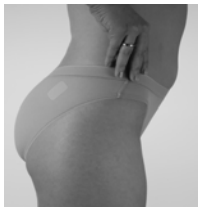
Use after Abortion or Miscarriage

After an abortion or miscarriage that occurs in the first trimester, Xulane may be started immediately. An additional method of contraception is not needed if Xulane is started immediately. If use of Xulane is not started within 5 days following a first trimester abortion, the woman should follow the instructions for a woman starting Xulane for the first time. In the meantime she should be advised to use a non-hormonal contraceptive method. Ovulation may occur within 10 days of an abortion or miscarriage.

Start Xulane no earlier than 4 weeks after a second trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. *[See Contraindications (4) and Warnings and Precautions (5.1).]*

2.3 How to Apply Xulane

CHOOSING A PLACE ON THE BODY TO PUT THE PATCH


- The patch may be placed on the upper outer arm, abdomen, buttock or back in a place where it won't be rubbed by tight clothing. For example, it should not be placed under the waistband of clothing.

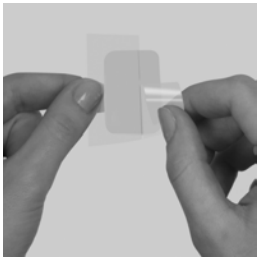
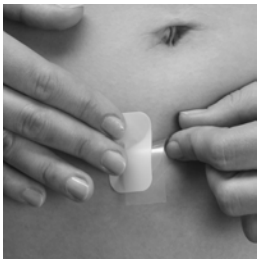
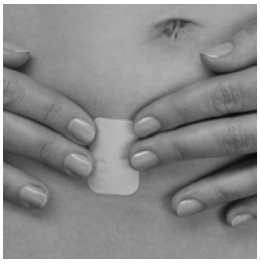
- The patch should not be placed on the breasts, on cut or irritated skin, or on the same location as the previous patch.

Before applying the patch:

- The woman should make sure the skin is clean and dry.

- She should not use lotions, creams, oils, powders, or make-up at the patch site. It may cause the patch to fail to stick properly or to become loose.

HOW TO APPLY THE PATCH

	• The woman should tear open the pouch at the top edge **and** one side edge. She should peel open the foil pouch. She should gently remove the contents of the foil pouch and discard the additional pieces of film above and below the patch.
	• The woman should peel away half of the clear plastic. She should avoid touching the sticky surface with her fingers.
	• The woman should apply the sticky side of the patch on the skin she has cleaned and dried. She should then remove the other half of the clear plastic and attach the entire patch to her skin.
	• The woman should press firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin. • She should run her fingers over the entire surface area to smooth out any "wrinkles" around the outer edges of the patch.

- The woman should check her patch every day to make sure all edges are sticking correctly.

WHEN TO CHANGE THE XULANE PATCH

- The patch works for 7 days (one week). The woman should apply a new patch on the same day each week (her Patch Change Day) for 3 weeks in a row. She must make sure she has removed her old patch prior to applying the new patch.
- During Week 4, she **DOES NOT** wear a patch. She must make sure she removes her old patch. (Her period should begin during this week.)

- Following Week 4, she repeats the cycle of three weekly applications followed by a patch-free week.

WHAT IF THE PATCH BECOMES LOOSE OR FALLS OFF?

The patch must stick securely to the skin to work properly. If the Xulane patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs. The woman should not try to reapply a patch if it is no longer sticky, if it has become stuck to itself or another surface, or if it has other material stuck to it.

If a patch edge lifts up:

- The woman should press down firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin. She should run her fingers over the entire surface area to smooth out any "wrinkles" around the edges of the patch.

- If her patch does not stick completely, she should remove it and apply a replacement patch.

- She should not tape or wrap the patch to her skin or reapply a patch that is partially adhered to clothing.

If the patch has been off or partially off:

- **For less than 1 Day,** she should try to reapply it. If the patch does not adhere completely, she should apply a new patch immediately. (No backup contraception is needed and her Patch Change Day will stay the same).

- **For more than 1 Day or if she is not sure for how long,** she may not be protected from pregnancy. To reduce this risk, she should apply a new patch and start a new 4-week cycle. She will now have a new Patch Change Day and **MUST USE NON-HORMONAL BACKUP CONTRACEPTION** (such as a condom and spermicide or diaphragm and spermicide) for the first week of her new cycle.

IF THE WOMAN FORGETS TO CHANGE HER PATCH

- **at the start of any patch cycle (Week 1/Day 1):** SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should apply the first patch of her new cycle as soon as she remembers. There is now a new "Patch Change Day" and a new "Day 1." The woman must use back-up contraception, such as a condom and spermicide or diaphragm and spermicide, for the first week of the new cycle.

- **in the middle of the patch cycle (Week 2/Day 8 or Week 3/Day 15),**

- for **1 or 2 days** (up to 48 hours), she should apply a new patch immediately. The next patch should be applied on the usual "Patch Change Day." No back-up contraception is needed.

- for more than 2 days (48 hours or more), SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new 4-week cycle immediately by putting on a new patch. There is now a new "Patch Change Day" and a new **"**Day 1." The woman must use back-up contraception for one week.

- **at the end of the patch cycle (Week 4/Day 22),**

  - If the woman forgets to remove her patch, she should take it off as soon as she remembers. The next cycle should be started on the usual "Patch Change Day," which is the day after Day 28. No back-up contraception is needed.

Under no circumstances should there be more than a 7-day patch-free interval between cycles. If there are more than 7 patch-free days, THE WOMAN MAY NOT BE PROTECTED FROM PREGNANCY and back-up contraception, such as a condom and spermicide or diaphragm and spermicide, must be used for 7 days. As with combined oral contraceptives, the risk of ovulation increases with each day beyond the recommended drug-free period. If she has had intercourse during such an extended patch-free interval, consider the possibility of pregnancy.

Change Day Adjustment
If the woman wishes to change her Patch Change Day, she should complete her current cycle, removing the third Xulane patch on the correct day. During the patch-free week, she may select an earlier Patch Day Change by applying a new Xulane patch on the desired day. In no case should there be more than 7 consecutive patch-free days.

Breakthrough Bleeding or Spotting
In the event of unscheduled or breakthrough bleeding or spotting (bleeding that occurs on the days that Xulane is worn), treatment should be continued. If unscheduled bleeding persists longer than a few cycles, consider causes other than Xulane.

If the woman does not have scheduled or withdrawal bleeding (bleeding that should occur during the patch-free week), she should resume treatment on the next scheduled Change Day. If Xulane has been used correctly, the absence of withdrawal bleeding is not necessarily an indication of pregnancy. Nevertheless, consider the possibility of pregnancy, especially if absence of withdrawal bleeding occurs in 2 consecutive cycles. Discontinue Xulane if pregnancy is confirmed.

In Case of Skin Irritation

If patch use results in uncomfortable irritation, the patch may be removed and a new patch may be applied to a different location until the next Change Day. Only one patch should be worn at a time.

Additional Instructions for Dosing
Unscheduled bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing hormonal contraceptives. In case of breakthrough bleeding, as in all cases of irregular bleeding from the vagina, consider nonfunctional causes. In case of undiagnosed persistent or recurrent abnormal bleeding from the vagina, take adequate diagnostic measures to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another method of contraception may solve the problem.

Use of Hormonal Contraceptives in the Event of a Missed Menstrual Period

1. If the woman has not adhered to the prescribed schedule, consider the possibility of pregnancy at the time of the first missed period. Discontinue use of Xulane if pregnancy is confirmed.

2. If the woman has adhered to the prescribed regimen and misses one period, she should continue using her contraceptive patches. However, if she has adhered to the prescribed regimen, misses one period and has symptoms associated with pregnancy, rule out pregnancy. Discontinue Xulane use if pregnancy is confirmed.

3. If the woman has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy. Discontinue Xulane use if pregnancy is confirmed.

3 DOSAGE FORMS AND STRENGTHS
Transdermal system: 150 mcg/day norelgestromin and 35 mcg/day ethinyl estradiol.

4 CONTRAINDICATIONS
Do not prescribe Xulane to women who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
    - Smoke, if over age 35 *[see Boxed Warning, and Warnings and Precautions (5.1)]*
    - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
    - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
    - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
    - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
    - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*

- Have uncontrolled hypertension *[see Warnings and Precautions (5.4)]*
- Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.6)]*
- Have headaches with focal neurological symptoms or have migraine headaches with aura
    - Women over age 35 with any migraine headaches *[see Warnings and Precautions (5.7)]*

- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.3)*, *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*

- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*

- Pregnancy, because there is no reason to use hormonal contraceptives during pregnancy *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]*

- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.11)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Xulane if an arterial or deep venous thrombotic event (VTE) occurs.

Stop Xulane if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

If feasible, stop Xulane at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE. Discontinue use of Xulane during prolonged immobilization and resume treatment based on clinical judgment.

Start Xulane no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

The use of combination hormonal contraceptives (CHCs) increases the risk of VTE. Known risk factors for VTE include smoking, obesity and family history of VTE, in addition to other factors that contraindicate use of CHCs *[see Contraindications (4)]*.
Five epidemiologic studies[1-9] that assessed the risk of VTE associated with use of Xulane are described below. These are four case control studies, that compared VTE rates among women using Xulane to rates among women using an OC comparator, and an FDA-funded cohort study that estimated and compared VTE rates among women using various hormonal contraceptives, including Xulane. All five studies were retrospective studies from U.S. electronic healthcare

databases and included women aged 15 to 44 (10 to 55 in the FDA-funded study) who used Xulane or oral contraceptives containing 20 mcg to 35 mcg of ethinyl estradiol (EE) and levonorgestrel (LNG), norethindrone, or norgestimate (NGM). NGM is the prodrug for NGMN, the progestin in Xulane.

Some of the data from the epidemiologic studies suggest an increased risk of VTE with use of Xulane compared to use of some combined oral contraceptives (see Table 1). The studies used slightly different designs and reported relative risk estimates ranging from 1.2 to 2.2. None of the studies have adjusted for body mass index, smoking, and family history of VTE, which are potential confounders. The interpretations of these relative risk estimates range from no increase in risk to an approximate doubling of risk. One of the studies found a statistically significant increased risk of VTE for current users of Xulane.

The five studies are:

- The i3 Ingenix study with NGM-containing oral contraceptives as the comparator, including a 24-month extension, based on the Ingenix Research Datamart; this study included patient chart review to confirm the VTE occurrence.

- The Boston Collaborative Drug Surveillance Program (BCDSP) with NGM-containing oral contraceptives as the comparator (BCDSP NGM), including two extensions of 17 and 14 months, respectively, based on the Pharmetrics database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.

- BCDSP with LNG-containing oral contraceptives as the comparator, based on the Pharmetrics database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.

- BCDSP with LNG-containing oral contraceptives as the comparator, based on the Marketscan database, using only non-fatal idiopathic cases. VTE cases were not confirmed by chart review.

- FDA-funded study with two groups of comparators [1) LNG-containing oral contraceptives, and 2) oral contraceptives that contain LNG, norethindrone or norgestimate], based on Kaiser Permanente and Medicaid databases. This study used all cases of VTE (idiopathic and non-idiopathic) and included patient chart review to confirm the VTE occurrence.

The i3 Ingenix and BCDSP NGM studies have provided data on additional cases identified in study extensions; however, each study extension was not powered to provide independent

estimates of risk. The pooled estimates provide the most reliable estimates of VTE risk. Risk ratios from the original and various extensions of the i3 Ingenix and BCDSP NGM studies are provided in Table 1. The results of these studies are presented in Figure 1.

Table 1: Estimates (Risk Ratios) of Venous Thromboembolism Risk in Current Users of Xulane Compared to Combined Oral Contraceptive Users

Epidemiologic Study[A]	Comparator Product	Risk Ratios (95% CI)
i3 Ingenix NGM Study in Ingenix Research Datamart[1,6,7,8]	NGM/35 mcg EE[B]	**2.2[C] (1.2 – 4.0)[D]**
BCDSP[E] NGM Study in Pharmetrics database[2,3,5]	NGM/35 mcg EE	**1.2 (0.9 - 1.8)[F]**
BCDSP[E] LNG Study in Pharmetrics database[4]	LNG[G]/30 mcg EE	**2.0 (0.9 - 4.1)[H]**
BCDSP[E] LNG Study in Marketscan database[4]	LNG/30 mcg EE	**1.3 (0.8 – 2.1)[I]**
FDA-funded Study in Kaiser Permanente and Medicaid databases[J, K, 9]	"All progestins[L]"/20 - 35 mcg EE	**1.4 (0.9 – 2.0)**
	LNG/30 mcg EE	**1.2 (0.8 – 1.9)**

[A] "New users" – i.e., women with no prior exposure to the drug studied during a pre-specified time period – are considered to be the most informative population to study in pharmacoepidemiologic safety studies. All estimates took account of new-user status. The method and time period used to identify "new users" varied from study to study.

[B] NGM = norgestimate; EE = ethinyl estradiol

[C] Increase in risk of VTE is statistically significant

[D] Pooled risk ratio from references 1 and 6 covering the initial 33-month study plus 24-month extension. [Initial 33 months of data: Risk Ratio (95% CI) = 2.5[C] (1.1-5.5); Separate estimate from the 24 months of data on new cases not included in the previous estimate: Risk Ratio (95% CI) = 1.4 (0.5-3.7)]. These risk ratios are based on idiopathic cases (those in women without other known risk factors for VTE). If all VTE cases are considered, the pooled risk ratio and 95% CI are 2.0 (1.2-3.3)[C].

[E] BCDSP = Boston Collaborative Drug Surveillance Program; the risk ratios are based on idiopathic cases.

[F] Pooled risk ratio from references 2, 3 and 5 covering the initial 36-month study, plus 17-month and 14-month extensions. [Initial 36 months of data: Risk Ratio (95% CI) = 0.9 (0.5-1.6); Separate estimate from 17 months of data on new cases not included in the previous estimate: Risk Ratio (95% CI) = 1.1 (0.6-2.1); Separate estimate from 14 months of data on new cases not included in the previous estimates: Risk Ratio (95% CI) = 2.4[C] (1.2-5.0)]

[G] LNG = levonorgestrel

[H] 48 months of data.

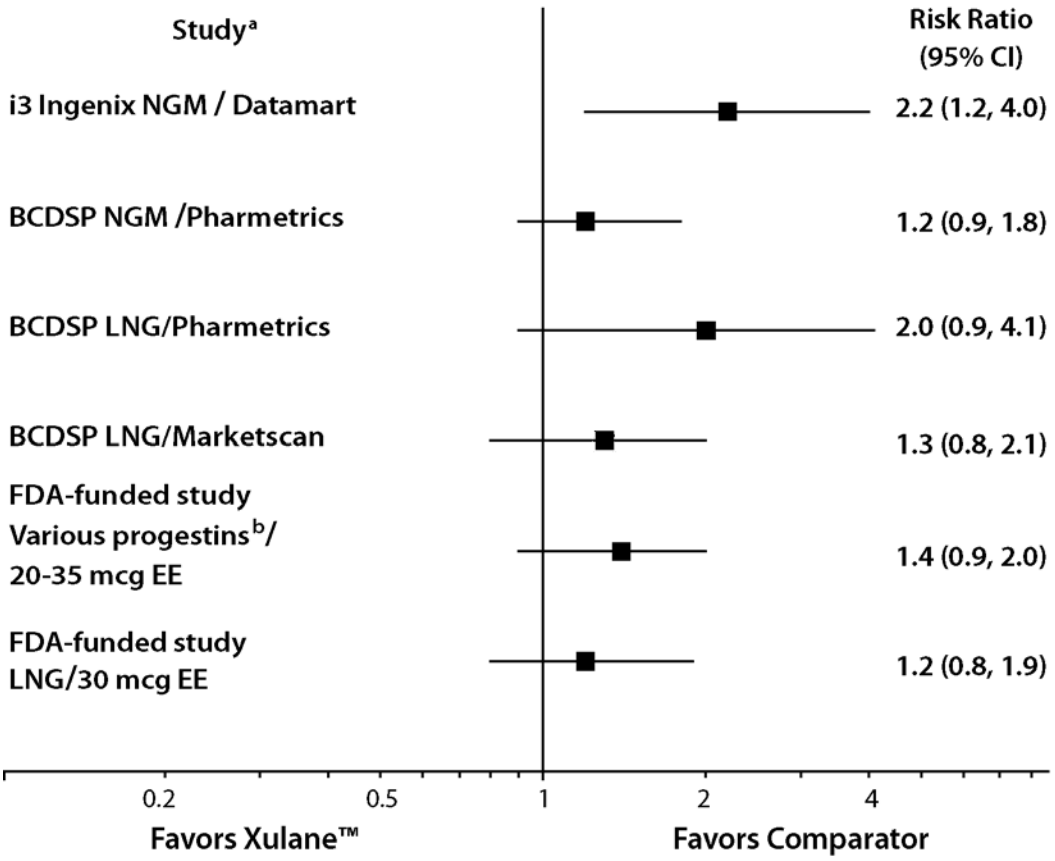
[I] 69 months of data.

[J] 84 months of data in FDA-funded study

[K] Results for "All users," i.e., initiation and continuing use of study combination hormonal contraception: "All progestins"/20-35 mcg EE, Risk Ratio (95% CI) = 1.6 (1.2-2.1)[C] and LNG/30 mcg EE, Risk Ratio (95% CI) = 1.3 (1.0-1.8).

[L] Includes the following progestins: LNG, norethindrone, norgestimate.

Figure 1: VTE Risk of Xulane Relative to Combined Oral Contraceptives



[a] All estimates took account of new-user status. The method and time period used to identify "new users" varied from study to study.

[b] Includes the following progestins: levonorgestrel (LNG), norethindrone, norgestimate (NGM).

BCDSP = Boston Collaborative Drug Surveillance Program

EE = ethinyl estradiol

An increased risk of thromboembolic and thrombotic disease associated with the use of combination hormonal contraceptives (CHCs) is well established. Although the absolute VTE rates are increased for users of CHCs compared to non-users, the rates associated with pregnancy are even greater, especially during the post-partum period (see Figure 2).

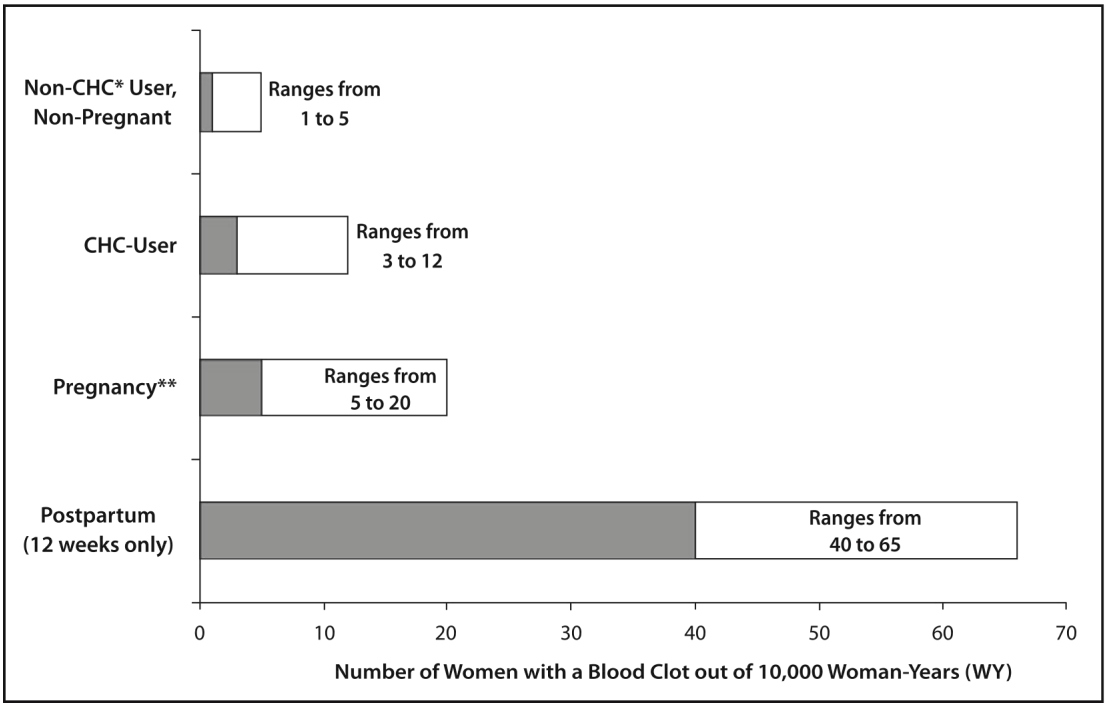
The frequency of VTE in women using CHCs has been estimated to be 3 to 12 cases per 10,000 woman-years.

The risk of VTE is highest during the first year of use of combination hormonal contraception. The risk of thromboembolic disease due to combination hormonal contraceptives gradually disappears after use is discontinued.

Figure 2 shows the risk of developing a VTE for women who are not pregnant and do not use CHCs, for women who use CHCs, for pregnant women, and for women in the post-partum period.

To put the risk of developing a VTE into perspective: If 10,000 women who are not pregnant and do not use CHCs are followed for one year, between 1 and 5 of these women will develop a VTE.

Figure 2: Likelihood of Developing a VTE



* CHC = combination hormonal contraception

** Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is 9 months, the rate is 7 to 27 per 10,000 WY.

Use of CHCs also increases the risk of arterial thromboses such as, cerebrovascular events (thrombotic and hemorrhagic strokes) and myocardial infarctions, especially in women with other risk factors for these events. In general, the risk is greatest among older (> 35 years of age), hypertensive women who also smoke. Use CHCs with caution in women with cardiovascular disease risk factors.

5.2 PK Profile of Ethinyl Estradiol

The PK profile for the Xulane patch is different from the PK profile for oral contraceptives in that it has a higher C_{ss} and a lower C_{max}. AUC and average C_{ss} for EE are approximately 60% higher in women using Xulane compared with women using an oral contraceptive containing EE 35 mcg. In contrast, the C_{max} for EE is approximately 25% lower in women using Xulane. Inter-subject variability results in increased exposure to EE in some women using either Xulane or oral contraceptives. However, inter-subject variability in women using Xulane is higher. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using Xulane compared with women using oral contraceptives containing 30 mcg to 35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including venous thromboembolism. *[See Boxed Warning and Clinical Pharmacology (12.3).]*

5.3 Liver Disease

Impaired Liver Function

Do not use Xulane in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver *[see Contraindications (4)]*. Discontinue Xulane if jaundice develops. Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal and CHC causation has been excluded.

Liver Tumors

Xulane is contraindicated in women with benign and malignant liver tumors *[see Contraindications (4)]*. Hepatic adenomas are associated with CHC use. An estimate of the attributable risk is 3.3 cases/100,000 CHC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) CHC users. However, the risk of liver cancers in CHC users is less than one case per million users.

5.4 High Blood Pressure

Xulane is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For women with well-controlled hypertension, monitor blood pressure and stop Xulane if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking hormonal contraceptives, and this increase is more likely in older women with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

5.5 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among CHC users. Use of CHCs may also worsen existing gallbladder disease. A past history of CHC-related cholestasis predicts an increased risk with subsequent CHC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for CHC-related cholestasis.

5.6 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who take Xulane. CHCs may decrease glucose tolerance in a dose-related fashion. In a 6-cycle clinical trial with Xulane there were no clinically significant changes in fasting blood glucose from baseline to end of treatment.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on hormonal contraceptives.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using hormonal contraceptives.

5.7 Headache

If a woman taking Xulane develops new headaches that are recurrent, persistent or severe, evaluate the cause and discontinue Xulane if indicated.

Consider discontinuation of Xulane in the case of increased frequency or severity of migraine during hormonal contraceptive use (which may be prodromal of a cerebrovascular event).

5.8 Bleeding Irregularities

Unscheduled Bleeding and Spotting

Unscheduled (breakthrough) bleeding and spotting sometimes occur in women using Xulane. Consider non-hormonal causes and take adequate diagnostic measures to rule out malignancy, other pathology, or pregnancy in the event of unscheduled bleeding, as in the case of any abnormal vaginal bleeding. If pathology and pregnancy have been excluded, time or a change to another contraceptive product may resolve the bleeding.

In the clinical trials, most women started their scheduled (withdrawal) bleeding on the fourth day of the drug-free interval, and the median duration of withdrawal bleeding was 5 to 6 days. On average, 26% of women per cycle had 7 or more total days of bleeding and/or spotting (this includes both scheduled and unscheduled bleeding and/or spotting). Three clinical studies of the efficacy of Xulane in preventing pregnancy assessed scheduled and unscheduled bleeding *[see Clinical Studies (14)]* in 3,330 women who completed 22,155 cycles of exposure. A total of 36 (1.1%) of the women discontinued Xulane at least in part, due to bleeding or spotting.

Table 2 summarizes the proportion of subjects who experienced unscheduled (breakthrough) bleeding/spotting by treatment cycle.

Table 2: Unscheduled (Breakthrough) Bleeding/Spotting (Subjects Evaluable for Efficacy)

Treatment Cycle	**Pooled data from 3 studies N = 3,319**	
	n	%[a]
Cycle 1	2,994	18.2
Cycle 2	2,743	11.9
Cycle 3	2,699	11.6
Cycle 4	2,541	10.1
Cycle 5	2,532	9.2
Cycle 6	2,494	8.3
Cycle 7	698	8.3
Cycle 8	692	8.7
Cycle 9	654	8.6
Cycle 10	621	8.7
Cycle 11	631	8.9
Cycle 12	617	6.3
Cycle 13	611	8.0

[a]Percentage of subjects with breakthrough bleeding/spotting events.

Amenorrhea and Oligomenorrhea

In the event of amenorrhea, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one patch or started the patch on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

Some women may encounter amenorrhea or oligomenorrhea after discontinuation of hormonal contraceptive use, especially when such a condition was pre-existent.

5.9 Hormonal Contraceptive Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Discontinue Xulane use if pregnancy is confirmed.

Administration of CHCs should not be used as a test for pregnancy *[see Use in Specific Populations (8.1)]*.

5.10 Depression

Carefully observe women with a history of depression and discontinue Xulane if depression recurs to a serious degree.

5.11 Carcinoma of Breasts and Cervix

Xulane is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive *[see Contraindications (4)]*.

There is substantial evidence that CHCs do not increase the incidence of breast cancer. Although some past studies have suggested that CHCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

5.12 Effect on Binding Globulins

The estrogen component of CHCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

5.13 Monitoring

A woman who is taking hormonal contraceptive should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Hereditary Angioedema

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.15 Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while using Xulane.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of combination hormonal contraceptives, including Xulane, are discussed elsewhere in the labeling:

- Serious cardiovascular events and stroke *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Vascular events, including venous and arterial thromboembolic events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.3)]*

Adverse reactions commonly reported by users of combination hormonal contraceptives are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to Xulane in 3,330 sexually active women (3,322 of whom had safety data) who participated in three Phase 3 clinical trials designed to evaluate contraceptive efficacy and safety. These subjects received six or 13 cycles of contraception (Xulane or an oral contraceptive comparator in two of the trials). The women ranged in age from 18 to 45 years and were predominantly white (91%).

The most common adverse reactions (≥ 5%) reported during clinical trials were breast symptoms, nausea/vomiting, headache, application site disorder, abdominal pain, dysmenorrhea, vaginal bleeding and menstrual disorders, and mood, affect and anxiety disorders. The most common events leading to discontinuation were application site reaction, breast symptoms (including breast discomfort, engorgement and pain), nausea and/or vomiting, headache and emotional lability.

Adverse drug reactions reported by ≥ 2.5% of Xulane-treated subjects in these trials are shown in Table 3.

Table 3: Adverse Drug Reactions Reported by ≥ 2.5% of Xulane-treated Subjects in Three Phase 3 Clinical Trials

System/Organ Class* Adverse reaction	**Xulane (n = 3,322)**
Reproductive system and breast disorders	
Breast symptoms†	22.4%
Dysmenorrhea	7.8%
Vaginal bleeding and menstrual disorders†	6.4%
Gastrointestinal disorders	
Nausea	16.6%
Abdominal pain†	8.1%
Vomiting	5.1%
Diarrhea	4.2%
Nervous system disorders	
Headache	21.0%
Dizziness	3.3%
Migraine	2.7%
General disorders and administration site conditions	
Application site disorder†	17.1%
Fatigue	2.6%
Psychiatric disorders	
Mood, affect and anxiety disorders†	6.3%
Skin and subcutaneous tissue disorders	
Acne	2.9%
Pruritus	2.5%
Infections and infestations	
Vaginal yeast infection†	3.9%
Investigations	
Weight increased	2.7%

*MedDRA version 10.0

† Represents a bundle of similar terms

Additional adverse drug reactions that occurred in < 2.5% of Xulane-treated subjects in the above clinical trials datasets are:

- **Gastrointestinal disorders:** Abdominal distension
- **General disorders and administration site conditions:** Fluid retention[1], malaise
- **Hepatobiliary disorders:** Cholecystitis
- **Investigations:** Blood pressure increased, lipid disorders[1]

- **Musculoskeletal and connective tissue disorders:** Muscle spasms
- **Psychiatric disorders:** Insomnia, libido decreased, libido increased
- **Reproductive system and breast disorders:** Galactorrhea, genital discharge, premenstrual syndrome, uterine spasm, vaginal discharge, vulvovaginal dryness
- **Respiratory, thoracic and mediastinal disorders:** Pulmonary embolism
- **Skin and subcutaneous tissue disorders:** Chloasma, dermatitis contact, erythema, skin irritation

[1]Represents a bundle of similar terms

6.2 Post-Marketing Experience

The following adverse reactions (Table 4) have been identified during post-approval use of Xulane. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 4: Alphabetical List of Adverse Drug Reactions Identified During Post-Marketing Experience with Xulane by System Organ Class*

System Organ Class	Adverse Drug Reactions
Cardiac disorders	Myocardial infarction†
Endocrine disorders	Hyperglycemia, insulin resistance
Eye disorders	Contact lens intolerance or complication
Gastrointestinal disorders	Colitis
General disorders and administration site conditions	Application site reaction†, edema†
Hepatobiliary disorders	Blood cholesterol abnormal, cholelithiasis, cholestasis, hepatic lesion, jaundice cholestatic, low density lipoprotein increased
Immune system disorders	Allergic reaction†, urticaria
Investigations	Blood glucose abnormal, blood glucose decreased
Metabolism and nutrition disorders	Increased appetite
Neoplasms benign, malignant and unspecified (Incl. cysts and polyps)	Breast cancer†, cervix carcinoma, hepatic adenoma, hepatic neoplasm
Nervous system disorders	Dysgeusia, migraine with aura
Psychiatric disorders	Anger, emotional disorder, frustration, irritability

Reproductive system and breast disorders	Breast mass, cervical dysplasia, fibroadenoma of breast, menstrual disorder†, suppressed lactation, uterine leiomyoma
Skin and subcutaneous tissues disorders	Alopecia, eczema, erythema multiforme, erythema nodosum, photosensitivity reaction, pruritus generalized, rash†, seborrheic dermatitis, skin reaction
Vascular disorders	Arterial thrombosis†, cerebrovascular accident†, deep vein thrombosis†, hemorrhage intracranial†, hypertension, hypertensive crisis, pulmonary embolism†, thrombosis†

*MedDRA version 10.0
† Represents a bundle of similar terms

7 DRUG INTERACTIONS

Consult the labeling of concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Hormonal Contraceptives

Substances Decreasing the Plasma Concentrations of CHCs and Potentially Diminishing the Efficacy of CHCs:

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of CHCs and potentially diminish the effectiveness of CHCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between hormonal contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with CHCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances Increasing the Plasma Concentrations of CHCs:

Coadministration of atorvastatin or rosuvastatin and certain CHCs containing EE increase AUC values for EE by approximately 20% to 25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) Protease Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors:

Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of coadministration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritnoavir, and tipranavir/ritonavir] or increase [e.g., indinavir and

atazanavir/ritonavir])/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine] or increase [e.g., etravirine]).

7.2 Effects of Combined Hormonal Contraceptives on Other Drugs

CHCs containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations. CHCs have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, and temazepam. Significant decrease in plasma concentration of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of CHCs *[see Warnings and Precautions (5.12)]*.

7.3 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use hormonal contraceptives during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following exposure to low dose hormonal contraceptives prior to conception or during early pregnancy.

The administration of hormonal contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Hormonal contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

8.3 Nursing Mothers

The effects of Xulane in nursing mothers have not been evaluated and are unknown. When possible, advise the nursing mother to use other forms of contraception until she has completely weaned her child. Estrogen-containing CHCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use

Safety and efficacy of Xulane have been established in women of reproductive age. Efficacy is expected to be the same for post-pubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Xulane has not been studied in postmenopausal women and is not indicated in this population.

8.6 Hepatic Impairment

No studies with Xulane have been conducted in women with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of combined hormonal contraceptive use until markers of liver function return to normal and combined hormonal contraceptive causation has been excluded. *[See Contraindications (4) and Warnings and Precautions (5.3).]*

8.7 Renal Impairment

No studies with Xulane have been conducted in women with renal impairment.

8.8 Women with Weight > 198 lbs (90 kg)

Xulane may be less effective in preventing pregnancy in women who weigh 198 lbs (90 kg) or more.

10 OVERDOSAGE

Overdosage may cause nausea and vomiting, and withdrawal bleeding may occur in females. In case of suspected overdose, all Xulane patches should be removed and symptomatic treatment given.

11 DESCRIPTION

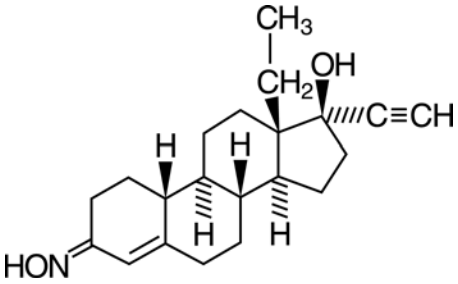
Xulane is a transdermal system with a contact surface area of 14 cm^2. It contains 4.86 mg norelgestromin (NGMN) and 0.53 mg ethinyl estradiol, USP (EE), and its delivery rate is approximately 150 mcg of NGMN and 35 mcg of EE per day. Systemic exposures (as measured by area under the curve [AUC] and steady-state concentration [C_{ss}]) of NGMN and EE during use of Xulane are higher and the C_{max} is lower than those produced by an oral contraceptive containing NGM 250 mcg / EE 35 mcg. *[see Boxed Warning and Clinical Pharmacology (12.3)]*.

Xulane is a thin, matrix-type transdermal system consisting of three layers. The backing layer is composed of a peach flexible film consisting of a pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutene adhesive, crospovidone, mineral oil, non-woven polyester fabric, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer are the hormones, NGMN and EE. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyester film with a fluoropolymer coating on the side that is in contact with the middle adhesive layer.

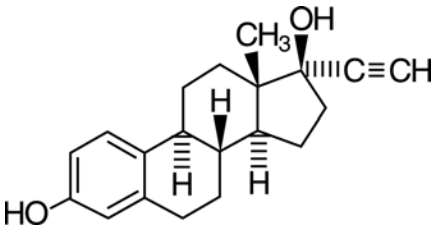
The outside of the backing layer is printed with "Xulane™ (norelgestromin and ethinyl estradiol) 150/35 mcg per day" in brown ink.

Xulane transdermal systems are packaged with additional pieces of protective film above and below the system within each pouch. These pieces of protective film are removed and discarded at the time of use.

The structural formulas of the components are:



norelgestromin



ethinyl estradiol

Molecular weight, NGMN: 327.47

Molecular weight, EE: 296.41

Chemical name for NGMN: 18, 19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, 3-oxime, (17α)

Chemical name for EE: 19-Norpregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol, (17α)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

NGMN is the active progestin largely responsible for the progestational activity that occurs in women following application of Xulane. NGMN is also the primary active metabolite produced following oral administration of NGM, the progestin component of some oral contraceptive products.

Combination hormonal contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

12.2 Pharmacodynamics

One clinical trial assessed the return of hypothalamic-pituitary-ovarian axis function post-therapy and found that follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol mean values, though suppressed during therapy, returned to near baseline values during the 6 weeks post therapy.

12.3 Pharmacokinetics

Absorption

The systemic delivery rate of NGMN and EE from Xulane is approximately 150 mcg of NGMN and 35 mcg of EE per day based on a comparative analysis with intravenous (IV) data.

Following a single application of Xulane, both NGMN and EE reach a plateau by approximately 48 hours. Pooled data from the three clinical studies have demonstrated that steady-state is reached within 2 weeks of application. In one of the clinical studies, C_{ss} concentrations across all subjects ranged from 0.305 to 1.53 ng/mL for NGMN and from 23 to 137 pg/mL for EE.

Absorption of NGMN and EE following application of Xulane to the buttock, upper outer arm, abdomen and upper torso (excluding breast) was examined. While absorption from the abdomen was slightly lower than from other sites, absorption from these anatomic sites was considered to be therapeutically equivalent.

The mean (%CV) PK parameters C_{ss} and $AUC_{0\text{-}168}$ for NGMN and EE following a single buttock application of Xulane are summarized in Table 5.

In multiple dose studies, $AUC_{0\text{-}168}$ for NGMN and EE was found to increase over time (Table 5). In a three-cycle study, these PK parameters reached steady-state conditions during Cycle 3 (Figures 3 and 4). Upon removal of the patch, serum levels of EE and NGMN reach very low or non-measurable levels within 3 days.

Table 5: Mean (%CV[*]) PK Parameters of NGMN and EE Following Three Consecutive Cycles of Xulane Wear on the Buttock

Analyte	Parameter	Cycle 1 Week 1	Cycle 3 Week 1	Cycle 3 Week 2	Cycle 3 Week 3
NGMN	$C_{ss\ (ng/mL)}$	0.70 (39.4)	0.70 (41.8)	0.80 (28.7)	0.70 (45.3)
	$AUC_{0\text{-}168\ (ng\cdot h/mL)}$	107 (44.2)	105 (43.2)	132 (43.4)	120 (43.9)
	$t_{1/2}$ (h)	nc	nc	nc	32.1 (40.3)
EE	$C_{ss\ (pg/mL)}$	46.4 (38.5)	47.6 (36.4)	59.0 (42.5)	49.6 (54.4)
	$AUC_{0\text{-}168\ (pg\cdot h/mL)}$	6,796 (39.3)	7,160 (40.4)	10,054 (41.8)	8,840 (58.6)
	$t_{1/2}$ (h)	nc	nc	nc	21.0 (43.2)

nc = not calculated, [*]%CV is % of Coefficient of variation = 100 (standard deviation/mean)

Figure 3: Mean Serum NGMN Concentrations (ng/mL) in Healthy Female Volunteers Following Application of Xulane on the Buttock for Three Consecutive Cycles (Vertical arrow indicates time of patch removal)

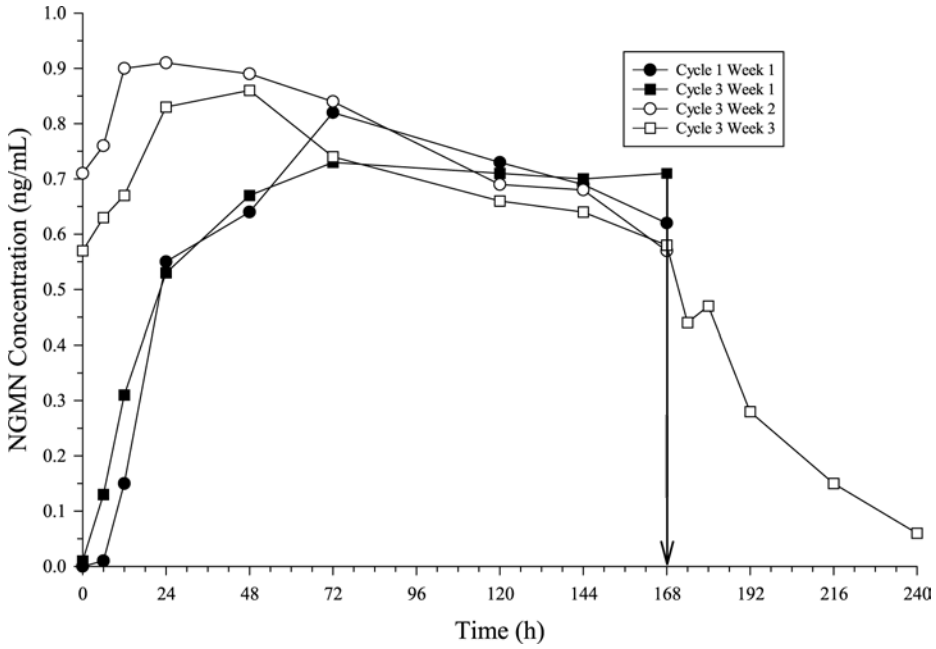
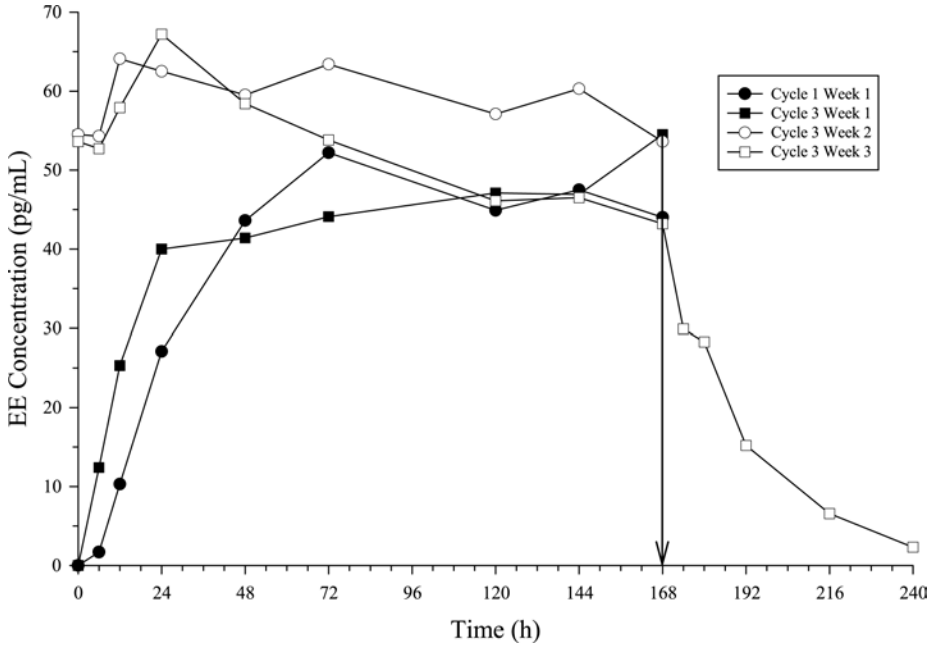


Figure 4: Mean Serum EE Concentrations (pg/mL) in Healthy Female Volunteers Following Application of Xulane on the Buttock for Three Consecutive Cycles (Vertical arrow indicates time of patch removal.)



The absorption of NGMN and EE following application of Xulane was studied under conditions encountered in a health club (sauna, whirlpool and treadmill) and in a cold water bath. The results indicated that for NGMN, there were no significant treatment effects on C_{ss} or AUC when compared to normal wear. For EE, increased exposures were observed due to sauna, whirlpool and treadmill. There was no significant effect of cold water on these parameters.

Results from a study of consecutive Xulane wear for 7 days and 10 days indicated that serum concentrations of NGMN and EE dropped slightly during the first 6 hours after the patch replacement, and recovered within 12 hours. By Day 10 of patch administration, both NGMN and EE concentrations had decreased by approximately 25% when compared to Day 7 concentrations.

Metabolism
Since Xulane is applied transdermally, first-pass metabolism (via the gastrointestinal tract and/or liver) of NGMN and EE that would be expected with oral administration does not occur. Hepatic metabolism of NGMN occurs and metabolites include norgestrel, which is highly bound to SHBG, and various hydroxylated and conjugated metabolites. EE is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

Distribution
NGMN and norgestrel (a serum metabolite of NGMN) are highly bound (> 97%) to serum proteins. NGMN is bound to albumin and not to SHBG, while norgestrel is bound primarily to SHBG, which limits its biological activity. EE is extensively bound to serum albumin and induces an increase in the serum concentrations of SHBG (see Table 5).

Elimination
Following removal of patches, the elimination kinetics of NGMN and EE were consistent for all studies with half-life values of approximately 28 hours and 17 hours, respectively. The metabolites of NGMN and EE are eliminated by renal and fecal pathways.

Transdermal versus Oral Contraceptives
The Xulane transdermal patch delivers EE and NGMN over a 7-day period while oral contraceptives (containing NGM 250 mcg / EE 35 mcg) are administered on a daily basis. Figures 5 and 6 present mean PK profiles for EE and NGMN following administration of an oral contraceptive (containing NGM 250 mcg / EE 35 mcg) compared to the 7-day transdermal Xulane patch (containing NGMN 4.86 mg / EE 0.53 mg) during Cycle 2 in 32 healthy female volunteers.

Figure 5: Mean Serum Concentration-Time Profiles of NGMN Following Once Daily Administration of an Oral Contraceptive for two cycles or Application of Xulane for two cycles to the Buttock in Healthy Female Volunteers. [Oral contraceptive: Cycle 2, Days 15 to 21, Xulane: Cycle 2, Week 3]

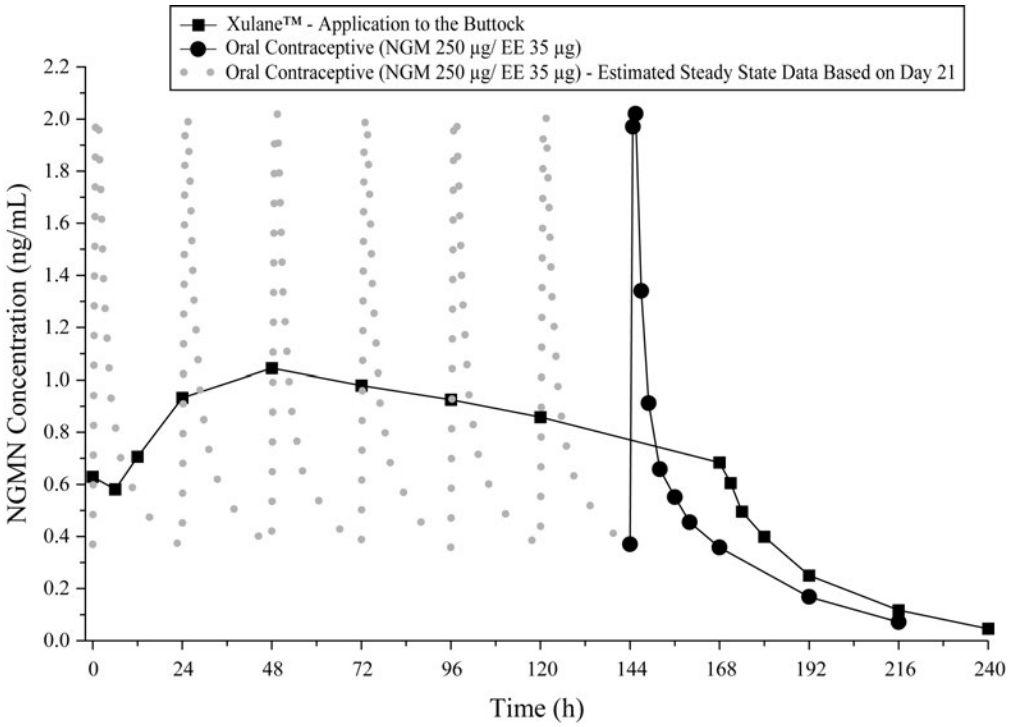


Figure 6: Mean Serum Concentration-Time Profiles of EE Following Once Daily Administration of an Oral Contraceptive for two cycles or Application of Xulane for two cycles to the Buttock in Healthy Female Volunteers. [Oral contraceptive: Cycle 2, Days 15 to 21, Xulane: Cycle 2, Week 3]

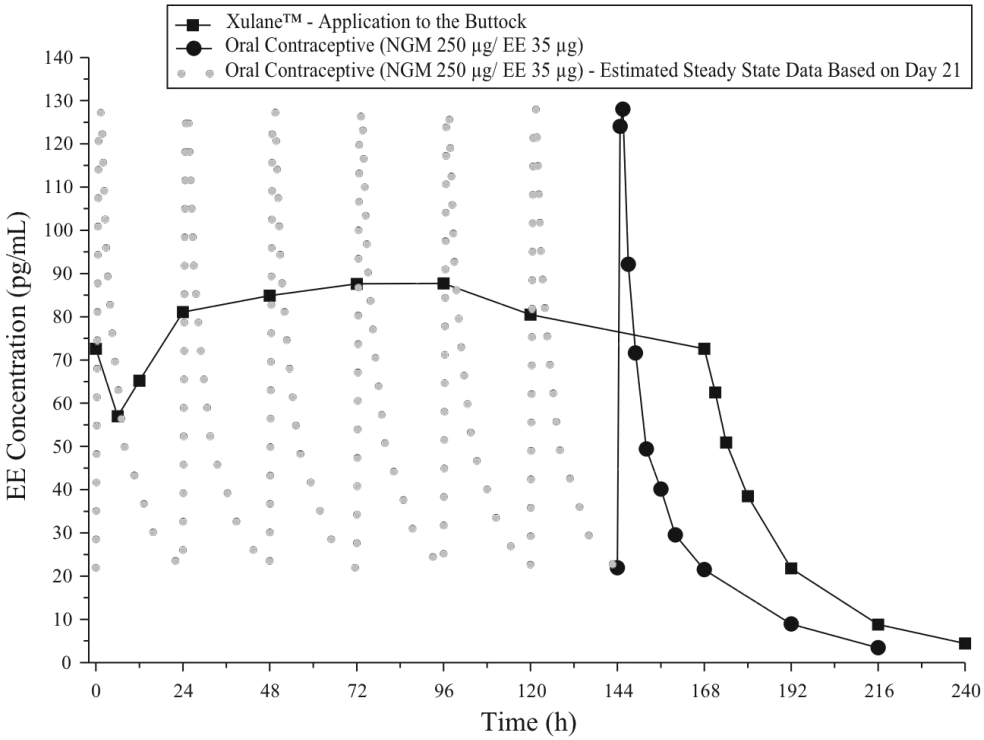


Table 6 provides the mean (%CV) for NGMN and EE pharmacokinetic (PK) parameters.

Table 6: Mean (%CV) NGMN and EE Steady-State Pharmacokinetic Parameters Following Application of Xulane and Once Daily Administration of an Oral Contraceptive (containing NGM 250 mcg / EE 35 mcg) in Healthy Female Volunteers

Parameter	Xulane[*]	ORAL CONTRACEPTIVE[†]
NGMN[‡]		
C_{max} (ng/mL)	1.12 (33.6)	2.16 (25.2)
AUC_{0-168} (ng·h/mL)	145 (36.8)	123 (30.2)[§]
C_{ss} (ng/mL)	0.888 (36.6)	0.732 (30.2)[¶]
EE		
C_{max} (pg/mL)	97.4 (31.6)	133 (27.7)
AUC_{0-168} (pg·h/mL)	12,971 (33.1)	8,281(26.9)[§]
C_{ss} (pg/mL)	80.0 (33.5)	49.3 (26.9)[¶]

[*] Cycle 2, Week 3
[†] Cycle 2, Day 21
[‡] NGM is rapidly metabolized to NGMN following oral administration
[§] Average weekly exposure, calculated as AUC_{24} x 7
[¶] C_{avg}

In general, overall exposure for NGMN and EE (AUC and C_{ss}) was higher in subjects treated with Xulane for both Cycle 1 and Cycle 2, compared to that for the oral contraceptive, while C_{max} values were higher in subjects administered the oral contraceptive. Under steady-state conditions, AUC_{0-168} and C_{ss} for EE were approximately 55% and 60% higher, respectively, for the transdermal patch, and the C_{max} was about 35% higher for the oral contraceptive, respectively. Inter-subject variability (%CV) for the PK parameters following delivery from Xulane was higher relative to the variability determined from the oral contraceptive. The mean PK profiles are different between the two products and caution should be exercised when making a direct comparison of these PK parameters.

In Table 7, percent change in concentrations (%CV) of markers of systemic estrogenic activity (Sex Hormone Binding Globulin [SHBG] and Corticosteroid Binding Globulin [CBG]) from Cycle 1 Day 1 to Cycle 1 Day 22 is presented. Percent change in SHBG concentrations was higher for Xulane users compared to women taking the oral contraceptive; percent change in CBG concentrations was similar for Xulane and oral contraceptive users. Within each group, the absolute values for SHBG were similar for Cycle 1, Day 22 and Cycle 2, Day 22.

Table 7: Mean Percent Change (%CV) in SHBG and CBG Concentrations Following Once Daily Administration of an Oral Contraceptive (containing NGM 250 mcg / EE 35 mcg) for One Cycle and Application of Xulane for One Cycle in Healthy Female Volunteers

Parameter	Xulane (% change from Day 1 to Day 22)	ORAL CONTRACEPTIVE (% change from Day 1 to Day 22)

SHBG	**334 (39.3)**	**200 (43.2)**
CBG	**153 (40.2)**	**157 (33.4)**

Drug Interactions
In a PK drug interaction study, oral administration of tetracycline HCl, 500 mg four times daily for 3 days prior to and 7 days during wear of Xulane did not significantly affect the PK of NGMN or EE.

Use in Specific Populations
Effects of Age, Body Weight, Body Surface Area and Race
The effects of age, body weight, body surface area and race on the PK of NGMN and EE were evaluated in 230 healthy women from nine pharmacokinetic studies of single 7-day applications of Xulane. For both NGMN and EE, increasing age, body weight and body surface area each were associated with slight decreases in C_{ss} and AUC values. However, only a small fraction (10% to 25%) of the overall variability in the PK of NGMN and EE following application of Xulane may be associated with any or all of the above demographic parameters. There was no significant effect of race with respect to Caucasians, Hispanics and Blacks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

See *Warnings and Precautions (5.3, 5.11)* and *Use in Specific Populations (8.1)*.

Norelgestromin was tested in *in vitro* mutagenicity assays (bacterial plate incorporation mutation assay, CHO/HGPRT mutation assay, chromosomal aberration assay using cultured human peripheral lymphocytes) and in one *in vivo* test (rat micronucleus assay) and found to have no genotoxic potential.

14 CLINICAL STUDIES

In 3 large clinical trials lasting 12 months, in North America, Europe and South Africa, 3,330 women (ages 18 to 45) completed 22,155 cycles of Xulane use, the pregnancy rate in women aged 18 to 35 years was 1.07 (95% confidence interval 0.60, 1.76) per 100 woman-years of Xulane use. The racial distribution was 91% Caucasian, 4.9% Black, 1.6% Asian, and 2.4% Other.

With respect to weight, 5 of the 15 pregnancies reported with Xulane use were among women with a baseline body weight ≥ 198 lbs. (90 kg), which constituted < 3% of the study population. The greater proportion of pregnancies among women at or above 198 lbs. was statistically significant and suggests that Xulane may be less effective in these women.

Patch Adhesion
In the clinical trials with Xulane, approximately 2% of the cumulative number of patches completely detached and 3% partially detached. The proportion of subjects with at least one patch that completely detached ranged from 2% to 6%, with a reduction from Cycle 1 (6%) to Cycle 13 (2%). For instructions on how to manage detachment of patches, refer to *Dosage and Administration (2)*.

15 REFERENCES

1. Cole JA, Norman H, Doherty M, Walker AM. Venous Thromboembolism, Myocardial Infarction, and Stroke among Transdermal Contraceptive System Users. Obstetrics & Gynecology 2007; 109(2):339-346.

2. Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 mcg of ethinyl estradiol. Contraception 2006; 73: 223-228.

3. Jick S, Kaye JA, Jick H. Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 µg of EE. Contraception 2007; 76: 4-7.

4. Jick S, Hagberg K, Hernandez R, Kaye J. Postmarketing study of ORTHO EVRA®** and levonorgestrel oral contraceptives containing hormonal contraceptives with 30 mcg of ethinyl estradiol in relation to nonfatal venous thromboembolism. Contraception 2010; 81: 16-21.

5. Jick S, Hagberg K, Kaye J. ORTHO EVRA®** and venous thromboembolism: an update. Letter to the Editor. Contraception 2010; 81: 452-453.

6. Dore D, Norman H, Loughlin J, Seeger D. Extended case-control study results on thromboembolic outcomes among transdermal contraceptive users. Contraception 2010; 81: 408-413.

7. Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users [published erratum appears in Obstet Gynecol 2008; 111:1449].

8. Dore D, Norman H, Seeger, J. Eligibility criteria in venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. Letter to the Editor. Obstetrics & Gynecology 2009; 114(1):175.

9. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular endpoints. Sidney,S. (primary author) http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf, accessed Oct 27, 2011.

10. Heit JA, Kobbervig CE, James AH, Petterson TM, Kent R. Bailey, KR; Melton LJ. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med. 2005; 143: 697-706.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Xulane™ (norelgestromin and ethinyl estradiol transdermal system) is available in one strength of 150 mcg/day NGMN and 35 mcg/day EE.

Xulane™ is a 14 cm² peach, transdermal system printed with "Xulane™ (norelgestromin and ethinyl estradiol) 150/35 mcg per day" in brown ink. Each system contains 4.86 mg norelgestromin and 0.53 mg ethinyl estradiol, USP.

Each transdermal system is packaged in a protective pouch.

Xulane™ (norelgestromin and ethinyl estradiol transdermal system) is available in folding cartons of one cycle each (NDC # 0378-3340-53); each cycle contains three patches.

16.2 Special Precautions for Storage and Disposal

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

Store patches in their protective pouches. Apply immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.

17 PATIENT COUNSELING INFORMATION

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

17.1 General

Counsel patients about the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from combined hormonal contraceptive use, and that women who are over 35 years old and smoke should not use combined hormonal contraceptives.

- Xulane does not protect against HIV infection (AIDS) and other sexually transmitted infections.

- The Warnings and Precautions associated with combined hormonal contraceptives.

- Xulane is not to be used during pregnancy; if pregnancy occurs during use of Xulane, instruct the patient to stop further use.

- Apply a single patch the same day every week (Weeks 1 through 3). Instruct patients what to do in the event a patch is missed. See "WHAT IF I FORGET TO CHANGE MY PATCH?" section in FDA-Approved Patient Labeling.

- Use a back-up or alternative method of contraception when enzyme inducers are used with Xulane.

- Combined hormonal contraceptives may reduce breast milk production; this is less likely to occur if breast-feeding is well established.

- Women who start combined hormonal contraceptives postpartum, and who have not yet had a period, should use an additional method of contraception until they have used a patch for 7 consecutive days.

- Amenorrhea may occur. Consider pregnancy in the event of amenorrhea. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles, amenorrhea in one cycle if the woman has not adhered to the dosing schedule, or if associated with symptoms of pregnancy, such as morning sickness or unusual breast tenderness.

- If the Xulane patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs.

    - A patch should not be re-applied if it is no longer sticky, becomes stuck to itself or another surface, has other material stuck to it, or has become loose or fallen off before. If a patch cannot be re-applied, a new patch should be applied immediately. Supplemental adhesives or wraps should not be used.

    - A woman may not be protected from pregnancy if a patch is partially or completely detached for ≥ 24 hours (or if the woman is not sure how long the patch has been detached). She should start a new cycle immediately by applying a new patch. Back-up contraception, such as a condom and spermicide or diaphragm and spermicide, must be used for the first week of the new cycle.

**The brand names mentioned are registered trademarks of their respective manufacturers.

PATIENT INFORMATION
Xulane™ [zhoo' lane]
(norelgestromin and ethinyl estradiol transdermal system)

What is the most important information I should know about Xulane?

Do not use Xulane if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects from hormonal birth control methods, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Women 15 to 44 years of age who use Xulane may have an increased risk of blood clots compared to women who use certain birth control pills.

You will be exposed to about 60% more estrogen if you use Xulane than if you use a typical birth control pill containing 35 micrograms of estrogen. In general, increased estrogen may increase the risk of side effects, including blood clots.

Hormonal birth control methods help to lower the chances of becoming pregnant. They do not protect against HIV infection (AIDS) and other sexually transmitted infections.

What is Xulane?
Xulane is a birth control patch. It contains two female hormones, an estrogen called ethinyl estradiol, and a progestin called norelgestromin.

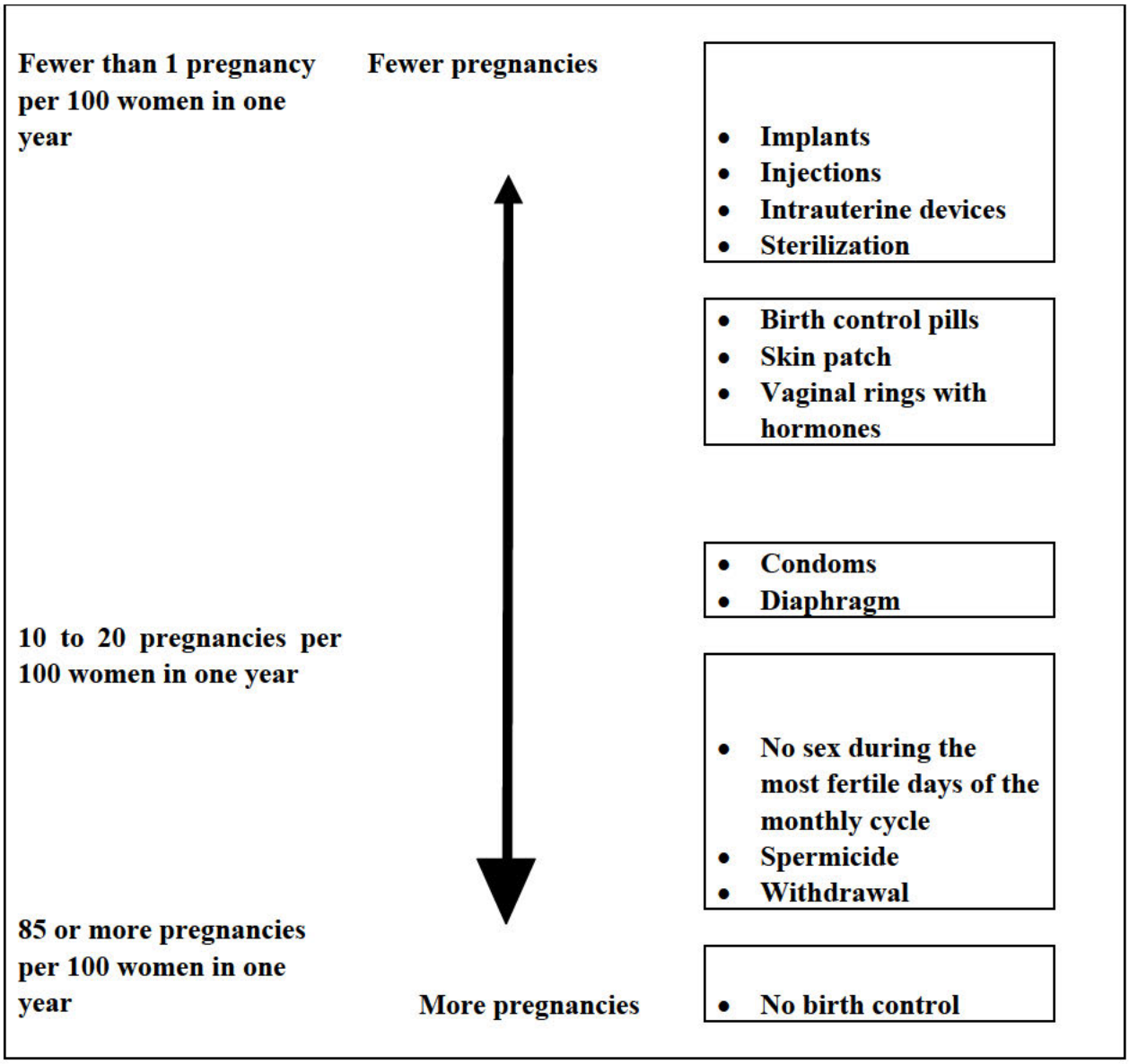
Hormones from Xulane get into the blood stream and are processed by the body differently than hormones from birth control pills. **You will be exposed to about 60% more estrogen if you use Xulane than if you use a typical birth control pill containing 35 micrograms of estrogen.** In general, increased estrogen may increase the risk of side effects.

How well does Xulane work?
Your chance of getting pregnant depends on how well you follow the directions for using Xulane. The better you follow the directions, the less chance you have of getting pregnant.

In clinical studies, 1 to 2 out of 100 women got pregnant during the first year that they used Xulane.

Xulane may not be as effective in women weighing more than 198 lbs. (90 kg). If you weigh more than 198 lbs. (90 kg), talk to your healthcare provider about which method of birth control is right for you.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



Who Should Not Use Xulane?
Do not use Xulane if you:

- smoke and are over 35 years old
- have or have had blood clots in your arms, legs, eyes or lungs
- have an inherited problem that makes your blood clot more than normal
- have had a stroke
- have had a heart attack
- have certain heart valve problems or heart rhythm problems that can cause blood clots to form in the heart
- have high blood pressure that medicine cannot control
- have diabetes with kidney, eye, nerve, or blood vessel damage

- have had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or have any migraine headaches if you are over age 35
- have liver disease, including liver tumors
- have unexplained vaginal bleeding
- are pregnant or think you may be pregnant. However, Xulane is not known to cause birth defects when used by accident during pregnancy.
- have had breast cancer or any cancer that is sensitive to female hormones

Hormonal birth control methods may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy or related to previous use of hormonal birth control.

Tell your healthcare provider if you have ever had any of the above conditions. Your healthcare provider may recommend another method of birth control.

What should I tell my healthcare provider before using Xulane?
Before you use Xulane tell your healthcare provider:

- about all your medical conditions
- if you are pregnant or think you are pregnant
- if you are scheduled for surgery. Xulane may increase your risk of blood clots after surgery. You should stop using your Xulane patch at least 4 weeks before you have surgery and not restart it until at least 2 weeks after your surgery.
- if you are scheduled for any laboratory tests. Certain blood tests may be affected by hormonal birth control methods.
- are breastfeeding or plan to breastfeed. Hormonal birth control methods that contain estrogen, like Xulane, may decrease the amount of milk you make. A small amount of hormones from the Xulane patch may pass into your breast milk. Consider another method of birth control until you are ready to stop breastfeeding.

Tell your healthcare provider about all medicines and herbal products that you take.

Some medicines and herbal products may make hormonal birth control less effective, including, but not limited to:

- certain seizure medicines (carbamazepine, felbamate, oxcarbazepine, phenytoin, rufinamide, and topiramate)
- aprepitant
- barbiturates
- bosentan

- griseofulvin
- certain combinations of HIV medicines (nelfinavir, ritonavir, ritonavir-boosted protease inhibitors)
- certain non-nucleoside reverse transcriptase inhibitors (nevirapine)
- rifampin and rifabutin
- St. John's wort

Use another birth control method (such as a condom and spermicide or diaphragm and spermicide) when you take medicines that may make the Xulane patch less effective.

Some medicines and grapefruit juice may increase your level of the hormone ethinyl estradiol if used together, including:

- acetaminophen
- ascorbic acid
- medicines that affect how your liver breaks down other medicines (itraconazole, ketoconazole, voriconazole, and fluconazole)
- certain HIV medicines (atazanavir, indinavir)
- atorvastatin
- rosuvastatin
- etravirine

Hormonal birth control methods may interact with lamotrigine, an anti-seizure medicine used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

Women on thyroid replacement therapy may need increased doses of thyroid hormone.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use Xulane?

- **For detailed instructions, see the step-by-step instructions for using Xulane at the end of this Patient Information.**
- Use Xulane exactly as your healthcare provider tells you to use it.
- Wear one Xulane patch at a time. Make sure you remove your old Xulane patch before applying your new Xulane patch.
- **Do not** skip using any Xulane patches, even if you do not have sex often.
- Xulane is applied in a 4-week cycle.
    - Apply your Xulane patch one time each week for 3 weeks (21 total days).

- o Apply each new Xulane patch on the same day of the week. This day will be your "Patch Change Day." For example, if you apply your first Xulane patch on a Monday, all of your Xulane patches should be applied on a Monday.
- o **Do not** apply your Xulane patch during Week 4. Make sure you remove your old Xulane patch. This is your patch-free week. Your menstrual period should start during your patch-free week.
- o Begin a new 4 week cycle by applying a new Xulane patch on the day after Week 4 ends. Repeat the cycle of 3 weekly applications followed by a patch-free week.

- Your Xulane patch should never be off for more than 7 days in a row. If your Xulane patch is off for more than 7 days in a row and you have sex during this time, you could become pregnant.
- If you miss a period you might be pregnant. Some women miss their periods or have light periods on hormonal birth control methods even when they are not pregnant. Call your healthcare provider if you miss one period and have not used your Xulane patch every day or you miss two periods in a row.

What are the possible side effects of Xulane?

See "What is the most important information I should know about Xulane?"

Xulane may cause serious side effects, including:

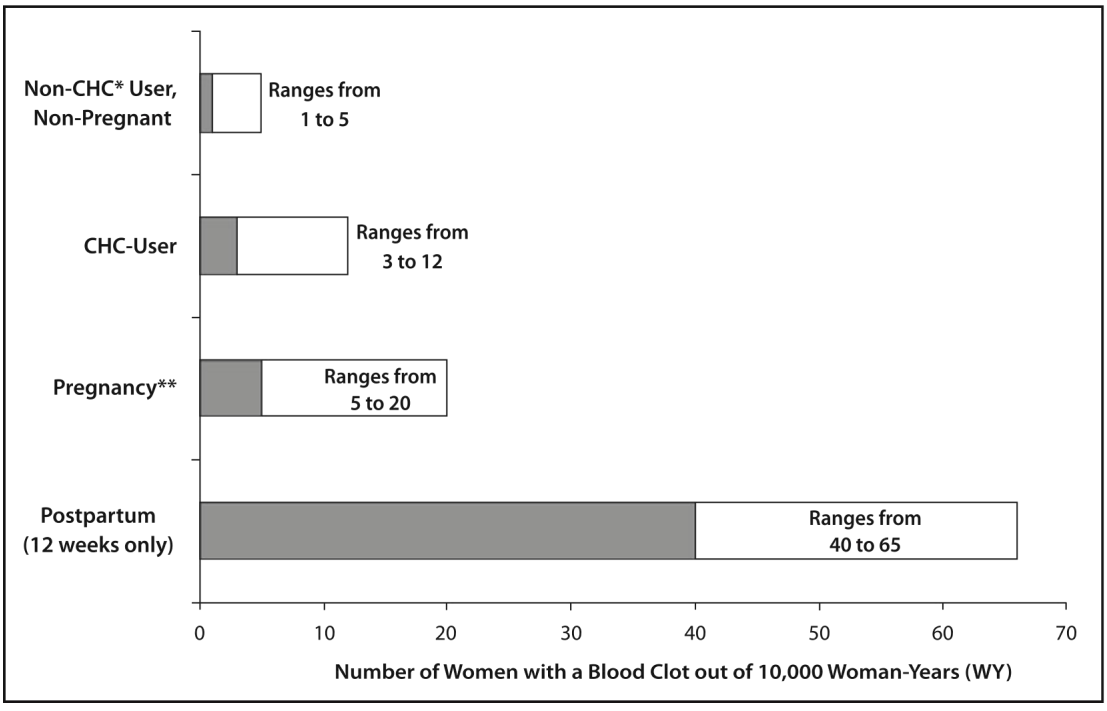
- **blood clots.** Like pregnancy, hormonal birth control methods increase the risk of serious blood clots (see following graph), especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. This increased risk is highest when you first start using hormonal birth control. Some studies have reported that women who use Xulane have a higher risk of getting a blood clot. Talk with your healthcare provider about your risk of getting a blood clot before using Xulane or deciding which type of birth control is right for you.

It is possible to die or be permanently disabled from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious blood clots are blood clots in the:

- legs (deep vein thrombosis)
- lungs (pulmonary embolus)
- eyes (loss of eyesight)
- heart (heart attack)
- brain (stroke)

To put the risk of developing a blood clot into perspective: If 10,000 women who are not pregnant and do not use hormonal birth control are followed for one year, between 1 and 5 of these women will develop a blood clot. The figure below shows the likelihood of developing a serious blood clot for women who are not pregnant and do not use hormonal birth control, for women who use hormonal birth control, for pregnant women, and for women in the first 12 weeks after delivering a baby.

Likelihood of Developing a Serious Blood Clot (Venous Thromboembolism [VTE])



*CHC = combination hormonal contraception

**Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

Call your healthcare provider right away if you have:

- leg pain that will not go away
- sudden shortness of breath
- sudden blindness, partial or complete
- severe pain or pressure in your chest
- sudden, severe headache unlike your usual headaches
- weakness or numbness in an arm or leg, or trouble speaking
- yellowing of the skin or eyeballs

Other serious risks include

- liver problems including liver tumors
- gallbladder disease
- high blood pressure

The most common side effects of Xulane are:

- breast symptoms (discomfort, swelling, or pain)
- nausea
- headache
- skin irritation, redness, pain, swelling, itching or rash at the patch application site
- stomach pain
- pain during menstruation
- vaginal bleeding and menstrual disorders, such as spotting or bleeding between periods
- mood, affect and anxiety disorders

Some women have spotting or light bleeding, breast tenderness, or feel sick to their stomach during Xulane use. If these symptoms occur, do not stop using the Xulane patch. The problem will usually go away. If it doesn't go away, check with your healthcare provider.

Less common side effects are:

- acne
- less sexual desire
- bloating or fluid retention
- blotchy darkening of your skin, especially your face
- high blood sugar, especially in women with diabetes
- high fat (cholesterol, triglycerides) levels in the blood
- depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- problems tolerating contact lenses
- weight gain

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of Xulane. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store and throw away used Xulane patches?

- Store at 20° to 25°C (68° to 77°F).
- Do not store Xulane patches outside of their pouches. Apply immediately upon removal from the protective pouch.
- Do not store in the refrigerator or freezer.
- Used Xulane patches still contain some active hormones. To throw away the Xulane patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Do not flush used Xulane patches down the toilet.
- Return unused, unneeded, or expired patches to your pharmacist.

Keep Xulane and all medicines out of the reach of children.

General information about the safe and effective use of Xulane

Medicines are sometimes prescribed for purposes other than those listed in Patient Information. Do not use Xulane for a condition for which it was not prescribed. Do not give Xulane to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about Xulane. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Xulane 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 Xulane?

Active ingredient: norelgestromin and ethinyl estradiol

Inactive ingredient: polyethylene, polyester, polyisobutene adhesive, crospovidone, mineral oil, non-woven polyester fabric, oleyl alcohol, dipropylene glycol, and a polyester film with a fluoropolymer coating.

Do hormonal birth control methods cause cancer?

Hormonal birth control methods do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use hormonal birth control methods because some breast cancers are sensitive to hormones.

Women who use hormonal birth control methods may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What should I know about my period when using Xulane?
When you use Xulane you may have bleeding and spotting between periods, called unplanned bleeding. Unplanned bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Unplanned bleeding occurs most often during the first few months of Xulane use, but may also occur after you have been using the patch for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue using the patch on schedule. If the unplanned bleeding or spotting is heavy or lasts for more than a few days, you should discuss this with your healthcare provider.

What if I miss my scheduled period when using Xulane?
Some women miss periods on hormonal birth control, even when they are not pregnant. However, if you go 2 or more months in a row without a period, or you miss your period after a month where you did not use all of your patches correctly, or you have symptoms associated with pregnancy, such as morning sickness or unusual breast tenderness, call your healthcare provider because you may be pregnant. Stop taking Xulane if you are pregnant.

What if I want to become pregnant?
You may stop using Xulane whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop using the patch.

INSTRUCTIONS FOR USE

Xulane is for skin use only.

Do not cut, damage, or alter the Xulane patch in any way.

How to start using your Xulane patch:

Figure A

- **If you are not currently using hormonal birth control,** you have 2 ways to begin using your Xulane patch. Choose the way that is best for you:
    - **First day start:** Apply your first Xulane patch during the first 24 hours of your menstrual period.
    - **Sunday start:** Apply your first Xulane patch on the first Sunday after your menstrual period begins. Use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If your period starts on Sunday, apply your first Xulane patch that day, and no back-up birth control is needed.

- **If you are changing from the pill or vaginal contraceptive ring to the Xulane patch:**
    - Complete your current pill cycle or vaginal ring cycle. Apply your first Xulane patch on the day you would normally start your next pill or insert your next vaginal ring.
    - If you do not get your period within one week after taking your last active pill or removing your last vaginal ring, check with your healthcare provider to make sure you are not pregnant. You may still go ahead and start Xulane for contraception.
    - If you apply your Xulane patch more than one week after taking your last active pill or removing your last vaginal ring, use a non-hormonal contraceptive method with the Xulane patch for the first 7 days of patch use.

- **If you are starting Xulane after childbirth:**
    - If you are not breast-feeding, wait 4 weeks before using Xulane and use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If you have had sex since your baby was born, wait for your first period, or see your healthcare provider to make sure you are not pregnant before starting Xulane.

- **If you are starting Xulane after a miscarriage or abortion:**
    - You may start Xulane immediately after a miscarriage or abortion that occurs in the first 12 weeks (first trimester) of pregnancy. You do not need to use another contraceptive method.

- If you do not start Xulane within 5 days after a first trimester miscarriage or abortion, use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, while you wait for your period to start. You have two ways to begin using your Xulane patch. Choose the way that is best for you:

    - **First day start:** Apply your first Xulane patch during the first 24 hours of your menstrual period.

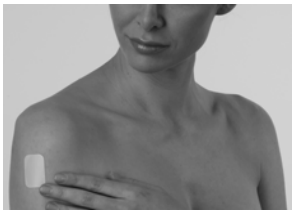
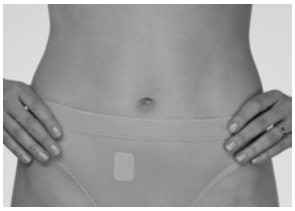
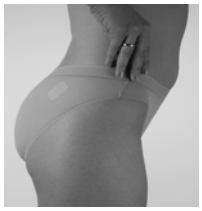
    - **Sunday start:** Apply your first Xulane patch on the first Sunday after your menstrual period begins. Use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If your period starts on Sunday, apply your first Xulane patch that day, and no back-up birth control is needed.

- If you are starting Xulane after a miscarriage or abortion that occurs **after** the first 12 weeks of pregnancy (second trimester), wait 4 weeks before using Xulane and use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If you have had sex since your miscarriage or abortion, wait for your first period, or see your healthcare provider to make sure you are not pregnant before starting Xulane.

Figure B is a picture of the Xulane patch.

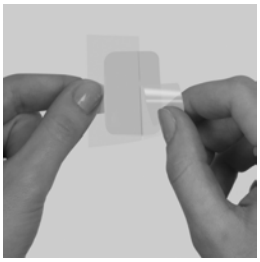
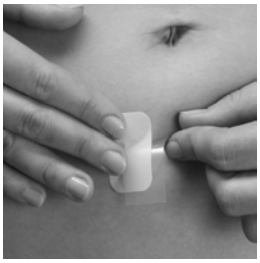
Figure B

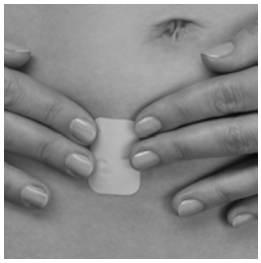
Step 1. Choose a place on your body for your Xulane patch


- The Xulane patch may be placed on your upper outer arm, abdomen, buttock or back in a place where it will not be rubbed by tight clothing. Avoid the waistline because clothing and belts may cause your patch to be rubbed off.
- **Do not** apply the patch to your breasts.
- Apply the Xulane patch only to skin that is clean, dry, and free of any powder, make-up, cream, oil, or lotion.
- Do not apply the Xulane patch to cut or irritated skin, or in the same location as the previous Xulane patch.

Step 2: Apply your Xulane patch

	• Tear open the pouch at the top edge **and** one side edge. Peel open the foil pouch. Gently remove the contents of the foil pouch and discard the additional pieces of film above and below the Xulane patch.
	• Peel away half of the clear plastic. Avoid touching the sticky surface with your fingers.
	• Apply the sticky side of the Xulane patch to clean, dry skin. Remove the other half of the clear plastic and apply the entire patch to your skin.

	• Press firmly on the Xulane patch with the palm of your hand for 10 seconds, making sure that the whole patch sticks to your skin. • Run your fingers over the entire surface area to smooth out any "wrinkles" around the outer edges of the Xulane patch. • Check your Xulane patch every day to make sure all edges are sticking correctly.

Step 3: Throwing away your Xulane patch

- To throw away the Xulane 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 Xulane patches should not be flushed in the toilet.

Important notes:

- **Your Xulane patch must stick securely to your skin to work properly.**

- **Do not** try to reapply a Xulane patch if it is no longer sticky, if it has become stuck to itself or another surface, or if it has other material stuck to it. **Do not** tape or wrap the patch to your skin or reapply a patch that is partially adhered to clothing.

- **If your Xulane patch edge lifts up:**

  - Press down firmly on the patch with the palm of your hand for 10 seconds, making sure that the whole patch sticks to your skin. Run your fingers over the entire surface area to smooth out any "wrinkles" around the edges of the Xulane patch.

  - If your Xulane patch does not stick completely, remove it and apply a new Xulane patch.

  - **Do not** tape or wrap the Xulane patch to your skin or reapply a Xulane patch that is partially stuck to clothing.

- **If your Xulane patch has been off or partially off:**

  - **For less than 1 Day,** try to reapply it. If the Xulane patch does not stick completely, apply a new Xulane patch immediately. No back-up contraception is needed and your "Patch Change Day" will stay the same.

- **For more than 1 Day or if you are not sure for how long,** you could become pregnant. To reduce this chance, apply a new Xulane patch and start a new 4 week cycle. You will now have a new "Patch Change Day." Use a non-hormonal back-up contraception method such as a condom and spermicide or diaphragm and spermicide for the first week of your new 4 week Xulane cycle.

- **If you want to move your "Patch Change Day" to a different day of the week,** finish your current cycle. Remove your third Xulane patch on the correct day.

    - **During week 4**, the "Patch Free Week" (Day 22 through Day 28), you may choose an **earlier** "Patch Change Day" by applying a new patch on the day you prefer. You now have a new Day 1 and a new "Patch Change Day."

- **If your Xulane patch becomes uncomfortable** or your application site is red, painful or swollen, change your Xulane patch. Remove your Xulane patch and apply a new patch to a new location until your next "Patch Change Day."

- **If you forget to change or remove your Xulane patch:**

    - **At the start of any patch cycle (Week 1, Day 1):**
        - **You could become pregnant. You must use a back-up contraception method for 7 days.** Apply the first Xulane patch of your new cycle as soon as you remember. You now have a new "Patch Change Day" and a new Day 1.
    - **In the middle of your patch cycle (Week 2 or Week 3):**
        - **If you forget to change your Xulane patch for 1 or 2 days,** apply a new Xulane patch as soon as you remember. Apply your next patch on your normal "Patch Change Day." No back-up contraception method is needed.
        - **If you forget to change your Xulane patch for more than 2 days,** you could become pregnant. Start a new 4 week cycle as soon as you remember by putting on a new Xulane patch. You now have a different "Patch Change Day" and a new Day 1. You must use a back-up contraception method for the first 7 days of your new cycle.
    - **At the end of your patch cycle (Week 4):**
        - **If you forget to remove your Xulane patch,** take it off as soon as you remember. Start your next cycle on your normal "Patch Change Day," the day after Day 28. No back-up contraception method is needed.

- **If you forget to apply your Xulane patch at the start of your next patch cycle,** you could become pregnant. Apply the first Xulane patch of your new cycle as soon as you remember. You now have a new "Patch Change Day" and a new Day 1. Use a non-hormonal back-up contraception method such as a condom and spermicide or diaphragm and spermicide for the first 7 days of your new 4 week Xulane cycle.

- **If you have trouble remembering to change your Xulane patch,** talk to your healthcare provider about how to make patch changing easier or about using another method of contraception.

- **If you are not sure how to use your Xulane patch:**

    - Use a back-up contraception method such as a condom and spermicide or diaphragm and spermicide anytime you have sex. Make sure to have one of these non-hormonal contraception methods ready at all times.

    - Talk to your healthcare provider for instructions on using your Xulane patch.

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

Mylan Pharmaceuticals Inc.

Morgantown, WV 26505 U.S.A.

REVISED APRIL 2014

NEETS:R8RX1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200910

LABELING REVIEWS

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (5 Cycle)

APPROVAL SUMMARY (Supersedes Approval Summary Dated 11/12/13)

ANDA Number	200910
Date of Submission	04/15/2014
Applicant's Name	Mylan Technologies Inc.
Established Name	Norelgestromin and Ethinyl Estradiol Transdermal System, 150 mcg/ 35 mcg per day).
Proprietary Name	Xulane™ Found conditionally acceptable on 5/6/2013 for 16 months

---

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 April 15, 2014.

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

	Date submitted	Final or Draft	Recommendation
PATCH LABEL:	08/20/13	FPL	No Further comments
POUCH LABEL	04/15/14	Draft	No Further comments
CARTON LABELING:	04/15/14	Draft	No Further comments
PATCH CHANGE REMINDER STICKERS:	10/18/12	FPL	No Further comments
PATIENT INFORMATION CARD:	08/20/13	FPL	No Further comments
PRESCRIBING INFORMATION/PATIENT INFORMATION	04/15/14	Draft	No Further comments
SPL	04/15/14		No Further comments

REVISIONS NEEDED POST APPROVAL?
-None

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

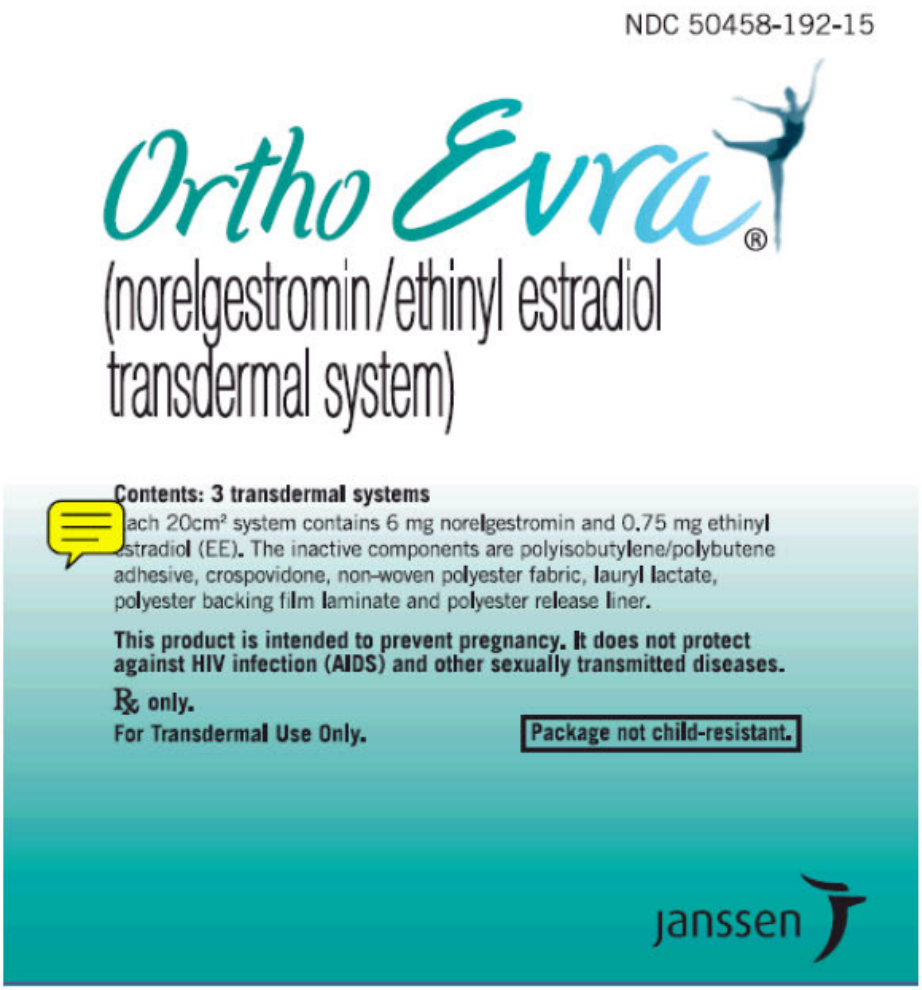
FOR THE RECORD:

1. **MODEL LABELING**
   Review is based on the labeling of Janssen Pharm's Ortho Evra®, NDA 021180/S-046, approved, April 14, 2014. The last approved prior approval supplement addresses the following:

   > "provides for the addition of a statement of strength (delivery rate) to the labeling components (package insert, carton, pouch, and packer).."

Model for the carton and pouch were taken from OND review:

Delivers approximately 150 mcg of norelgestromin and 35 mcg of ethinyl estradiol per day



Reviewer Comment: Adding a sentence to the already there text is not an appropriate declaration of strength based on current practice. The strength should not be solely a sentence about delivery; rather it should also include a "statement of strength" and its prominence noticeable on the label.

Reviewer Evaluation: The addition of the proposed statement is acceptable however, the Applicant still needs to state the strength of the product. Communicate the following to the Applicant:

Include "150/35 mcg/day" (or similar presentation) after the established name in similar size font for all packaging configurations (Carton, Packer, Pouch).

2. **BIOEQUIVALENCE:**
   Bioequivalence and dissolution portions of the current ANDA are **adequate** on 2/5/14

3. **PATENTS AND EXCLUSIVITIES (P&E):**

Patent No.	Expiration	Use Code	Use	Filed	Labeling Impact
5876746	Nov 20, 2015	U-514	Prevention of ovulation in Women	IV	None
5972377	Jun 7, 2015	U-514	Prevention of ovulation in Women	IV	None

There is no unexpired exclusivity for this product.

4. **USP :**
   No monograph currently listed

5. **PF 38:**
   No monograph currently listed

6. **MedWatch:**
   No entries after last approved supplement.

7. **QUANTITATIVE COMPOSITION**
   Norelgestromin and ethinyl estradiol transdermal system is a thin, matrix-type transdermal contraceptive patch consisting of three layers. The backing layer is composed of a peach flexible film consisting of a pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutene adhesive, crospovidone, mineral oil, non-woven polyester fabric, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer are the hormones, norelgestromin and ethinyl estradiol.

   The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyester film with a fluoropolymer coating on the side that is in contact with the middle adhesive layer.

   The outside of the backing layer is printed with “xulane (norelgestromin and ethinyl estradiol)” in brown ink.

Table Ia: Pharmaceutical Function of Components, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Adhesive Matrix

Components	Pharmaceutical Function	% w/w	mg/ patch	Maximum Level listed in the FDA *IID*[1] (mg)	Quality Standards
Active Ingredients					
Norelgestromin	Active Ingredient	2.31	4.86	NA	(b) (4)
Ethinyl Estradiol, USP (b) (4)	Active Ingredient	0.25	0.53	NA	
Inactive Ingredients					
Polyisobutene Adhesive	(b) (4)				
Oleyl Alcohol, NF					
Dipropylene Glycol					
(b) (4) Mineral Oil, NF					
Crospovidone, NF					
(b) (4)					
Theoretical Total Matrix		100.00	210.00		

Table Ib: Pharmaceutical Function of Components, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Other Components of Norelgestromin and Ethinyl Estradiol Transdermal System

Components	Pharmaceutical Function	mg/ patch	Maximum Level listed in the FDA *IID* [1] (mg)	Quality Standards
Polyethylene/ Polyester Film	(b) (4)			
Brown Ink				
Nonwoven Polyester				
Fluoropolymer Coated Polyester Film				

Labeling Ingredients Consistent with :	
CMC submission	**YES**
Package Insert	**YES**
SPL	**YES**
Iron Content acceptable	**NA**

8. MANUFACTURING FACILITY

Manufacturing, Packaging, Labeling, Quality Control Testing of Components, Testing of Finished Dosage Form:

Mylan Technologies Inc
110 Lake Street
Saint Albans, VT 05478
Establishment Registration Number (CFN): 1220747

9. CONTAINER SYSTEM

Figure: Diagram of Primary Container/Closure System for Norelgestromin and Ethinyl Estradiol Transdermal System

A schematic drawing is enclosed for the container/closure system for Norelgestromin and Ethinyl Estradiol Transdermal System

Pouching Material:

The pouching material, (b) (4) is manufactured and distributed by:

Since instructions for use of this system differ from the RLD the sponsor was requested to inform us about other applications that have been approved with similar instructions for the system. Two applications use a similar system and have had labeling approved:

ANDA 076258 – Fentanyl Transdermal System
ANDA 076166 – Clonidine Transdermal System

10. PACKAGING CONFIGURATION DESCRIPTION:

RLD:

ORTHO EVRA (norelgestromin/ethinyl estradiol transdermal system) is available in one strength of 150 mcg/day NGMN and 35 mcg/day EE.

ORTHO EVRA is a 20 cm^2 beige, transdermal system heat stamped with ORTHO EVRA. Each system contains 6 mg NGMN and 0.75 mg EE.

Each transdermal system is packaged in a protective pouch.

ORTHO EVRA is available in folding cartons of 1 cycle each (NDC 50458-192-15); each cycle contains 3 systems.

ORTHO EVRA is available for clinic usage in folding cartons of 1 cycle each (NDC 50458-192-24); each cycle contains 3 systems.

ORTHO EVRA is also available in folding cartons containing a single system (NDC 50458-192-01), intended for use as a replacement in the event that a patch is inadvertently lost or destroyed.

ANDA:

Xulane™ (norelgestromin and ethinyl estradiol transdermal system) is available in one strength of 150 mcg/day NGMN and 35 mcg/day EE.

Xulane™ is a 14 cm^2 peach, transdermal system printed with "Xulane™ (norelgestromin and ethinyl estradiol) 150/35 mcg per day" in brown ink. Each system contains 4.86 mg norelgestromin and 0.53 mg ethinyl estradiol, USP.

Each transdermal system is packaged in a protective pouch.

Xulane™ (norelgestromin and ethinyl estradiol transdermal system) is available in folding cartons of one cycle each (NDC # 0378-3340-53); each cycle contains three patches.

11. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD:

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F).

Store patches in their protective pouches. Apply immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.

ANDA:

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

Store patches in their protective pouches. Apply immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.

12. **MEDICATION GUIDES/PATIENT PACKAGE INSERT**

Sponsor provided the Patient Information Leaflet

13. LABELING FORMAT:

Style: HelveticaNeueLTStd-Cn Size: 8 Sample of Detailed Patient Labeling:	Style: TradeGothic-CondEighteen Size: 6 Sample of package insert:
DESCRIPTION The contraceptive patch XULANE™ is a thin, peach, plastic patch that sticks to the skin. The (b) (4) patch contains the following hormones: norelgestromin (progestin) and ethinyl estradiol (estrogen). (b) (4)	**INDICATIONS AND USAGE** XULANE™ is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception. The pharmacokinetic profile for the XULANE™ transdermal patch is different from that of an oral contraceptive (b) (4) (See BOLDED WARN NG, WARN NGS and CL NICAL PHARMACOLOGY: Transdermal versus Oral Contraceptives).

13. **SPL DATA ELEMENTS**

XULANE
norelgestromin and ethinyl estradiol patch

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0378-3340
Route of Administration	TRANSDERMAL	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
NORELGESTROMIN (NORELGESTROMIN)	NORELGESTROMIN	150 ug in 1 d
ETHINYL ESTRADIOL (ETHINYL ESTRADIOL)	ETHINYL ESTRADIOL	35 ug in 1 d

Inactive Ingredients	
Ingredient Name	**Strength**
CROSPOVIDONE	
MINERAL OIL	
OLEYL ALCOHOL	
DIPROPYLENE GLYCOL	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-3340-53	3 in 1 CARTON		
1	NDC:0378-3340-16	1 in 1 POUCH		
1		7 d in 1 PATCH		

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
ANDA	ANDA200910	04/15/2020	

Labeler - Mylan Pharmaceuticals Inc. (059295980)

Registrant - Mylan Pharmaceuticals Inc. (059295980)

Establishment

Name	Address	ID/FEI	Business Operations
Mylan Technologies Inc.		063790265	ANALYSIS(0378-3340), MANUFACTURE(0378-3340), PACK(0378-3340), LABEL(0378-3340)

Revised: 4/2014

Mylan Pharmaceuticals Inc.

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

3.2 CONTAINER LABEL AND CARTON LABELING COMMENTS TO THE APPLICANT

1. Pouch Label and Carton Labeling

a. Revise the presentation of the proprietary name on all labels and labeling to appear in title case lettering (i.e., Xulane).

b. Revise the principle display panel of all labels and labeling to include the total amount of drug delivered per unit of time (i.e., hour, day, or week) to appear directly under the established name.

Any reference to drug amount delivered over time has been withdrawn from RLD labeling and the Orange Book at the request of OND.

c. Add directions to never cut, damage, or alter the patch on all labels and labeling.

Patient labeling has the following statement:

RLD: Do not cut, damage, or alter the ORTHO EVRA patch in any way.

ANDA: Do not cut, damage, or alter the Xulane patch in any way.

d. Add an expiration date and lot number to the pouch label.

5. (b) (4) (b) (4)

Date of Review	04/15/2015
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
04/15/2014

LILLIE D GOLSON
04/15/2014

REVIEW OF PROFESSIONAL LABELING #4
TENTATIVE APPROVAL SUMMARY (Supersedes Approval Summary Dated 09/28/2012)
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH
FIRST GENERIC

ANDA Number	200910
Date of Submission	08/20/13 and 09/18/2013
Applicant's Name	Mylan Technologies Inc.
Established Name	Norelgestromin and Ethinyl Estradiol Transdermal System
Proprietary Name	Xulane™ Found conditionally acceptable on 5/6/2013 for 90 days

---

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 20, 2013 and September 18, 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
PATCH LABEL:	08/20/13	FPL	No Further comments
POUCH LABEL	08/20/13	FPL	No Further comments
CARTON LABELING:	08/20/13	FPL	No Further comments
PATCH CHANGE REMINDER STICKERS:	10/18/12	FPL	No Further comments
PATIENT INFORMATION CARD:	08/20/13	FPL	No Further comments
PRESCRIBING INFORMATION	09/18/13	FPL	No Further comments
SPL	09/18/13		No Further comments

REVISIONS NEEDED POST APPROVAL?
-None

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

FOR THE RECORD:

1. **UPDATE TO THE FTR:**
   The sponsor updated its labeling to be in accordance with the recently approved RLD labeling. See FTR #2 on RLD update.

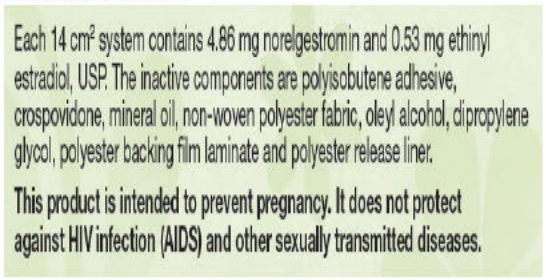
2. **MODEL LABELING**
   Review is based on the labeling of Janssen Pharm's Ortho Evra®, NDA 021180/S-044, approved, July 1, 2013. The last approved supplement addresses the following:

   > "provides for reformatting labeling in the Physician Labeling Rule (PLR) format, as well as for corresponding revisions to patient labeling and the patient information card."

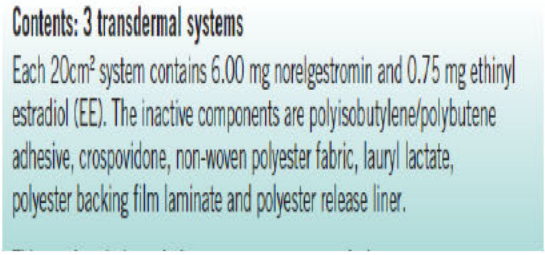
2. **BIOEQUIVALENCE:**
   This is a patch which delivers 0.15 mg Norelgestromin and 0.02 mg Ethinyl Estradiol per 24 hours. The rate of distribution is not found anywhere in the package insert or carton/pouch labeling of the RLD, and thus also not found in the ANDAs labeling.

   The ANDA total contents in the drug are different than the RLD. The first imagines below are from the carton labels:

ANDA carton



RLD Carton



Furthermore if looking at the SPL the following is stated:

From SPL for ANDA:

NORELGESTROMIN (NORELGESTROMIN)	NORELGESTROMIN	4.86 mg in 168 h
ETHINYL ESTRADIOL (ETHINYL ESTRADIOL)	ETHINYL ESTRADIOL	0.53 mg in 168 h

From SPL of NDA:

NORELGESTROMIN (NORELGESTROMIN)	NORELGESTROMIN	6 mg in 7 d
ETHINYL ESTRADIOL (ETHINYL ESTRADIOL)	ETHINYL ESTRADIOL	0.75 mg in 7 d

The chemist acknowledges the difference stating that the RLD has overage. However, Bio has not evaluated the ANDA, and yet to conclude the rate of release is equivalent to the RLD.

The fact the release rate is not on the labels should not lead to confusion over product selection, when compared to other products that are patches (e.g., Fentanyl and estradiol patches). These examples have several release rates, but this product is only available in one release rate.

3. **PATENTS AND EXCLUSIVITIES (P&E):**

Patent No.	Expiration	Use Code	Use	Filed	Labeling Impact
5876746	Nov 20, 2015	U-514	Prevention of ovulation in Women	IV	None
5972377	Jun 7, 2015	U-514	Prevention of ovulation in Women	IV	None

There is no unexpired exclusivity for this product.

4. **USP :**
No monograph currently listed

5. **PF 38:**
No monograph currently listed

6. **MedWatch:**
No entries after last approved supplement.

7. **QUANTITATIVE COMPOSITION**
Norelgestromin and ethinyl estradiol transdermal system is a thin, matrix-type transdermal contraceptive patch consisting of three layers. The backing layer is composed of a peach flexible film consisting of a pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutene adhesive, crospovidone, mineral oil, non-woven polyester fabric, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer are the hormones, norelgestromin and ethinyl estradiol.

The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyester film with a fluoropolymer coating on the side that is in contact with the middle adhesive layer.

The outside of the backing layer is printed with “xulane (norelgestromin and ethinyl estradiol)” in brown ink.

Table Ia: Pharmaceutical Function of Components, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Adhesive Matrix

Components	Pharmaceutical Function	% w/w	mg/ patch	Maximum Level listed in the FDA *IID*[1] (mg)	Quality Standards
Active Ingredients					
Norelgestromin	Active Ingredient	2.31	4.86	NA	(b) (4)
Ethinyl Estradiol, USP (b) (4)	Active Ingredient	0.25	0.53	NA	
Inactive Ingredients					
Polyisobutene Adhesive					(b) (4)
Oleyl Alcohol, NF					
Dipropylene Glycol					
(b) (4) Mineral Oil, NF					
Crospovidone, NF					
(b) (4)					
Theoretical Total Matrix		100.00	210.00		

Table Ib: Pharmaceutical Function of Components, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Other Components of Norelgestromin and Ethinyl Estradiol Transdermal System

Components	Pharmaceutical Function	mg/ patch	Maximum Level listed in the FDA *IID* [1] (mg)	Quality Standards
Polyethylene/ Polyester Film				(b) (4)
Brown Ink				
Nonwoven Polyester				
Fluoropolymer Coated Polyester Film				

Labeling Ingredients Consistent with :	
CMC submission	**YES**
Package Insert	**YES**
SPL	**YES**
Iron Content acceptable	**NA**

8. MANUFACTURING FACILITY

Manufacturing, Packaging, Labeling, Quality Control Testing of Components, Testing of Finished Dosage Form:

Mylan Technologies Inc
110 Lake Street
Saint Albans, VT 05478
Establishment Registration Number (CFN): 1220747

9. **STORAGE CONDITION**

RLD Store at 25° C (77 ° F); excursions permitted to 15-30 ° C (59-86 ° F)

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

10. CONTAINER SYSTEM

Figure: Diagram of Primary Container/Closure System for Norelgestromin and Ethinyl Estradiol Transdermal System

(b) (4)

A schematic drawing is enclosed for the container/closure system for Norelgestromin and Ethinyl Estradiol Transdermal System

Pouching Material:

The pouching material, (b) (4) is manufactured and distributed by:

(b) (4)

Since instructions for use of this system differ from the RLD the sponsor was requested to inform us about other applications that have been approved with similar instructions for the system. Two applications use a similar system and have had labeling approved:

ANDA 076258 – Fentanyl Transdermal System
ANDA 076166 – Clonidine Transdermal System

11. **PACKAGING CONFIGURATION AND DESCRIPTION:**

ANDA: Each peach Xulane™ (norelgestromin and ethinyl estradiol transdermal system) patch contains 4.86 mg norelgestromin and 0.53 mg ethinyl estradiol, USP.

Each patch surface is printed with "Xulane™ (norelgestromin and ethinyl estradiol)" in brown ink. Each patch is packaged in a protective pouch.

Xulane™ (norelgestromin and ethinyl estradiol transdermal system) is available in folding cartons of one cycle each (NDC # 0378-3340-53); each cycle contains three patches.

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

Store patches in their protective pouches. Apply immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.

RLD: Each beige ORTHO EVRA® patch contains 6.00 mg norelgestromin and 0.75 mg EE.

Each patch surface is heat stamped with ORTHO EVRA®. Each patch is packaged in a protective pouch.

ORTHO EVRA® is available in folding cartons of 1 cycle each (NDC 0062-1920-15 or NDC 50458-192-15); each cycle contains 3 patches.

ORTHO EVRA® is available for clinic usage in folding cartons of 1 cycle each (NDC 0062-1920-24 or NDC 50458-192-24); each cycle contains 3 patches.

ORTHO EVRA® is also available in folding cartons containing a single patch (NDC 0062-1920-01 or NDC 50458-192-01), intended for use as a replacement in the event that a patch is inadvertently lost or destroyed..

Special Precautions for Storage and Disposal
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Store patches in their protective pouches. Apply immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.

Taken from PI

12. LABELING FORMAT:

Style: HelveticaNeueLTStd-Cn Size: 8 Sample of Detailed Patient Labeling:	Style: TradeGothic-CondEighteen Size: 6 Sample of package insert:
DESCRIPTION The contraceptive patch XULANE™ is a thin, peach, plastic patch that sticks to the skin. The (b) (4) patch contains the following hormones: norelgestromin (progestin) and ethinyl estradiol (estrogen). (b) (4)	**INDICATIONS AND USAGE** XULANE™ is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception. The pharmacokinetic profile for the XULANE™ transdermal patch is different from that of an oral contraceptive. (b) (4) . (See BOLDED WARN NG, WARN NGS and CL NICAL PHARMACOLOGY: Transdermal versus Oral Contraceptives).

13. **SPL DATA ELEMENTS**

14. **XULANE**
norelgestromin and ethinyl estradiol patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0378-3340
Route of Administration	TRANSDERMAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NORELGESTROMIN (NORELGESTROMIN)	NORELGESTROMIN	4.86 mg in 168 h

ETHINYL ESTRADIOL (ETHINYL ESTRADIOL)	ETHINYL ESTRADIOL	0.53 mg in 168 h

Inactive Ingredients

Ingredient Name	Strength
CROSPOVIDONE	
MINERAL OIL	
OLEYL ALCOHOL	
DIPROPYLENE GLYCOL	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-3340-53	3 in 1 CARTON		
1	NDC:0378-3340-16	1 in 1 POUCH		

1		168 h in 1 PATCH		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200910	09/03/2016	

Labeler - Mylan Pharmaceuticals Inc. (059295980)

Registrant - Mylan Pharmaceuticals Inc. (059295980)

Establishment

Name	Address	ID/FEI	Business Operations
Mylan Technoligies Inc.		063790265	MANUFACTURE(0378-3340), ANALYSIS(0378-3340), PACK(0378-3340), LABEL(0378-3340)

Revised: 8/2013

Mylan Pharmaceuticals Inc.

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

3.2 CONTAINER LABEL AND CARTON LABELING COMMENTS TO THE APPLICANT

1. Pouch Label and Carton Labeling

a. Revise the presentation of the proprietary name on all labels and labeling to appear in title case lettering (i.e., Xulane).

b. Revise the principle display panel of all labels and labeling to include the total amount of drug delivered per unit of time (i.e., hour, day, or week) to appear directly under the established name.

Any reference to drug amount delivered over time has been withdrawn from RLD labeling and the Orange Book at the request of OND.

c. Add directions to never cut, damage, or alter the patch on all labels and labeling.

Patient labeling has the following statement:

RLD: Do not cut, damage, or alter the ORTHO EVRA patch in any way.

ANDA: Do not cut, damage, or alter the Xulane patch in any way.

d. Add an expiration date and lot number to the pouch label.

(b) (4)

5. (b) (4)

Date of Review	10/28/2013
Primary Reviewer	Malik Imam
Team Leader	Lillie Golson

Following this page, 9 Pages of Draft Labeling have been Withheld in Full as (b)(4)

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
11/12/2013

LILLIE D GOLSON
11/12/2013

REVIEW OF PROFESSIONAL LABELING #3
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH
FIRST GENERIC

ANDA Number	200910
Date of Submission	10/18/2012
Applicant's Name	Mylan Technologies Inc.
Established Name	Norelgestromin and Ethinyl Estradiol Transdermal System
Proprietary Name	Xulane™ Found conditionally acceptable on 5/6/2013

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:

Labeling Deficiencies determined on May 16, 2013 based on your submission dated October 18, 2012:

1. GENERAL
   Revise the presentation of the proprietary name on all labels and labeling to appear in title case lettering (i.e., Xulane).

2. SPL
   Please note that you are required to submit SPL labeling from which we will review the data elements. For additional information, please refer to 21 CFR 314.94(d)(ii), the SPL Implementation Guide for FDA Content of Labeling Submissions at:

   http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Submit your revised labeling electronically in final print format.

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

Prior to the submission of your amendment, please check labeling resources, including 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
PATCH LABEL:	10/18/2012	FPL	See Comments above
POUCH LABEL	10/18/2012	FPL	See Comments above
CARTON LABELING:	10/18/2012	FPL	See Comments above
PATCH CHANGE REMINDER STICKERS:	10/18/2012	FPL	See Comments above
PRESCRIBING INFORMATION	10/18/2012	FPL	See Comments above
PATIENT INFORMATION	10/18/2012	FPL	See Comments above
PATIENT INFORMATION CARD:	10/18/2012	FPL	See Comments above
SPL	Not Provided		See Comments above

REVISIONS NEEDED POST APPROVAL?
-None

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

FOR THE RECORD:

1. **MODEL LABELING**
   Review is based on the labeling of Janssen Pharm's Ortho Evra®, NDA 021180/S-043, approved, August 22, 2012. The last approved supplement addresses the following:

   A. Revised Package Insert, including revisions to the WARNINGS section, the WARNINGS subsection titled "Thromboembolic Disorders and Other Vascular Problems," and the REFERENCES section.
   B. Revised Patient Labeling, including revisions to the sections titled "OTHER CONSIDERATIONS BEFORE USING ORTHO EVRA®" and "RISK OF USING HORMONAL CONTRACEPTIVES, INCLUDING ORTHO EVRA®, Risk of Developing Blood Clots."
   C. Other minor modifications are also described in the revised Boxed Warning, INDICATIONS AND USAGE, CLINICAL PHARMACOLOGY, Pharmacokinetics subsection and HOW SUPPLIED sections of the package insert.

   The revised label continues to indicate that ORTHO EVRA® may be associated with a higher risk of venous thromboembolism (VTE) than combined oral contraceptives containing levonorgestrel or some other progestins. This label also reports absolute rates of VTE across various groups of reproductive-aged women and continues to advise prescribers to balance the possible increased risk of VTE with ORTHO EVRA® against the chance of pregnancy if the patient cannot reliably take a contraceptive pill on a daily basis.

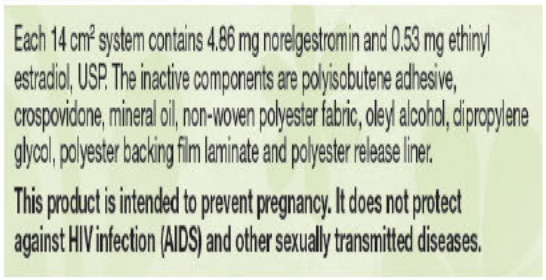
   There have been 2 supplements approved, but they were manufacter changes with no labeling changes.

2. BIOEQUIVALENCE:

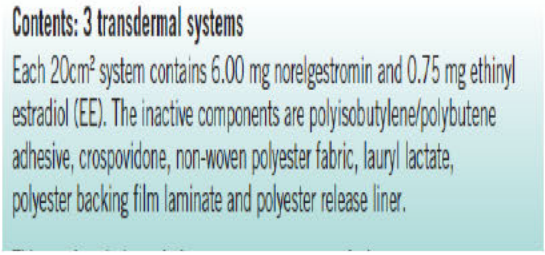
   This is a patch which delivers 0.15 mg Norelgestromin and 0.02 mg Ethinyl Estradiol per 24 hours. The rate of distribution is not found anywhere in the package insert or carton/pouch labeling of the RLD, and thus also not found in the ANDAs labeling.

   The ANDA total contents in the drug are different than the RLD. The first imagines below are from the carton labels:

ANDA carton



RLD Carton



Furthermore if looking at the SPL the following is stated:

From SPL for ANDA:

NORELGESTROMIN (NORELGESTROMIN)	NORELGESTROMIN	4.86 mg in 7 d
ETHINYL ESTRADIOL (ETHINYL ESTRADIOL)	ETHINYL ESTRADIOL	0.53 mg in 7 d

From SPL of NDA:

NORELGESTROMIN (NORELGESTROMIN)	NORELGESTROMIN	6 mg in 7 d
ETHINYL ESTRADIOL (ETHINYL ESTRADIOL)	ETHINYL ESTRADIOL	0.75 mg in 7 d

The chemist acknowledges the difference stating that the RLD has overage. However, Bio has not evaluated the ANDA, and yet to conclude the rate of release is equivalent to the RLD.

3. PATENTS AND EXCLUSIVITIES (P&E):

Patent No.	Expiration	Use Code	Use	Filed	Labeling Impact
5876746	Nov 20, 2015	U-514	Prevention of ovulation in Women	IV	None
5972377	Jun 7, 2015	U-514	Prevention of ovulation in Women	IV	None

There is no unexpired exclusivity for this product.

4. USP :
   No monograph currently listed

5. PF 38:
   No monograph currently listed

6. MedWatch:
   No entries after last approved supplement.

7. QUANTITATIVE COMPOSITION
   Norelgestromin and ethinyl estradiol transdermal system is a thin, matrix-type transdermal contraceptive patch consisting of three layers. The backing layer is composed of a peach flexible film consisting of a pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutene adhesive, crospovidone, mineral oil, non-woven polyester fabric, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer are the hormones, norelgestromin and ethinyl estradiol.

   The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior
   to application. It is a transparent polyester film with a fluoropolymer coating on the side that is in contact with
   the middle adhesive layer.

   The outside of the backing layer is printed with "xulane (norelgestromin and ethinyl estradiol)" in brown ink.

Table Ia: Pharmaceutical Function of Components, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Adhesive Matrix

Components	Pharmaceutical Function	% w/w	mg/ patch	Maximum Level listed in the FDA *IID*[1] (mg)	Quality Standards
Active Ingredients					
Norelgestromin	Active Ingredient	2.31	4.86	NA	(b) (4)
Ethinyl Estradiol, USP (b) (4)	Active Ingredient	0.25	0.53	NA	
Inactive Ingredients					
Polyisobutene Adhesive					(b) (4)
Oleyl Alcohol, NF					
Dipropylene Glycol					
(b) (4) Mineral Oil, NF					
Crospovidone, NF (b) (4)					
Theoretical Total Matrix		100.00	210.00		

Table Ib: Pharmaceutical Function of Components, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Other Components of Norelgestromin and Ethinyl Estradiol Transdermal System

Components	Pharmaceutical Function	mg/ patch	Maximum Level listed in the FDA *IID* [1] (mg)	Quality Standards
Polyethylene/ Polyester Film	[redacted]			(b) (4)
Brown Ink				
Nonwoven Polyester				
Fluoropolymer Coated Polyester Film				

Labeling Ingredients Consistent with :	
CMC submission	**YES**
Package Insert	**YES**
SPL	**YES**
Iron Content acceptable	**NA**

8. MANUFACTURING FACILITY

Manufacturing, Packaging, Labeling, Quality Control Testing of Components, Testing of Finished Dosage Form:

Mylan Technologies Inc
110 Lake Street
Saint Albans, VT 05478
Establishment Registration Number (CFN): 1220747

9. STORAGE CONDITION

RLD Store at 25° C (77 ° F); excursions permitted to 15-30 ° C (59-86 ° F)

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

10. CONTAINER SYSTEM

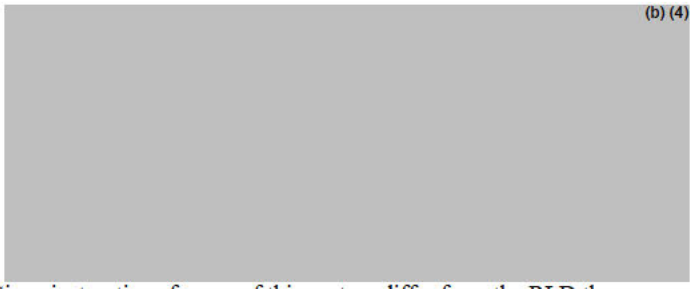
Figure: Diagram of Primary Container/Closure System for Norelgestromin and Ethinyl Estradiol Transdermal System

(b) (4)

A schematic drawing is enclosed for the container/closure system for Norelgestromin and Ethinyl Estradiol Transdermal System

Pouching Material:

The pouching material, (b) (4) is manufactured and distributed by:



Since instructions for use of this system differ from the RLD the sponsor was requested to inform us about other applications that have been approved with similar instructions for the system. Two applications use a similar system and have had labeling approved:

ANDA 076258 – Fentanyl Transdermal System
ANDA 076166 – Clonidine Transdermal System

11. PACKAGING CONFIGURATION AND DESCRIPTION:

ANDA: Each peach XULANE™ (norelgestromin and ethinyl estradiol transdermal system) patch contains 4.86 mg norelgestromin and 0.53 mg ethinyl estradiol, USP. Each patch surface is printed with "xulane™ (norelgestromin and ethinyl estradiol)" in brown ink. Each patch is packaged in a protective pouch.

XULANE™ (norelgestromin and ethinyl estradiol transdermal system) is available in folding cartons of 1 cycle each (NDC # 0378-3340-53); each cycle contains 3 patches.

Special Precautions for Storage and Disposal: Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Store patches in their protective pouches. Apply immediately upon removal from the protective pouch.
Do not store in the refrigerator or freezer.
Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.

RLD: Each beige ORTHO EVRA® patch contains 6.00 mg norelgestromin and 0.75 mg EE.

Each patch surface is heat stamped with ORTHO EVRA®. Each patch is packaged in a protective pouch.

ORTHO EVRA® is available in folding cartons of 1 cycle each (NDC 0062-1920-15 or NDC 50458-192-15); each cycle contains 3 patches.

ORTHO EVRA® is available for clinic usage in folding cartons of 1 cycle each (NDC 0062-1920-24 or NDC 50458-192-24); each cycle contains 3 patches.

ORTHO EVRA® is also available in folding cartons containing a single patch (NDC 0062-1920-01 or NDC 50458-192-01), intended for use as a replacement in the event that a patch is inadvertently lost or destroyed..

Special Precautions for Storage and Disposal

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Store patches in their protective pouches. Apply immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.

Taken from PI

12. LABELING FORMAT:

Style: HelveticaNeueLTStd-Cn Size: 8 Sample of Detailed Patient Labeling:	Style: TradeGothic-CondEighteen Size: 6 Sample of package insert:
DESCRIPTION The contraceptive patch XULANE™ is a thin, peach, plastic patch that sticks to the skin. The (b) (4) patch contains the following hormones: norelgestromin (progestin) and ethinyl estradiol (estrogen). (b) (4)	**INDICATIONS AND USAGE** XULANE™ is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception. The pharmacokinetic profile for the XULANE™ transdermal patch is different from that of an oral contraceptive. (b) (4) (See BOLDED WARN NG, WARN NGS and CL NICAL PHARMACOLOGY: Transdermal versus Oral Contraceptives).

13. **SPL DATA ELEMENTS**

Not provided for proprietary name.

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

3.2 CONTAINER LABEL AND CARTON LABELING COMMENTS TO THE APPLICANT

1. Pouch Label and Carton Labeling
   a. Revise the presentation of the proprietary name on all labels and labeling to appear in title case lettering (i.e., Xulane).
   b. Revise the principle display panel of all labels and labeling to include the total amount of drug delivered per unit of time (i.e., hour, day, or week) to appear directly under the established name.
   c. Add directions to never cut, damage, or alter the patch on all labels and labeling.
   d. Add an expiration date and lot number to the pouch label.

Date of Review	05/16/2013
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
05/29/2013

LILLIE D GOLSON
05/31/2013

REVIEW OF PROFESSIONAL LABELING

APPROVAL SUMMARY (Supersedes Approval Summary Dated 06/19/2012)

DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	200910
Date of Submission	09/19/2012
Applicant's Name	Mylan Technologies Inc.
Established Name	stromin and Ethinyl Estradiol Transdermal System
Proprietary Name	(b) (4) found unacceptable in letter to sponsor dated 06/29/2012

REMS REQUIREMENTS:

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

APPROVAL SUMMARY:

Patch Label:
Satisfactory in FPL with submission dated 12/22/2011

Pouch Label
Satisfactory in FPL with submission dated 03/12/2012

Carton Labeling:
Satisfactory in FPL with submission dated 06/07/2012

Patch change Reminder Stickers:
Satisfactory in FPL with submission dated 09/19/2012

Package Insert Labeling:
Satisfactory in FPL with submission dated 03/12/2012

Patient Information Card:
Satisfactory in FPL with submission dated 03/12/2012

Detailed Patient Labeling:
Satisfactory in FPL with submission dated 09/19/2012

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Ortho Evra®
NDA Number: 021180
NDA Drug Name: Ortho Evra®
NDA Firm: Janssen Pharms
Date of Approval of NDA Insert and supplement #: S-040 approved 12/28/2011
Was this approval based upon an OGD labeling guidance? No

FOR THE RECORD

1. **UPDATES TO FTR:**
   - Amendment dated 9/19/2012 was due to recently approved RLD PAS approval.
   - Updates below are with the review of the submission dated 06/07/2012:
     - This ANDA review is based on the established name.
     - The sponsor addressed the deficiency regarding the removal of the following statement from the carton labeling (b) (4)
   - Updates below are with the review of the submission dated 03/12/2012:
     - UPDATE in Bioequivalence section number 2

Following this page, 20 Pages Withheld in Full as (b)(4)

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
09/28/2012

LILLIE D GOLSON
09/28/2012

REVIEW OF PROFESSIONAL LABELING

APPROVAL SUMMARY

DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	200910
Date of Submission	06/07/2012
Applicant's Name	Mylan Technologies Inc.
Established Name	Norelgestromin and Ethinyl Estradiol Transdermal System
Proprietary Name	(b) (4) preliminarily found unacceptable in email dated 04/12/2012

UPDATES TO FTR:

- Updates below are with the review of the submission dated 06/07/2012:
  - This ANDA review is based on the established name.
  - The sponsor addressed the deficiency regarding the removal of the following statement from the carton labeling (b) (4)

- Updates below are with the review of the submission dated 03/12/2012:
  - UPDATE in Bioequivalence section number 2
  - UPDATE in Dispensing Recommendations/ Storage Condition/ Compatibility/and Disposal
  - This amendment answers deficiencies sent on 01/03/2012 and an update to the RLD labeling.
  - (b) (4)

From: Juliane.Foley@mylanlabs.com [mailto:Juliane.Foley@mylanlabs.com]
Sent: Tuesday, May 29, 2012 2:41 PM
To: Imam, Malik
Cc: (b) (4)
Subject: Norelgestromin and Ethinyl Estradiol Transdermal System ANDA 200910

Dear Mr. Imam,

In response to your phone request earlier today, I am writing to confirm that should the proprietary (b) (4) name not be approved in time for launch, (b) (4)

Please let me know if you have any additional questions.

thanks

Juliane

REMS REQUIREMENTS:

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

Following this page, 21 Pages Withheld in Full as (b)(4)

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
06/18/2012

LILLIE D GOLSON
06/19/2012

REVIEW OF PROFESSIONAL LABELING #3
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	200910
Date of Submission	03/12/2012
Applicant's Name	Mylan Technologies Inc.
Established Name	Norelgestromin and Ethinyl Estradiol Transdermal System
Proprietary Name	(b) (4) preliminarily found unacceptable in email dated 04/12/2012

Labeling Deficiencies:

A. Carton Label:

1. Please note that the following statement appears on the side panel of the carton:

   (b) (4)

   As this statement does not appear on the RLD Carton labeling please remove it.

Please submit final printed labeling 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

Following this page, 13 Pages Withheld in Full as (b)(4)

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
06/01/2012

LILLIE D GOLSON
06/01/2012

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 200910 Date of Submission: 12/22/2011

Applicant's Name: Mylan Technologies

Proprietary Name: (b) (4)

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

---

Labeling Deficiencies:

A. GENERAL COMMENTS:

We acknowledge your comments regarding review submission of certain labeling pieces with respect to the ongoing review of your proposed proprietary name. The name continues to be under review in the Division of Medication Error Prevention and Analysis (DMEPA) of the Office of Safety and Epidemiology. We will inform you of their comments when they become available to us.

B. PATIENT LABELING:

With regard to the request to delete, "[See USP Controlled Room Temperature]", from the storage statement of your patient information:

We acknowledge that you have not consistently applied this terminology to your patient labeling, sometimes omitting reference to "USP" and "Controlled Room Temperature", as you state you use this term on the "majority" (but not all) patient information. (b) (4)

There is a group in the Office of New Drugs (OND) which reviews patient information associated with NDA labeling for patient comprehension. Part of the goal for this Center-level review is to ensure that patient labeling is simple and understandable. The majority of patient labeling (including the RLD labeling of the product for which you are seeking approval) reviewed by OND in the Center does not include reference to "USP" or "Controlled Room Temperature".

For these reasons, we request that you revise your labeling to be the **same as the RLD**, silent to the above mentioned terminology. Alternatively, if you prefer, we can consult the CDER group which reviews labeling for patient comprehension as to whether or not these terms should appear in your labeling.

If you choose the latter approach, please explain how you believe patients will understand the meaning of "USP" or Controlled Room Temperature", or provide any other information to support your request to retain these terms.

You need not submit labeling at this time as your proprietary name is under review.

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

Following this page, 8 Pages Withheld in Full as (b)(4)

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
12/28/2011

JOHN F GRACE
01/03/2012

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

ANDA Number: 200910 Dates of Submission: 12/31/2009, 6/29/2010, 6/9/2011 6/28/2011, 10/3/2011

Applicant's Name: Mylan Technologies

Proprietary Name: (b) (4)

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

---

Labeling Deficiencies:

A. GENERAL COMMENTS:

We acknowledge that your proposed proprietary name is under review in the Division of Medication Error Prevention and Analysis (DMEPA) of the Office of Safety and Epidemiology. We will inform you of their comments when they become available to us. Additionally we note that there is a mixture of labeling which does and does not reference the proposed proprietary name. For, example if the name (b) (4) is found acceptable by DMEPA, the most recently submitted package insert labeling must be revised to reflect the proprietary name as it refers to labeling pieces, such as the patch print in terms of the established name rather than the proprietary name.

B. PATCH LABEL:

1. See GENERAL COMMENTS above.

2. Include the established name with the proprietary name. We refer you to 21 CFR 201.10(g)(1), for guidance.

C. POUCH LABEL:

1. See GENERAL COMMENTS above.

2. Increase the contrast of print which appears beneath the principal display panel by lightening the background.

D. CARTON LABELING (3 Systems and Outer Carton Labeling):

See GENERAL COMMENTS and comments for POUCH LABEL above.

E. PACKAGE INSERT:

See GENERAL COMMENTS above.

F. DETAILED PATIENT LABELING:

1. We note that the patch application direction you propose differ from the RLD. Have similar application directions/pictorials for your transdermal system been approved in a different application? If so, which?

2. OTHER INFORMATION – Revise to delete "[See USP Controlled Room Temperature]".

Following this page, 8 Pages Withheld in Full as (b)(4)

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
11/08/2011

JOHN F GRACE
11/15/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200910

MEDICAL REVIEWS

Addendum Review of Skin Irritation, Sensitization and Adhesion Studies

ANDA:	200910
Drug Product:	Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day
Sponsor:	Mylan Pharmaceuticals Inc.
Reference Listed Drug (RLD):	Ortho-Evra® Transdermal System (NDA 021180), Ortho McNeil Janssen Pharmaceuticals, Inc.
Original Submission Date:	12/23/2009
Original Primary Reviewer:	Nicol Lee, Pharm.D.

On 12/23/2009, Mylan Pharmaceuticals Inc. (Mylan) submitted an abbreviated new drug application (ANDA) for Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day. In support for the ANDA, Mylan conducted a skin irritation and sensitization study (#ORTH-0943) and a skin adhesion study (#ORTH-09198).

Study #ORTHO-0943 was an open-label, multiple dose, randomized application site, two-treatment, three-phase, one-period study investigating the 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-five (225) subjects, and 214 subjects completed the study. According to the FDA statistical review, this study demonstrated that Mylan's Norelgestormin/Ethinyl Estradiol Transdermal is no more irritating and has no more potential to cause sensitization than that expected with use of the reference listed product Ortho Evra®.

Study #ORTH-09198 was an open-label, randomized, single dose, two-treatment, two-period crossover study to compare the adhesive properties of test and reference patches following a single application. Of the 40 subjects that were dosed, 37 subjects completed the study. Using the adhesion analysis as outlined in the Draft Guidance on Ethinyl Estradiol/Norelgestromin Film, Extended Release/Transdermal (May 2009, Revised July 2009), the FDA statistician concluded that test product failed to demonstrate that its adhesion performance is no worse than that of the RLD. 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. (Appendix 1), the adhesion data in Mylan's skin adhesion study (#ORTH-09198) was reconsidered. In re-evaluation, this study meets the new 90/90 analysis criteria (See FDA Statistical Review by Vicki Lancaster, Ph.D. finalized on 2/14/14 by Stella Grosser, Ph.D. in Appendix 2). Therefore the statistical adhesion non-inferiority analysis with the RLD can be considered satisfactory based on this new memorandum by the Science team. As such, **this application is recommended for approval**.

{See appended electronic signature page}

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

{See appended electronic signature page}

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

{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 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

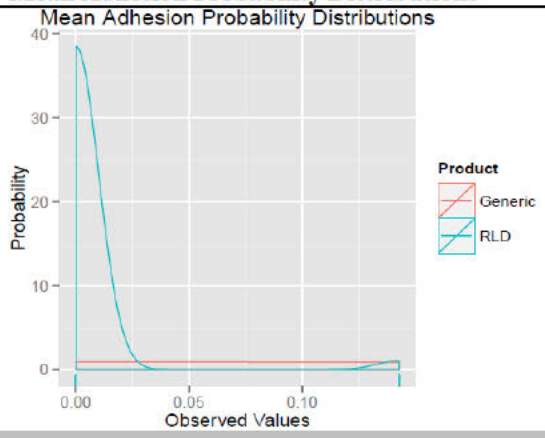
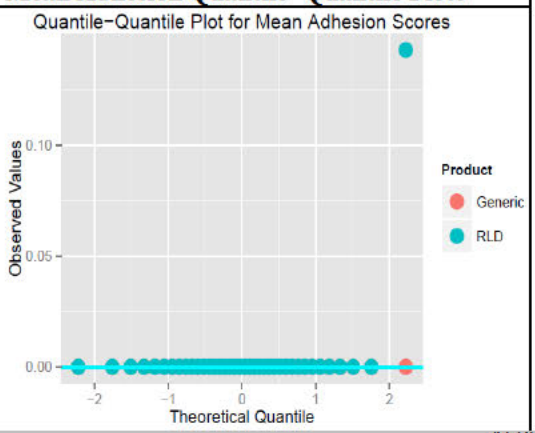
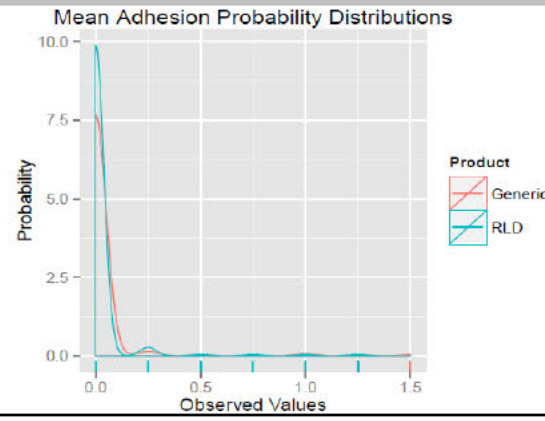
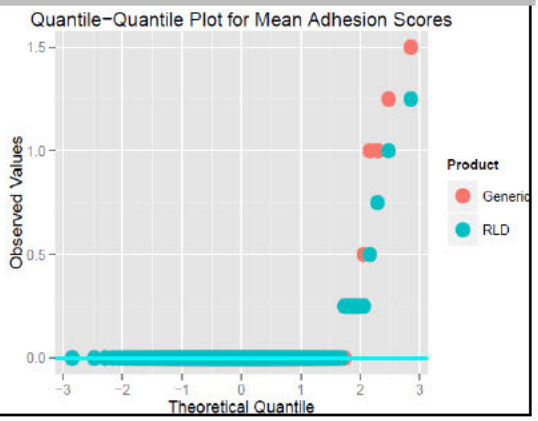
Drug Products	ANDA	RLD	Number of Time Points	TEST %Score = 0	TEST %Score = 1	TEST %Score = 2	TEST %Score = 3	TEST %Score = 4	REFERENCE %Score = 0	REFERENCE %Score = 1	REFERENCE %Score = 2	REFERENCE %Score = 3	REFERENCE %Score = 4	Passed NI (Ran by Statistician)	Passed NI (Ran by Bryan Newman)
Norelgestromin/ 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)															
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**

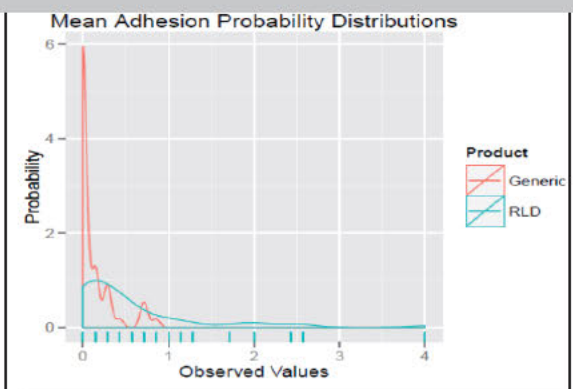
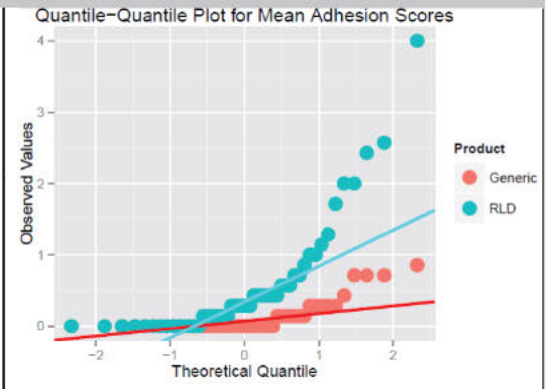
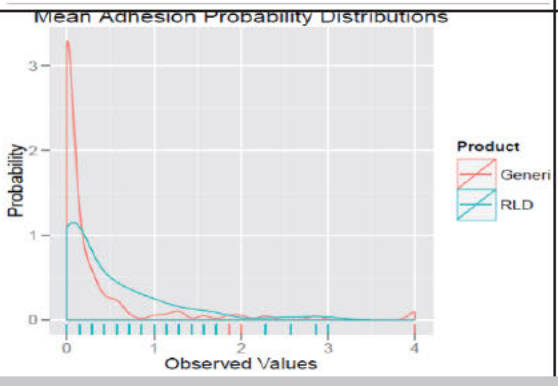
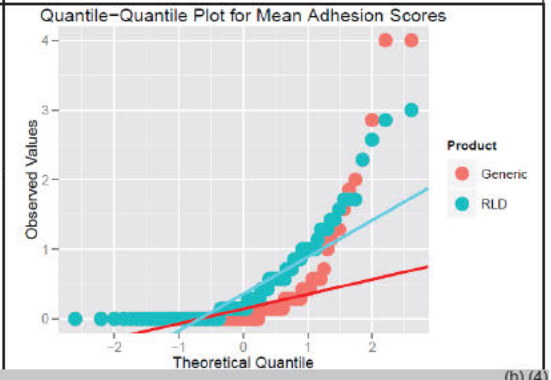
As shown in Table 2, adhesion scoring frequency varies considerably, with the highest adhering products Norelgestromin/Ethinyl Estradiol (ANDA 200910), (b) (4) (b) (4) Estradiol (ANDA 201675), (b) (4) and Lidocaine (ANDA 200675) having greater than 90% of the reported adhesion scores being zero. Importantly, 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 (b) (4) 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

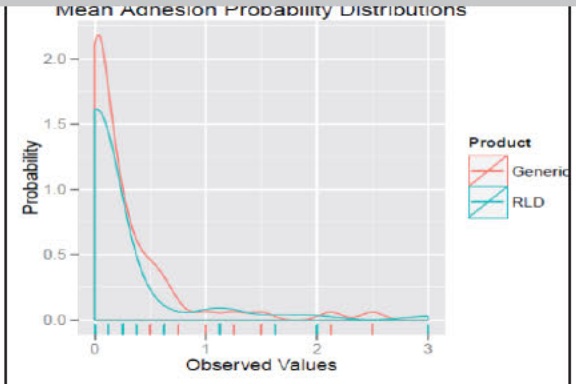
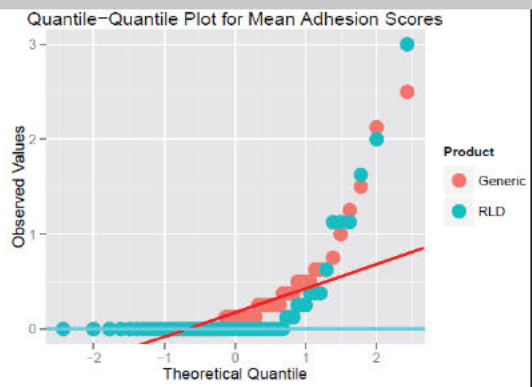
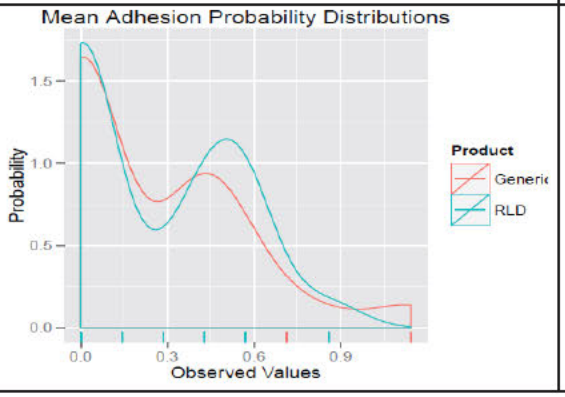
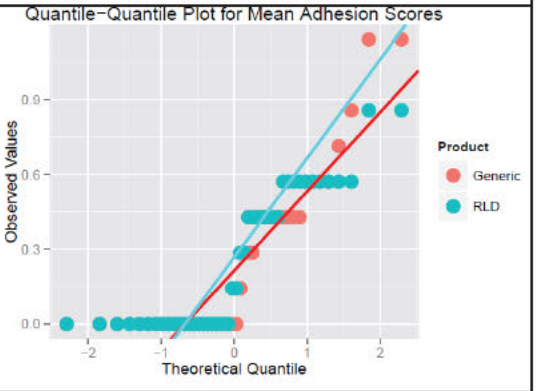
Drug Product	ANDA	RLD	Mean Adhesion Probability Distributions	Mean Adhesion Quantile- Quantile Plots
Norelgestromin/ Estradiol TDS	200910	21180		
(b) (4)				
Estradiol TDS	201675	20538		

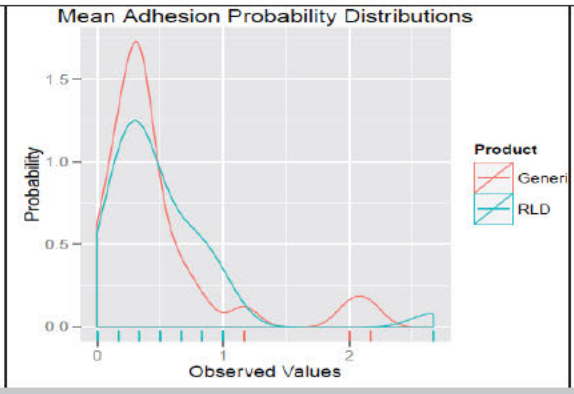
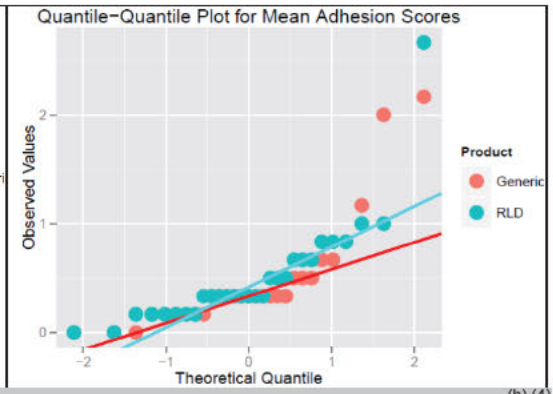
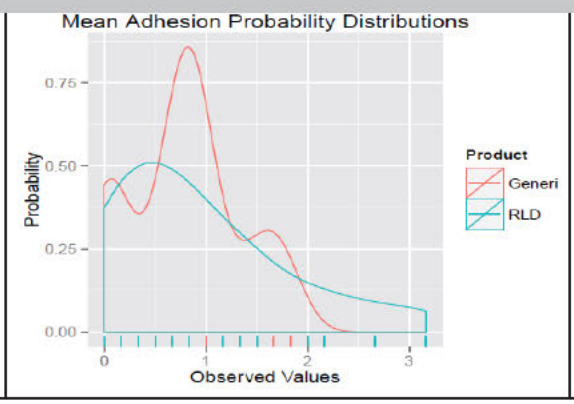
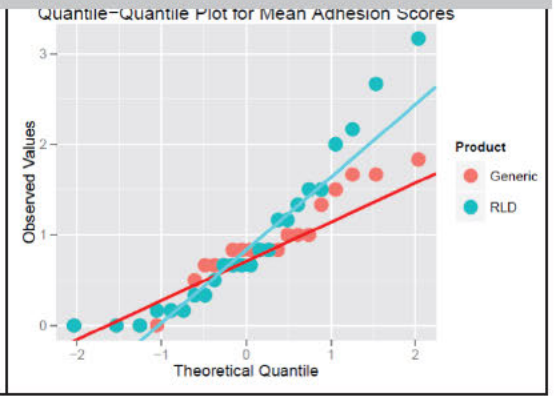
(b) (4)

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

(b) (4)

(b) (4)

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

Scopolamine	**78830**	**17874**		
			(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

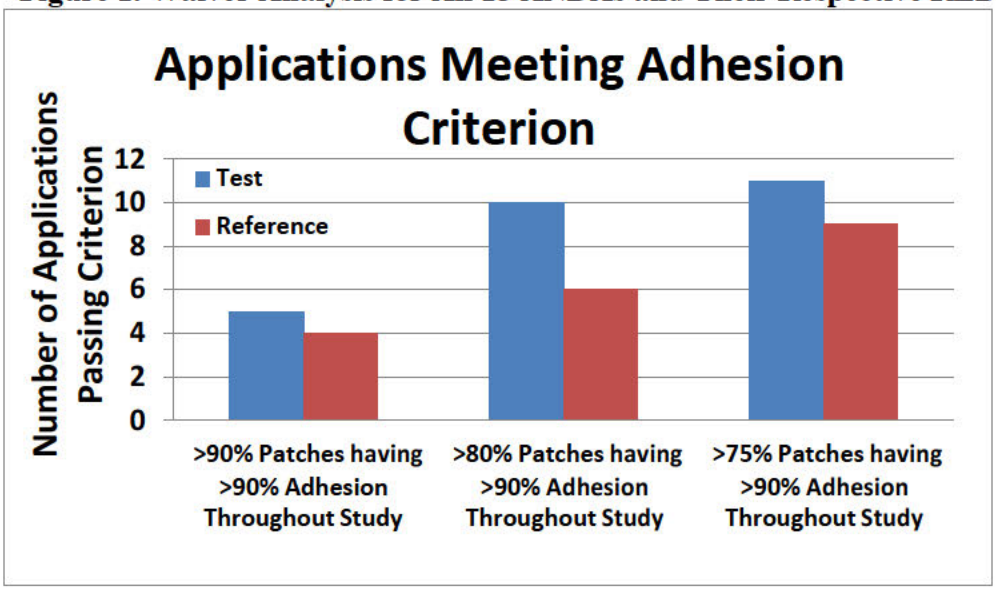


Table 5. Waiver Analysis for All 15 ANDAs and Their Respective RLD

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
[redacted]					(b) (4)
Estradiol TDS	201675	no	no	20538	yes
[redacted]					(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
[redacted]					(b) (4)
Clonidine TDS	79090	yes	yes	18891	no
Fentanyl	202097	no	no	19813	no
Scopolamine	78830	no	no	17874	no
[redacted]					(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)

[redacted] (b) (4)

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

[4] [redacted] (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

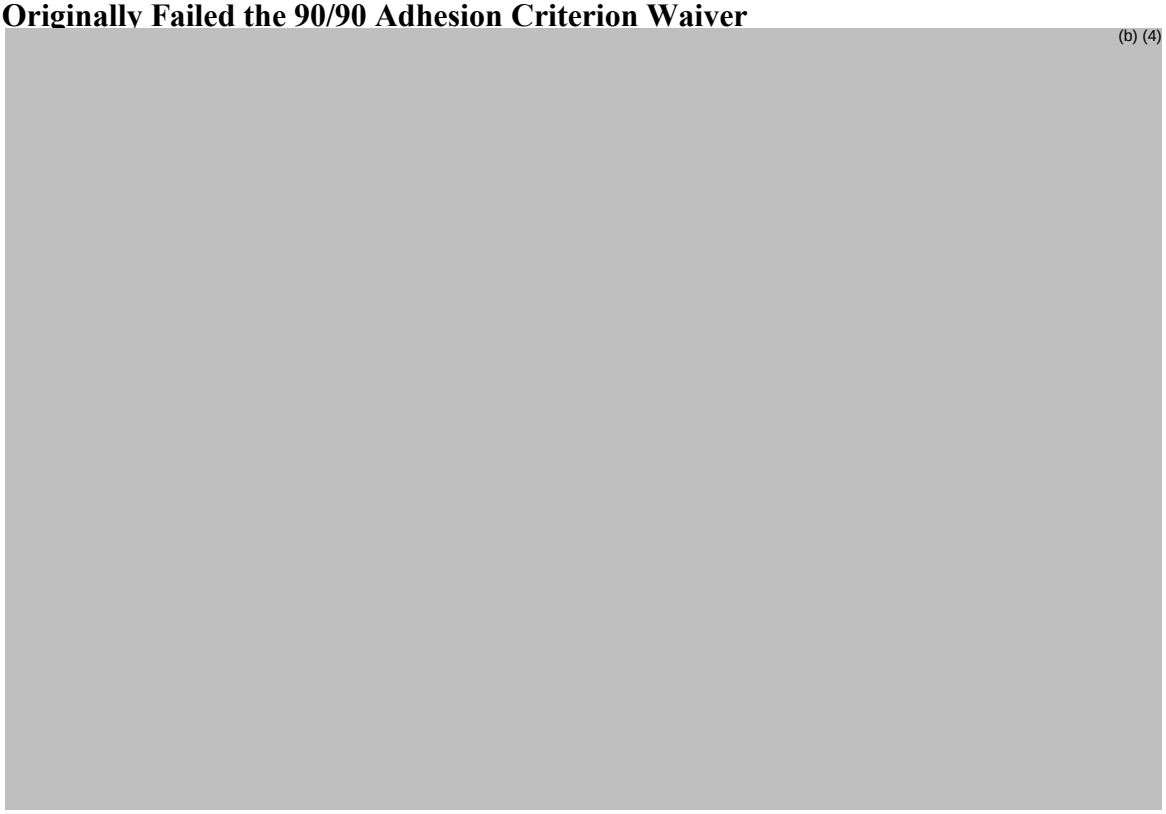
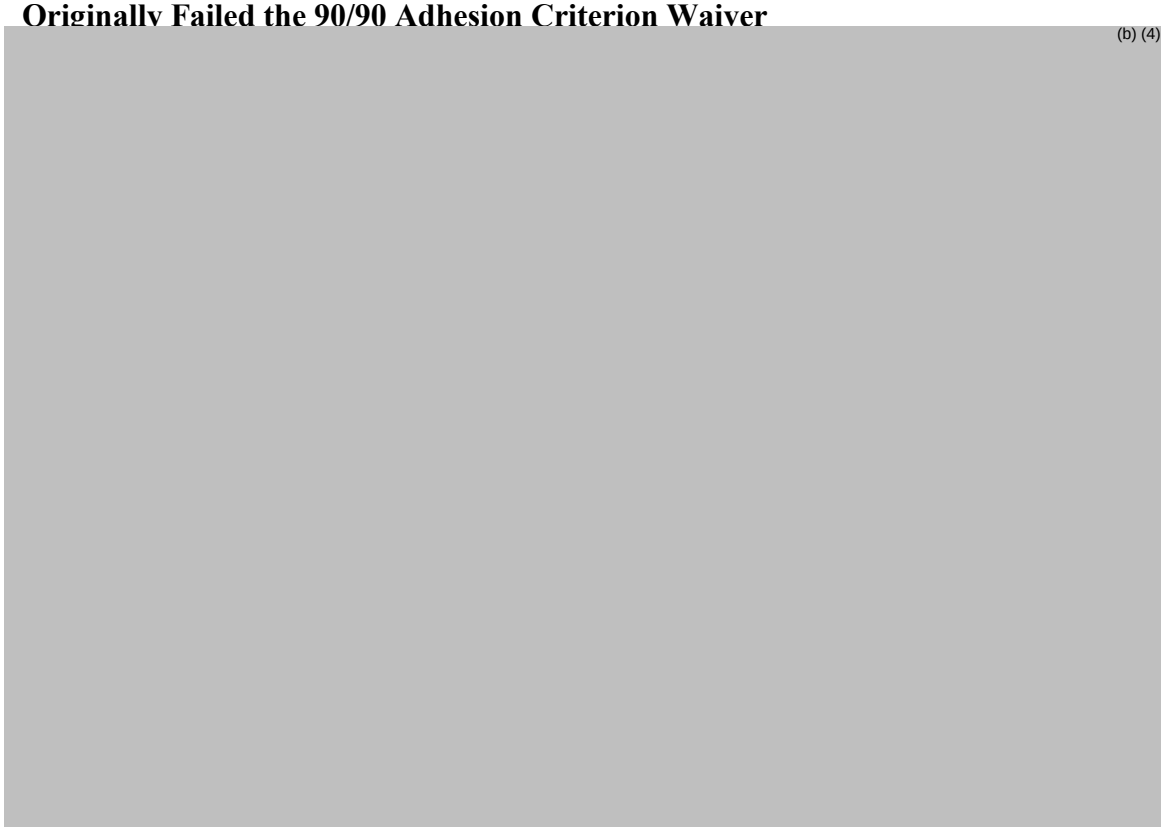


Figure 5. Effect of Sample Size on Percentage of Studies Passing for RLDs that Originally Failed the 90/90 Adhesion Criterion Waiver

(b) (4)



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%. (b) (4)

(b) (4)

(b) (4) 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]

---

[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

Clonidine	079090	118891	Study 10616246	Crosstab.xpt

A= Test Clonidine Patch B = Test Overlay
C =Reference Clonidine Patch D = Reference Overlay

TRT dy1ADH

Frequency Row 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	Total
A	- 3.28	0 0.00	0 0.00	0 0.00	1 1.64	1 3.61	16 26.23	12 19.67	31 50.82	
B	- 1.63	1 1.61	0 0.00	1 1.61	0 0.00	1 1.61	4 6.45	12 19.35	42 67.74	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	- 1.63	0 0.00	0 0.00	0 0.00	0 0.00	2 3.23	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)

(b) (4)

Following this page, 3 Pages Withheld in Full as (b)(4)

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	

Following this page, 1 Page Withheld in Full as (b)(4)

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

Following this page, 2 Pages Withheld in Full as (b)(4)

(b) (4)

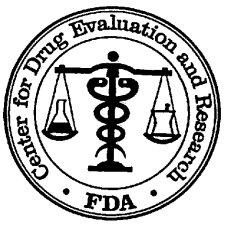
Scopolamine	078830	17874	Study PRG-604	Adh31201.xpt

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.

Appendix 2



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL ANALYSIS FOR

ADHESION WAIVER

AMENDMENT TO THE STATISTICAL REVIEW

CLINICAL STUDIES

ANDA/Serial Number:	200910
Drug Name:	Norelgestromin/Ethinyl Estradiol Transdermal System, 14 cm^2, 0.15mg/0.02 mg/day
Indication(s):	Prevention of pregnancy in women
Reference Listed Drug:	Ortho Evra®, 20 cm^2, 0.15mg/0.02 mg/day Janssen-Ortho, LLC
Applicant:	Mylan Technologies Inc.
Date(s):	February 3, 2014
Biometrics Division:	DBVI
Statistical Reviewer:	Vicki A. Lancaster, Ph.D., Generics Team, DBVI/OB/CDER
Concurring Reviewers:	Stella C. Grosser, Ph.D., Generics Team Leader, DBVI/OB/CDER
Medical Division:	Division of Clinical Reviewers OGD/OPS/CDER
Clinical Team:	Sarah Seung, Pharm.D., DCR/OGD/OPS/CDER
Keywords:	Estradiol, Crossover Design, Patch Adhesion

TABLE OF CONTENTS

List of Tables

1. Executive Summary

1.1 Conclusions and Recommendations

The adherence of the TEST product is 100% throughout the duration of wear for 100% of the patches. This statistical review and evaluation of the adhesion data submitted for ANDA 200910 support approval.

1.2 Brief Overview of the Clinical Study

The primary objective of this study was to evaluate the adhesion of Mylan's norelgestromin/ethinyl estradiol transdermal (NEETS) patch to Ortho Evra® patch manufactured by Janssen Ortho, LLC following a 7 day application of one Ortho Evra® or one Mylan NEETS patch for two treatment periods.

This was an open-label, single-dose, randomized, two-period, two-treatment, crossover study investigating the adhesive properties of Mylan's norelgestromin/ethinyl estradiol 0.15 mg/0.02 mg/day transdermal system to Ortho Evra® transdermal system, 0.15 mg/0.02 mg/day manufactured by Janssen Ortho, LLC for Ortho Women's Health & Urology. Forty (40) healthy female volunteers were enrolled in the study. Each subject wore each patch for 7 days. No washout period was required for this study. The second patch was applied as soon as possible after the first patch was removed. Adhesion was assessed every 24 hours the patch was worn.
Each subject that completed the study had seven measurements taken 24, 48, 72, 96, 120, 144, and 168 hours after application.

Adhesion Scoring and Endpoint
For assessment of adhesion, Mylan employed a 10-point scale where a score of '95' indicated > 90% to ≤ 100% adhered to the skin, while a score of '5' meant the transdermal system was completely detached from the skin. The Mylan 10-point scale was converted to the FDA recommended scale prior to statistical analysis. The conversion template is provided in Table 1.

Table 1. FDA and Mylan Adhesion Scales

Mylan Adhesion Scale		Conversion to FDA adhesion scale
Adhesion: > 90% to ≤ 100%	95	0 (essentially no lift-off from the skin)
Adhesion: > 80% to ≤ 90%	85	1 (some edges only lifting off the skin)
Adhesion: > 70% to ≤ 80%	75	1
Adhesion: > 60% to ≤ 70%	65	2 (< ½ of the system lifting off the skin)
Adhesion: > 50% to ≤ 60%	55	2
Adhesion: > 40% to ≤ 50%	45	3 (> ½ the system lifting off the skin without falling off)
Adhesion: > 30% to ≤ 40%	35	3

Adhesion: > 20% to ≤ 30%	25	3
Adhesion: > 10% to ≤ 20%	15	3
Adhesion: > 0% to ≤ 10%	5	4 (patch completely off the skin)

Statistician Note: Conversion from the Mylan to the FDA scale does not impact the inferential analysis. All measurements except one indicated perfect adhesion throughout the duration of wear.

The endpoint is the mean adhesion score calculated as the sum of the observed scores divided by the total number of observations.

Patient Disposition

Forty subjects were planned for enrollment and 40 subjects were initially dosed in the study. Thirty-seven subjects completed the clinical portion of the study. The adhesion data for 38 of 40 subjects was used in the statistical analysis.

- Subject 09 voluntarily withdrew consent during Period II.
- Subject 11 was discontinued from the study during Period I due to non-compliance (exposed patch to excessive water).
- Subject 12 voluntarily withdrew consent during Period II, but had an adequate number of adhesion scores to be included in the statistical analysis as required by the protocol.

The adhesion per-protocol population included 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.

1.3 Statistical Issues

Table 2. Distribution of Adhesion Scores by Product over Time

Hour	Product	0	1	2	3	4
24	RLD	38	0	0	0	0
	TEST	38	0	0	0	0
48	RLD	38	0	0	0	0
	TEST	38	0	0	0	0
72	RLD	38	0	0	0	0
	TEST	38	0	0	0	0
96	RLD	37	1	0	0	0
	TEST	38	0	0	0	0
120	RLD	38	0	0	0	0
	TEST	38	0	0	0	0
144	RLD	38	0	0	0	0
	TEST	38	0	0	0	0
168	RLD	38	0	0	0	0
	TEST	38	0	0	0	0

The FDA recommended statistical analysis for adhesion data proposed in the *Draft Guidance on Estradiol* relies on the normal distribution for evaluating non-inferiority. The guidance recommends, "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." The guidance makes no provision for a scenario where the normality assumption does not hold and there is no between or within subject variability as is the case for the adhesion data from ANDA 200910. Table 2 summarizes the responses for the TEST and

RLD over the duration of wear; all TEST measurements are 0 and there is only one non-zero RLD measurement. The distribution of the adhesion data from ANDA 200910 requires an alternative approach for making inferences.

The science staff in the Office of Generic Drugs, proposed an alternative approach for making inferences in their document *Waiver of Statistical Non-Inferiority Analysis for Highly Adhering Patch Drug Products* on February 10, 2014. In lieu of the FDA recommended approach, the data are summarized based on an approach described in the in the 2012 European Medicines Agency's (EMA) *Draft Guidance on Quality Transdermal Patches*. The EMA document 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."

The FDA has incorporated this idea in the waiver document. This document states that,

> "…, 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."

1.4 Statistical Analysis

For both the TEST and RLD products the mean adherence is greater than 90%. The adherence of the TEST product is 100% adherence throughout the duration of wear for 100% of the patches.

2. References

Food and Drug Administration Draft Guidance on Estradiol, November 2010.
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234962.pdf

European Medicines Agency Draft Guideline on Quality of Transdermal Patches, August 23, 2012.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/09/WC500132404.pdf

Waiver of Statistical Non-Inferiority Analysis for Highly Adhering Patch Drug Products, February 10, 2014.

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
02/19/2014

JOHN R PETERS
02/20/2014

DALE P CONNER
02/21/2014

Review of Skin Irritation, Sensitization and Adhesion Studies

ANDA #200910

Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day
Mylan Pharmaceuticals Inc.

Nicole Lee, Pharm.D.
Clinical Review Team

Dates of submissions reviewed:
December 23, 2009

Table of Contents

Review of Skin Irritation, Sensitization and Adhesion for ANDA 200910

Executive Summary

Norelgestromin/Ethinyl Estradiol Transdermal System (Ortho Evra®, approved November 20, 2001) is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception. Mylan Pharmaceuticals, Inc. (Mylan) submitted ANDA 200910 on 12/23/2009 for a generic formulation of Ortho Evra®. This review focuses on the studies submitted to ensure that the skin irritation and sensitization potential of this proposed generic topical patch product 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 #ORTH-0943 for skin irritation and sensitization. Study #ORTHO-0943 was an open-label, multiple dose, randomized application site, two-treatment, three-phase, one-period study investigating the 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-five (225) subjects, and 214 subjects completed the study.

Mylan also conducted study #ORTH-09198 for adhesion performance. This was an open-label, randomized, single dose, two-treatment, two-period crossover study to compare the adhesive properties of test and reference patches following a single application. Of the 40 subjects that were dosed, 37 subjects completed the study.

According to the sponsor's data, these studies demonstrate that Mylan's Norelgestromin/Ethinyl Estradiol Transdermal System is no more irritating and has no more potential to cause sensitization than that expected with use of the reference listed product Ortho Evra®. Adhesion data from Study #ORTH-09198 demonstrated that it adheres as well as the RLD.

According to the FDA statistical review, this study demonstrates that Mylan's Norelgestormin/Ethinyl Estradiol Transdermal is no more irritating and has no more potential to cause sensitization than that expected with use of the reference listed product Ortho Evra®. **However, the test product failed to demonstrate that its adhesion performance is no worse than that of the RLD.**

I. Approval Recommendation

The data submitted to ANDA 200910, for irritation, sensitization and adhesion of Mylan's Norelgestromin/Ethinyl Estradiol Transdermal System are adequate to demonstrate that it is no more irritating and has no greater potential to cause sensitization than the reference listed drug (RLD), Ortho Evra®. **However, the study failed to demonstrate that its adhesion performance is no worse than that of the RLD.** Since adhesion performance is considered

critical to both safety and efficacy, this application is **not** recommended for approval from a clinical bioequivalence perspective.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Study #ORTH-0943 was a open-label, multiple dose, randomized application site, two-treatment, three-phase, one-period study of Mylan's Norelgestromin/Ethinyl Estradiol Transdermal System vs. the reference listed drug, Ortho Evra® for irritation potential and sensitization potential.

Treatments Administered:
One half patch of Treatment A and One half patch of Treatment B

A. Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15mg/0.02mg/day, Lot No: R6A0014, Mfg Date: May 2009, Mylan Technologies Inc.
B. Ortho Evra® transdermal system, 0.15mg/0.02mg/day, Lot No: 7LM5212, Exp. Date: Oct 2009, Manufactured by: Janssen Ortho, LLC

Due to safety concerns related to administering twice the recommended dose of this hormonal contraceptive product continuously for 21 days, OGD has recommended that the skin irritation and sensitization studies for generic versions of Ortho Evra be conducted using one half of the test patch and one half of the reference patch.

Two hundred twenty five (225) subjects received one half of a 0.15 mg/0.02mg/day norelgestromin/ethinyl estradiol transdermal system (generic) and one half of a 0.15 mg/0.02 mg/day Orthro Evra® transdermal system (reference) simultaneously according to the randomization scheme. Patch applications were made once weekly for 21 days. This was followed by a 14-day rest period, followed by a 48-hour challenge phase. In the challenge phase, each subject received one half of a 0.15 mg/0.02mg/day norelgestromin/ethinyl estradiol transdermal system (generic) and one half of a 0.15 mg/0.02 mg/day Orthro Evra® transdermal system (reference) simultaneously applied to a naïve site on the abdomen according to the randomization scheme. Irritation was assessed for 3 days (at 0.5, 24, 48, and 72 hours) after removal of the challenge phase patches.

Patches were applied to test sites on the abdomen according to the application site randomization. The edges of the patches were marked with a surgical marker to ensure patch reapplication at the same site. Within 60 minutes prior to the first application and following the 30 minute irritation evaluation for all other applications, the test sites were wiped gently three times with a warm water washcloth, then lightly patted dry with a soft towel. The skin was to be completely dry before any patches were applied.

B. Comparative Irritation

Mylan's norelgestromin/ethinyl estradiol transdermal system appears to be no more irritating than the RLD.

According to the sponsor's skin irritation analysis, the upper bound of the one-sided 95% CI for the mean irritation score of the test product minus 1.25 X the mean irritation score of the reference product was -0.1751 which shows that the skin irritation potential of the test product is no worse than that of the reference product.

There were two subjects (Nos. 123 and 192) who had their test sites moved due to maximum irritation scores for both test and reference patches. Subject 123 reached the maximum irritation score at day 15 for both patches and Subject 192 reached the maximum irritation score at day 8 for both patches.

According to the FDA statistical analyses, the 95% upper confidence bounds (CB) for the adjusted mean difference (μ_T -1.25μ_R) was less than zero (-0.17) for irritation. The least mean cumulative score for irritation was 0.89 for the test and 0.87 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 2.6% with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 2.

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 to be considered potentially sensitized by the sponsor. No re-challenge was performed.

This reviewer found that two subjects (#31, 106) were potentially sensitized to both the test product the RLD. One additional subject(#80) was potentially sensitized to the reference product. Subjects 80 and 106 had a dermal response score of 2 or more at both 48 and 72 hours post challenge patch removal while subject 31 had a dermal response score of 2 at both 24 and 48 hours post challenge patch removal. Of these five patches, four had a dermal response no higher than a score of 1 during the induction phase. Subject 106 had a dermal score of 2 for the test product on day 22 of the irritation phase.

According to the FDA statistical review, the test product was found to be statistically better than or non-inferior to the reference product for the response rate, provided the non-inferiority margin is set no lower than 0.77 percentage points for Days 40 and 41. The contact sensitization property of the test product is better or no worse than that of the reference product, since the upper bound of the 90% confidence interval of the difference is relatively small (0.77%).

D. Comparative Adhesion

The sponsor used a different adhesion scale than that generally recommended by OGD for assessing adhesion performance. Based on the sponsor's adhesion analysis, adhesion performance of the test product appears to be non-inferior to that of the RLD.

According to the sponsor's adhesion data, 38 out of 38 subjects with the test product had a score of 95 (>90 to 100% attached, the same as the recommended score of 0), while 37 out of 38 subjects with the reference product had a score of 95. One subject had a score of 85 (>80 to 90% attached, consistent with a recommended score of 1) for the reference product.

According to the FDA statistical review, the 95% upper confidence bound (CB) for the adjusted mean difference (μ_T -1.25μ_R) was greater than zero (0.0025). Thus, the test product was found to be inferior to the reference product. Additionally, analysis based on the dichotomized (adhered / not adhered) endpoint showed that for the test product to be non-inferior to the reference product, a non-inferiority bound $\delta \geq 2.63$ percentage points would be required.

It was noted by the FDA statistician that the Mean Adhesions Score of the test product is zero ($\mu T=0$): i.e., all the test's patches have essentially no lift off the skin) and is less than that of the reference product ($\mu R = 0.0038$, where subject No 18 has an Adhesion Score of 1 at 96 hour). Therefore, according to the sponsor's data, a better property as measured by the point estimate for the Test product than the Reference product was observed. Clinical decision should be assessed with medical judgment as well as statistics.

E. Adverse Events

No serious adverse events were reported. There were 1208 AEs reported by 220 subjects over the course of the study. AEs were mild to moderate in severity. There were 533 AEs at the application site (erythema, pruritus, pain, irritation, and skin laceration) considered probably related to the test product. There were 544 similar AEs considered probably related to the RLD. There was one additional AE considered possibly related to RLD. No deaths or serious or life threatening adverse events associated with study drug administration were reported for this study.

III. Design and Formulation

Schematic diagram of Generic Transdermal System (per sponsor)

Backing Film	
Adhesive Matrix ----------Nonwoven Polyester---------- Adhesive Matrix	
Slit Release Liner	Slit Release Liner

Mylan's Norelgestromin and Ethinyl Estradiol Transdermal System – A 14.0 cm^2 patch that contains 4.86 mg of norelgestromin and 0.53 mg of ethinyl estradiol. It is a (b) (4) patch (b) (4) (b) (4) consisting of a peach-colored backing film (b) (4) printed with "Norelgestromin and Ethinyl Estradiol" in brown ink, an adhesive layer containing a non-woven polyester, (b) (4) release liner. Each individual patch is packaged (b) (4) pouch.

Test Formulation

Components	% w/w	mg/patch	Pharmaceutical Function
Active Ingredients			
Norelgestromin	2.31	4.86	Active ingredient
Ethinyl Estradiol, USP	0.25	0.53	Active ingredient
Inactive Ingredients			
Polyisobutene Adhesive	(b) (4)		
Oleyl alcohol, NF			
Dipropylene glycol			
(b) (4) mineral oil, NF			
Crospovidone, NF			
(b) (4)			
Theoretical Total Matrix	100	210.00	

Composition of Components of Other components of Norelgestromin and Ethinyl Estradiol Transdermal System

Components	g/m^2	mg/patch
Polyethylene/polyester film	(b) (4)	
Brown ink		
Nonwoven polyester		
Fluoropolymer coated polyester film		

Reference Formulation[1]

Component	% w/w	mg/patch	Function
Active ingredients			
Norelgestromin	2.00	6.00	Active
Ethinyl estradiol	0.25	0.75	Active
Inactive ingredients			
Polyisobutylene/polybutene	(b) (4)		
Lauryl lactate			
Total adhesive matrix			
Polyester non-woven	(b) (4)		
Polyester backing film			
Polyester release liner			

[1]Data from NDA Clin Pharm review dated 11/19/2001

(b) (4)

Ortho Evra® is a thin, matrix-type transdermal contraceptive patch consisting of three layers with a contact surface area of 20 cm^2. The backing layer is composed of a beige flexible film consisting of a low-density pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, crospovidone, non-woven polyester fabric and lauryl lactate as inactive components. The active components in this layer are the hormones, norelgestromin and ethinyl estradiol. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a polydimethylsiloxane coating on the side that is in contact with the middle adhesive layer.

Reviewer's comments: *The test product contains* (b) (4) *of active ingredients per patch than the RLD.*

According to the chemistry review dated February 18, 2013, all excipients are either (b) (4) *the maximum level listed in the Inactive Ingredients Database (IID) for this dosage form or a comprehensive review of the safety is provided as follows:*

- (b) (4) *polyethylene/polyester film is not specifically listed in the FDA's electronic Inactive Ingredients Database for Approved Drug Products.* (b) (4)
- *The* (b) (4) *Brown Ink is not listed in the IID; however the ink is approved for other Mylan commercial transdermal products.*
- *The nonwoven polyester in Mylan's patch is* (b) (4) *the IID limit for a polyester film. It is the same as was used in the RLD.*

(b) (4) *Mylan chose to use a different type of release liner following comparative evaluations that showed the fluoropolymer-coated liner demonstrated superior* (b) (4) *behavior. Mylan chose* (b) (4) *dipropylene glycol* (b) (4) *The chemistry review states that Mylan explained their rationale for these differences, mainly due to patent issues.*

In the last chemistry review dated February 18, 2013, a minor deficiency was noted which states:

"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". To ensure this, the ANDA applicant should provide information about the formulation performance to ensure that the sensitivity to in-use conditions like heat /hot water exposure 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 release data to the RLD at normal and "stress" situations: 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 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"

Overall, the skin irritation, sensitization and adhesion studies provided show that these differences do not affect these properties of the generic transdermal patch compared to the reference patch.

Clinical Review

I. Introduction and Background

Norelgestromin (NGMN) is the active progestin largely responsible for the progestational activity that occurs in women following application of Ortho Evra®. Norelgestromin is also the primary active metabolite produced following oral administration of norgestimate (NGM). Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus, which increase the difficulty of sperm entry into the uterus, and changes in the endometrium, which may reduce the likelihood of implantation. Receptor and human sex hormone-binding globulin (SHBG) binding studies, as well as studies in animals and humans, have shown that both NGM and NGMN exhibit high progestational activity with minimal intrinsic androgenicity. Transdermally-administered norelgestromin, in combination with ethinyl estradiol (EE), does not counteract the estrogen-induced increases in SHBG, resulting in lower levels of free testosterone in serum compared to baseline.

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 and NGMN 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.

A. Drug Established Name, Drug Class

Established Name: Norelgestromin/Ethinyl Estradiol Transdermal System
Drug Class: Combination Transdermal Contraceptive Patch

B. Trade Name of Reference Drug, NDA number, Date of approval, Approved Indication(s), Dose, Regimens

Reference Drug: Ortho-Evra® Transdermal System, Ortho McNeil Janssen Pharmaceuticals, Inc.
NDA number: 021180
Date of Approval: November 20, 2001
Approved Indication(s): ORTHO EVRA® is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception**.**
Dosing Regimen: This system uses a 28-day (four-week) cycle. A new patch is applied each week for three weeks (21 total days). Week four is patch-free. Withdrawal bleeding is expected during this time. Every new patch should be applied on the same day of the week.

C. Regulatory Background

No other ANDAs have previously been approved for this product.

(b) (4)

Controls/Protocols

(b) (4)

There are 8 controls in the OGD database:

Control No	Title	Description	Status	Doc Date
04-024	Norelgestromin/ethinyl estradiol transdermal system	Regulatory drug release parameters	Closed 6/23/2004	12/24/2003
04-859	Norelgestromin/ethinyl estradiol transdermal system	Bioequivalence Study	Closed 9/1/2004	11/9/2004

05-0875	Norelgestromin/ethinyl TDS	Follow-up to controlled correspondence	Closed 5/25/2006	6/30/2005
05-1555	Norelgestromin/ethinyl estradiol transdermal contraceptive patch	Termination of the bioequivalence ortho evra. Skin irritation and sensitization study	Closed 1/26/2006	11/17/2005
06-0080	Norelgestromin/ethinyl estradiol patch	Formulation and dissolution test issue	Closed 5/9/2006	1/12/2006
06-0869	Norelgestromin/ethinyl estradiol patch	Seeking comments/recommendations regarding applying tape to reinforce any patches that are lifting during the PK bio study.	Closed 8/8/2006	7/6/2006
07-0512	Norelgestromin/ethinyl estradiol transdermal system	Request for BE and dissolution recommendations	Closed 6/3/2009	3/22/2007
08-0527	Ethinyl estradiol; norelgestromin transdermal system (ortho evra)	BE/dissolution method recommendations	Closed 5/29/2009	5/8/2008

Individual Product Bioequivalence Recommendations: Draft Guidance on Ethinyl Estradiol/Norelgestromin (May 2009,) can be found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM162407.pdf

The draft guidance general recommendations are attached in Appendix A.

Reviewer's comments: *The study submitted is consistent with the draft guidance except for the adhesion scale used. The FDA statistician was requested to analyze the adhesion study results with the FDA recommended scale. Note that , the FDA statistician stated " The sponsor's proposed statistical analysis is not acceptable*

II. Description of Clinical Data and Sources

CRO: Cetero Research

Study Center:

- 4801 Amber Valley Parkway Fargo, ND 58104
- 625 Demers Ave East Grand Forks, MN 56721

Study Period: June 22, 2009 to September 4, 2009

Investigator(s): Alan K. Copa, Pharm.D.

Enrollment: A total of 225 subjects were enrolled into the study.

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

Original Submission: \\CDSESUB1\N77775\N_000\2005-06-30

Based on the Office of Scientific Investigations Report dated May 1, 2012, the following observations were made:
Inspection of Cetero Research, Miami was conducted on 7/1/2011 to 7/21/2011. Form FDA-483 was issued at the end of the inspection. The following observations were noted:

1. The investigation was not conducted in accordance with the investigational plan. The clinic staff involved in adhesion and irritation scoring was to be blinded to the randomization scheme at the time of evaluation and scoring. The document on file disclosed that in several instances during Period 2, the irritation evaluator also conducted the last adhesion assessment at the 16 hour interval post patch application. Irritation evaluations were to be conducted at 30 and 60 minute time points post patch removal after completion of the 16 hour adhesion period. The physical appearance of both study test articles is clearly distinctive. Therefore, blinding of the evaluator could have been compromised.

In the written response, Cetero acknowledged the deficiency. They stated they will use different evaluators for assessing adhesion and irritation for similar future studies.

Although the firm did not adhere to the study protocol, the OSI reviewer is of the opinion that maintaining blinding during the patch adhesion assessment was not possible. Lack of blinding during irritation evaluation is not likely to have significant impact on the study outcome, because the results of irritation scoring for Test and Reference drug patches did not differ significantly.

Final classification: Cetero Research, Miami, FL (VAI)

***Reviewer's comments**: This reviewer agrees with the OSI conclusion that the lack of blinding under the circumstances will not have a significant impact on the study outcome.*

B. Overview of Methods Used to Evaluate Data Quality and Integrity

This reviewer carefully reviewed data sets provided by the sponsor to verify appropriate adjudication of study patches among analysis groups. A statistical consultation was requested to verify the firm's data and calculations.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

According to the sponsor, this study was conducted in accordance with the ethical principles set forth in the International Conference on Harmonization Guidelines on Good Clinical Practice, and the US Code of Federal Regulations, Title 21 CFR Part 50 and 56.

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 200910 for Mylan's Norelgestromin/Ethinyl Estradiol Transdermal System show that the irritation and sensitization potentials of the generic are no worse than expected with use of the RLD, and the adhesion performance is at least as good as that of the RLD over the intended duration of wear.

B. General Approach to Review of the Comparative Skin Sensitization, Irritation, and Adhesion

The sponsor's data were reviewed to verify that their generic patch is no more irritating than the reference patch. In addition, skin sensitization potential and adhesion performance were evaluated to verify that they are no worse than those expected with use of the reference patch.

C. Detailed Review of Skin Sensitization, Irritation, and Adhesion Study

Study #ORTH-0943

Title:
Comparative Evaluation of the Cumulative Irritation and Contact Sensitization Potential of Norelgestromin/Ethinyl Estradiol Transdermal System (NEETS) (0.15 mg/0.02 mg/day: Mylan) to Ortho Evra® (0.15 mg/0.02 mg/day: Ortho) in Healthy Female Volunteers

Objective
To compare the cumulative irritation and sensitization potential of Mylan's norelgestromin/ethinyl estradiol transdermal system (0.15 mg/0.02 mg/day) to Ortho Evra® (0.15 mg/0.02 mg/day) in two hundred (200) healthy female volunteers.

Study Design
This was an open-label, multiple dose, randomized application site, two-treatment, three-phase,

one-period study investigating the human dermal safety of Mylan's norelgestromin/ethinyl estradiol transdermal system (NEETS) (0.15 mg/0.02 mg/day) compared to Ortho's Ortho Evra® transdermal system (0.15 mg/0.02 mg/day).

Study Population

Inclusion Criteria

Subjects could participate if they met the following inclusion criteria:

1. Age: 18 to 35 years old.
2. Sex: Non-pregnant, non-lactating female.
   a. Women of childbearing potential had a negative serum beta human chorionic gonadotropin (β-HCG) pregnancy tests performed within 28 days prior to the start of the study and prior to each transdermal system application. An additional serum (β-HCG) pregnancy test was performed upon completion of the study.
   b. Women of childbearing potential were required to practice abstinence or use an acceptable form of contraception from 7 days before dosing until 30 days post final patch removal. The subjects were notified that they were not protected from pregnancy during this study. This requirement was documented in the informed consent form. Acceptable forms of contraception included the following:
      i. barrier methods containing or used in conjunction with a spermicidal agent, or
      ii. surgical sterilization

   c. Women were not considered of childbearing potential if one of the following was reported and documented on the medical history:
      i. postmenopausal with spontaneous amenorrhea for at least one (1) year, or
      ii. bilateral oophorectomy with or without a hysterectomy and an absence of bleeding for at least 6 months, or
      iii. total hysterectomy and an absence of bleeding for at least 3 months
3. Weight: At least 48 kg (106 lbs) with all subjects having a Body Mass Index (BMI) less than or equal to 35 but greater than or equal to 19.
4. All subjects were judged by the principal or sub-investigator physician listed on the Form FDA 1572 as normal and healthy during a pre-study medical evaluation performed within 28 days of the initial dose of study medication which included:
   a. a normal or non-clinically significant physical examination, including vitals signs
   b. within normal limits or non-clinically significant laboratory evaluation results for the following tests
      i. 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
      ii. Hematology: Platelet Count, Leukocyte Count with Differential, Hemoglobin, Hematocrit, Red Blood Cell Count
      iii. Urinalysis: Appearance, Specific Gravity, Protein, pH, Microscopic Examination (performed based on clinical judgment)
      iv. Additional tests may have been performed, if necessary
   c. negative Hepatitis B and Hepatitis C tests,

d. negative HIV test,
e. normal or non-clinically significant 12-lead ECG
f. negative urine drug screen for all of the following compounds: amphetamines, barbiturates, benzodiazepines, cannabinoid, cocaine, methadone, opiates, and phencyclidine
g. if warranted, tests for sexually transmitted diseases (STD) may have been performed at the discretion of the Principal Investigator or responsible physician.

5. The pre-study physical examination included breast and pelvic exams including a Pap smear performed as follows:
   a. The breast examination must be preformed within 28 days of the initial dose administration.
   b. A pelvic exam including a Pap smear was required on subjects if one had not been performed within the 6 months prior to dosing. Subjects provided written documentation of normal results from their physician.

Exclusion Criteria

Subjects could not be enrolled if they met any of the following exclusion criteria:

1. Institutionalized
2. History of skin diseases (eczema, psoriasis, atopic dermatitis).
3. Social Habits:
   a. Use of any tobacco-containing products within 1 year of the start of the study.
   b. Any recent, significant change in dietary or exercise habits.
   c. A positive test for any drug included in the urine drug screen.
   d. History of drug and/or alcohol abuse.
4. Medications:
   a. Use of any prescription or over-the-counter (OTC) systemic or topical analgesics or antihistamines within 72 hours of initial patch application or use of systemic or topical corticosteroids within 3 weeks of initial patch application.
   b. A depot injection or implant of any drug within 3 months prior to administration of study medication.
   c. Use of any medication or herbal products known to inhibit CYP3A4 enzyme activity within 7 days prior to the initial dose of study medication
5. Diseases:
   a. 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 Sub-Investigator.
   b. Acute illness at the time of either the pre-study medical evaluation or dosing.
   c. History of severe allergic reaction.
   d. Thrombotic disorders, especially thrombophlebitis or pulmonary embolism.
   e. Coronary artery or cerebrovascular disease.
   f. Liver or kidney dysfunction/disorders.
   g. Gall bladder disease.
   h. Fibrocystic disease or breast nodules.
   i. Family history of breast cancer (direct genetic link, i.e. mother, sister, etc.).
   j. Diabetes or any other endocrinological disease.

k. Estrogen-dependent neoplasia.
l. Cervical dysplasia.

6. Subjects who had an acute illness at the time of either the screening evaluation or patch application(s).
7. Damaged skin in or around test sites that included sunburn, uneven skin tones, tattoos, scars, or other disfigurations of the test site.
8. Donation or loss of a significant volume of blood or plasma (>450 mL) within 28 days prior to the initial dose of study medication.
9. Subjects who had received an investigational drug within 30 days prior to the initial patch application and/or participated in any transdermal system or patch study for irritation or sensitization within the last 4 weeks.
10. Sunbathing or the use of tanning salons for 7 days prior to transdermal system application.
11. Use of perfumes, body lotions, or oils within 7 days prior to transdermal system application.
12. Allergy or hypersensitivity to tapes or adhesives (ex. Band-aids, medical tape), isopropyl alcohol, progestins, estrogens, other hormonal products, or to any other component of product.
13. Consumption of grapefruit or grapefruit-containing products within 7 days of drug administration.

Reviewer's comments: *The inclusion/exclusion criteria are acceptable and consistent with the draft guidance.*

Procedures/Observations, and safety measures

Treatments included patch applications once a week for three weeks. Subjects received one half patch of Mylan's norelgestromin/ethinyl estradiol transdermal system and one half patch of Ortho's Ortho Evra® transdermal system simultaneously once a week for three weeks. A 14-day rest phase followed with a subsequent 48-hour challenge phase. The challenge phase was followed by a 3 day observation and irritation evaluation. Within two weeks afterwards subjects had a post study clinical and laboratory evaluation to assess their health condition after drug administration.

Patches were applied to test sites on the abdomen according to the application site randomization. The edges of the patches were marked with a surgical marker to ensure patch reapplication at the same site. Within 60 minutes prior to the first application and following the 30 minute irritation evaluation for all other applications, the test sites were wiped gently three times with a warm water washcloth, then lightly patted dry with a soft towel. The skin was completely dry before any patches were applied.

Induction Phase

The patches were removed 168 hours $\pm$ 2 hours after application. Patch applications were made once weekly for 21 days. The three applications (per transdermal system) performed during this three-week phase were designated Applications 1 through 3, respectively. The appropriate transdermal system was re-applied to the identical site until after the third 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 the 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 appropriately documented and diagrammed. All other treatment applications continued as scheduled.

If a subject developed a reaction of 3 or greater, according to the irritation rating scale found in Appendix 3 of the protocol (Appendix 16.1.1), the subject did not have any further transdermal systems applied to the same application site during the Induction phase of the study. The original application site continued to be evaluated until a reaction score of 0 was achieved. This score was recorded separately. In this case, any reapplications for Induction were made at a designated alternate site and appropriately documented and diagrammed. All other treatment applications continued as scheduled.

Rest Phase
A rest period (no patch applications) of 14 days followed Induction application 3.

Sensitization Evaluation-Challenge Phase
Following the Rest Phase, a Challenge application of one half patch of 0.15 mg/0.02 mg/day norelgestromin/ethinyl estradiol transdermal system (Mylan) and one half patch of 0.15 mg/ 0.02 mg/day Ortho Evra® transdermal system simultaneously applied to a clean, dry area of the skin on the abdomen (naïve site) according to the application site randomization. All application and wear procedures outlined in the Induction phase were followed. Transdermal systems were removed at 48 hours (+ 2 hours) after application. Irritation was assessed at 0.5, 24, 48, and 72 hours after removal of the transdermal system, according to the irritation rating scale.

Endpoints
Description of scales or instruments used

IRRITATION:

Dermal Response (per key on Irritation Raw Data Listing)**:**

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

Other Effects:

0(A)	Slight glazed appearance
1(B)	Marked glazing
2(C)	Glazing with peeling and cracking
3(F)	Glazing with fissures
3(G)	Film of dried serous exudates covering all or part of the patch site
3(H)	Small petechial erosions and/or scabs

Statistical analysis plan

Irritation

A one-sided hypothesis test was used to determine if the irritation score of Mylan's NEETS was equivalent to or better than the Ortho Evra® (for the reference product). For the mean irritation scores, the null and alternative hypotheses were: H_0: $\mu_1/\ \mu_2 > 1.25$ and H_1: $\mu_1/\ \mu_2 \leq 1.25$, which (assuming $\mu_2 > 0$) can be written as: H_0: $\mu_1 - 1.25\mu_2 > 0$ and H_1: $\mu_1 - 1.25\mu_2 \leq 0$, where μ_1 is the mean irritation score for the test product and μ_2 is the mean irritation score for the reference product. The null hypothesis H_0 was rejected when the upper limit of the 90% confidence interval (that is the 95% upper confidence bound) for the quantity $\mu_1 - 1.25\mu_2$ was ≤ 0.

The actual patch test scores were consistent with the definitions given in the grading using the greater of the dermal response and the other effects scores (e.g. dermal response of 2 + other effects of B (l) = actual score of 2). A total cumulative irritation score for each subject and product was calculated by summing each individual's scores for each patch application. The mean cumulative irritation score for each subject and product was calculated by dividing the total cumulative scores by 3.

Reviewer's comments: *For calculation of the cumulative irritation score, the sponsor used the greater of the dermal response and other effects scores [e.g., dermal response of 2 + other effects of B (1)=actual score of 2] in the statistical analysis. The cumulative mean irritation score should be evaluated by adding the dermal response and "other effect" scores.*

Sensitization

The source data for the analysis of sensitization is the narrative description of each reaction in the Challenge phase recorded following visual evaluation of the dermal test sites for the test and reference products. The primary objective for the Challenge Phase assessment was to evaluate the sensitization potential of Mylan's NEETS compared to Ortho Evra®. Sensitization reactions following application of Mylan's NEETS were to have been comparable to those seen with Ortho Evra®. No formal statistical evaluation was performed on these data.

Study Conduct

Discussion of safety and PP populations

Safety population- All subjects who received at least one treatment.

Evaluable population-All subjects who are not withdrawn by the clinic or pharmacokineticist.

Discussion of compliance
Dosing was completed under the direct supervision of the Cetero Research staff to ensure treatment compliance and proper drug administration. During the washout interval between study periods, staff was available for subject queries during regular working hours and via an answering service after hours.

According to the protocol, each subject was to keep a diary in which she was to record the length and number of baths or showers and any type of contact with water that may affect patch adhesion. If less than 24 hours elapsed after patch detachment, the transdermal system could be replaced by the clinical site staff and patch removal and irritation evaluation were to occur at the previously scheduled time for the original application. If more than 24 hours elapsed after patch detachment, the treatment was to be discontinued.

Reviewer's comments:
A statistical consult should identify those subjects who had a patch off continuously for more than 24 hours and exclude those subjects from the per protocol analysis of cumulative irritation and sensitization for both patches because the induction period is invalid.

Blinding/randomization/retention
This was an open-label study. The application site randomization scheme used to assign each subject number to a treatment sequence was generated by Mylan Inc. The randomization scheme utilized a one-period, two-treatment design. Suitably trained Cetero Research personnel that performed the adhesion and irritation scoring were blinded to the randomization scheme at the time of evaluations. According to the study protocol, the sponsor was to supply sufficient quantities of the study formulation for retention, as per applicable regulations.

Demographics

Parameters	All Subjects N=214 (females)
Age	24.0 ± 4.7
Weight	69.7 ± 12.5
Height	165 ± 6.0
BMI	25.4 ± 4.3

Results

Subject disposition:

	Total
Subjects Randomized	225
Subjects Successfully Completed	214
Subjects Who Withdrew Consent	7
Subjects Discontinued by the Investigator	4
Subjects Discontinued by Sponsor	0

Disposition of Enrolled Subjects

Total number of subjects enrolled	225	100.00%
Number of premature discontinuations	11	4.89%
• Subjects who withdrew consent	7	3.11%
• Subjects dropped due to positive pregnancy	1	0.44%
• Subjects dropped due to noncompliance	3	1.33%
Safety Population Total	225	100.00%
Evaluable Population	214	95.11%

Irritation: (per sponsor):

Clinical Site	Least-Squares Mean		μ_1-1.25μ_2	Upper Bound of 95% Lower confidence Region	P-value
	Treatment A (test)	Treatment B (reference)			
All	0.8951	0.8781	-0.2025	-0.1751	<0.0001
Fargo, ND	0.9196	0.8968	-0.2014	-0.1734	<0.0001
East Grand Forks, MN	0.3347	0.44331	-0.2191	-0.0926	0.0135

Frequency of Irritation Score Occurrence (per sponsor)

Time after initial patch application	*Treatment A, Mylan (Lot #R6A0014)*					*Treatment B, Ortho Evra® (Lot # 7LM5212)*				
Score	*0*	*1*	*2*	*3*	*5*	*0*	*1*	*2*	*3*	*5*
Day 8	*36*	*163*	*16*	*1*	*0*	*30*	*172*	*13*	*1*	*0*
Day 15	*57*	*146*	*11*	*1*	*1*	*62*	*142*	*10*	*1*	*1*
Day 22	*32*	*166*	*16*	*1*	*1*	*40*	*158*	*16*	*1*	*1*

Overall Frequency of Mean Cumulative Dermal Irritation

Treatment	Frequency of the Mean Irritation Score				
	0	> 0 to ≤ 1	> 1 to ≤ 2	> 2 to ≤ 3	> 3 to ≤ 4
Test	13	172	29	1	1
Reference	10	177	27	1	1

FDA statistical Analysis:

Non-inferiority Analyses, mean irritation score (Per Protocol Population)

Test placebo (LS mean μ_{TP})	Positive control (LS mean μ_{PC})	Upper limit one-sided 95% CB (μ_{TP} - 1.25μ_{PC})	Pass the Non-inferiority test?
0.89	0.87	-0.17	Yes

Frequency of Maximum Irritation Score per Patch Per Subject (PP)

Product/Score	0	1	2	3	4	5	Total
Test	13	170	31	1	0	1	216
Reference	10	176	28	1	0	1	216

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. 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, two subjects (#31, 106) were potentially sensitized to both the test product the RLD. One additional subject(#80) was potentially sensitized to the reference product. Subjects 80 and 106 had a dermal response score of 2 or more at both 48 and 72 hours post challenge patch removal while subject 31 had a dermal response score of 2 at both 24 and 48 hours post challenge patch removal. Of these five patches, four had a dermal response no higher than a score of 1 during the induction phase. Subject 106 had a dermal score of 2 for the test product on day 22 of the irritation phase.

Raw Data for Induction and Challenge Phase

Subject	Treatment	Day 8	Day 15	Day 22	Day 38	Day 39	Day 40	Day 41
31	Test	1	1	1	2	2	2	1
	Reference	1	1	1	1	2	2	1
80	Reference	1	1	1	1	2	2	2
106	Test	1	0	2	2	2	2	2G
	Reference	1	1	1	2	2	2	2G

FDA Statistical Analyses

According to the statistical reviewer, using Fleiss's confidence bound formula, the test product was found to be statistically better than or non-inferior to the reference product for the response rate, provided the non-inferiority margin is set no lower than 0.77 percentage points for Day 40 and Day 41 respectively. The contact sensitization property of the test product is better or not worse than that of the reference product, since the upper bound of the 90% confidence interval of the difference is relatively small (0.77%).

Protocol: ORTH-09198

Title: Adhesion Evaluation Study of Norelgestromin/Ethinyl Estradiol Transdermal System (NEETS) Patch (0.15 mg/0.02 mg/day; Mylan) and Active Wear of Ortho Evra® Patch (0.15 mg/0.02 mg/day; Ortho- McNeil-Jannsen) in Normal Healthy Female Volunteers

Objective: The primary objective of this study was to evaluate the adhesion of Mylan's norelgestromin/ethinyl estradiol transdermal (NEETS) patch to Ortho Evra® patch manufactured by Janssen Ortho, LLC following a 7 day application of one Ortho Evra® or one Mylan NEETS patch for two treatment periods.

Study Design: This was an open-label, single-dose, randomized, two-period, two-treatment, crossover study investigating the adhesive properties of Mylan's norelgestromin/ethinyl estradiol 0.15 mg/0.02 mg/day transdermal system to Ortho Evra® transdermal system, 0.15 mg/0.02 mg/day manufactured by Janssen Ortho, LLC for Ortho Women's Health & Urology. Forty (40) healthy female volunteers were enrolled in the study and 37 subjects completed the study. The adhesion data for 38 of 40 subjects was used in the statistical analysis. Each subject wore each patch for 7 days. No washout period was required for this study. The second patch was applied as soon as possible after the first patch was removed. Adhesion was assessed every 24 hours the patch was worn.

Study Population: **S**ame inclusion/exclusion criteria as protocol #ORTH-0943 (Irritation/Sensitization Study)

Procedures/Observations: Subjects were to wear one Ortho Evra® patch or one Mylan Neets patch with the treatments applied to the subject's right or left lower abdomen in a randomized fashion. Each subject wore each patch for 7 days. No washout period was required for this study. The second patch was applied as soon as possible after the first patch was removed. Adhesion was assessed every 24 hours the patch was worn. All subjects returned to the clinical facility on Days 2 (24 hours), Day 3 (48 hours) Day 4 (72 hours) Day 5 (96 hours), Day 6 (120 hours) and Day 7 (144 hours) after patch application for patch adhesion evaluation. On Day 8 (168 hours) of Period 1 the patch was removed and another patch was applied (according to the randomization scheme). It was placed on the opposite side (right or left) of the abdomen from the previous patch. On Day 8 of Period 2, following removal of the patch, the End of Study Procedures were initiated. The following products were administered:

Treatment A:
Norelgestromin/Ethinyl Estradiol Transdermal System, 14 cm^2, 0.15 mg/0.02 mg/day, Mylan Technologies Inc. (Mylan), Lot #R6A0014
Treatment B:
Ortho Evra®, 20 cm^2, 0.15 mg/0.02 mg/day, Janssen Ortho, LLC, Lot # 7LM5212

Endpoints:
Rating Scale for Assessing Patch Adhesion

Adhesion	Score
>90% to <100%	95
>80% to 90%	85
>70% to 80%	75
>60% to 70%	65
>50% to 60%	55
>40% to 50%	45
>30% to 40%	35
>20% to 30%	25
>10% to 20%	15
0% (falloff) to 10%	5

Reviewer's comments: *The sponsor used a different adhesion scale for assessing adhesion performance than that recommended by the OGD. The adhesion scale recommended by OGD is the following:*

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)

Reviewer's comments: *Although the statistician did not comment on the adhesion scale used by the firm, the FDA statistician stated " The sponsor's proposed statistical analysis is not acceptable. The sponsor's proposed statistical hypotheses are only appropriate when adhesion score is reversed, as described in the table below:*

Reversed System Adherence	
Score	**Definitions**
4	≥90% adhered (essentially no lift off the skin)
3	≥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)
1	>0% to <50% adhered but not detached (more than half of the system lifting off the skin without falling off)
0	0% adhered-test system detached (test system completely off the skin)

Statistical Analysis:
A one-sided hypothesis test was used to determine if the adhesion score of Mylan's NEETS was equivalent to or better than the Ortho Evra® (for the reference product). For the mean adhesion scores, the null and alternative hypotheses were: H_0: $\mu_1/\mu_2 < 0.8$ and H_1: $\mu_1/\mu_2 < 0.8$, which (assuming $\mu_2 > 0$) can be written as: H_0: $\mu_1 - 0.8\mu_2 < 0$ and H_1: $\mu_1 - 0.8\mu_2 \geq 0$, where μ_1 is the mean adhesion score for the test product and μ_2 is the mean adhesion score for the reference product. The null hypothesis H_0 was rejected when the lower limit of the 90% confidence interval (that is the 95% lower confidence bound) for the quantity $\mu_1 - 0.8\mu_2$ was ≥ 0.

Results:

Summary of Subject Disposition

	Sequence		Total
	AB	BA	
Subjects Randomized	20	20	40
Subjects Successfully Completed	18	19	37
Subjects Who Withdrew Consent	1	1	2
Subjects Discontinued by the Investigator	0	0	0
Subjects Discontinued by Sponsor	1	0	1
Subjects included in the adhesion statistical analysis	19	19	38

Treatment A: Test
Treatment B: Reference

Adhesion Statistical Analysis

Statistical Analysis of Adhesion				
Least-Squares Mean		$\mu_1 - 0.8\mu_2$	Lower bound of 95% confidence region	P-value
Test	Reference			
95.00	94.96	19.03	18.97	<0.0001

Mean Adhesion Scores

Hour	Arithmetic Mean, A (Test)	Arithmetic Mean, B (Reference)
24	95.00 (0.0%)	95.00 (0.0%)
48	95.00 (0.0%)	95.00 (0.0%)
72	95.00 (0.0%)	95.00 (0.0%)
96	95.00 (0.0%)	94.74 (1.7%)
120	95.00 (0.0%)	95.00 (0.0%)
144	95.00 (0.0%)	95.00 (0.0%)
168	95.00 (0.0%)	95.00 (0.0%)
Cumulative Mean	95.00 (0.0%)	94.96 (0.2%)

Adhesion Scores by Hour

Treatment A			Treatment B		
Hour	Score		Hour	Score	
Frequency	85	95	Frequency	85	95
24	0	38	24	0	38
48	0	38	48	0	38
72	0	38	72	0	38
96	0	38	96	1	37
120	0	38	120	0	38
144	0	38	144	0	38
168	0	38	168	0	38
Total	0	266	Total	1	265

FDA statistical Analyses

Adhesion analyses results (Non-inferiority)- PP population

Parameters	Test (Ls mean)	Reference (Ls mean)	Upper limit one-sided 95% CB (test-1.25ref)	Pass the non-inferiority test
Mean Adhesion Score	0.0000	0.0038	0.0025	No
Cumulative Adhesion Score	0.000	0.026	0.02	No

Frequency of Adhesion Score (PP)

Frequency of Adhesion score per patch per observation (PP)						
	Score					
Patch	**0**	**1**	**2**	**3**	**4**	**Total**
Test	266	0	0	0	0	266
Reference	265	1	0	0	0	266

According to the FDA statistical review: The Test product was ***not*** found to be Non-inferior to the Reference product for the Mean Adhesion Score (primary endpoint), treating the Mean Adhesion Score as a continuous variable. However, the observed mean Adhesion score of the Test product in this study is better than that of the Reference product, indicating better adhesion property.

For the additional dichotomized endpoint, where a patch was classified as adhered if the adhesion score at the end of the study was 0 or 1, the 95% upper confidence bounds for the difference in the Adhesion rates of the Test and the Reference Products (T p - R p) is 2.63%. This upper confidence bound may be compared to any appropriate Non-inferiority bound δ that may be set by the Office of Generic Drugs.

The sponsor's proposed statistical analysis was not acceptable. The sponsor's proposed statistical hypotheses are only appropriate when adhesion score is reversed, i.e. 4 (best) to 0 (worst).

***Reviewer's comments**: Although from a clinical perspective, the sponsor's adhesion data appears to be acceptable, the clinical significance cannot be ascertained with any confidence based on numerous factors, for example sample size and the subjective nature of the scoring as well as failure to demonstrate non-inferiority in statistical analysis. In addition, according to the FDA statistical reviewer, the sponsor's analysis was methodologically incorrect using the sponsor's proposed scale. Therefore, the statistical findings must be upheld.*

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 irritation raw data, two subjects (#31, 106) could be considered potentially sensitized for both the test and reference products, and one additional subject (#80) could be considered potentially sensitized for the reference product. Subjects 80 and 106 had a dermal response score of 2 or more at both 48 and 72 hours post challenge patch removal while subject 31 had a dermal response score of 2 at both 24 and 48 hours post challenge patch removal. Of these five patches, four had a dermal response no higher than a score of 1 during the induction phase. Subject 106 had a dermal score of 2 for the test product on day 22 of the irritation phase.

Raw Data for Induction and Challenge Phase

Subject	Treatment	Day 8	Day 15	Day 22	Day 38	Day 39	Day 40	Day 41
31	Test	1	1	1	2	2	2	1
	Reference	1	1	1	1	2	2	1
80	Reference	1	1	1	1	2	2	2
106	Test	1	0	2	2	2	2	2G
	Reference	1	1	1	2	2	2	2G

According to the FDA statistical review, the test product was found to be statistically better than or non-inferior to the reference product for the response rate, provided the non-inferiority margin is set no lower than 0.77 percentage points for Days 40 and 41. The contact sensitization property of the test product is better or no worse than that of the reference product, since the upper bound of the 90% confidence interval of the difference is relatively small (0.77%).

E. Comparative Irritation Conclusion

Mylan's norelgestromin/ethinyl estradiol transdermal system appears to be no more irritating than the RLD.

According to the sponsor's skin irritation analysis, the upper bound of the one-sided 95% CI for the mean irritation score of the test product minus 1.25 X the mean irritation score of the reference product was -0.1751 which shows that the skin irritation potential of the test product is no worse than that of the reference product.

There were two subjects (Nos. 123 and 192) who had their test sites moved due to maximum irritation scores for both test and reference patches. Subject 123 reached the maximum irritation score at day 15 for both patches and Subject 192 reached the maximum irritation score at day 8 for both patches.

According to the FDA statistical analyses, the 95% upper confidence bounds (CB) for the adjusted mean difference (μ_T -1.25μ_R) was less than zero (-0.17) for irritation. The least mean cumulative score for irritation was 0.89 for the test and 0.87 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 2.6% with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 2.

F. Adhesion Conclusion

The sponsor used a different adhesion scale than that generally recommended by the OGD for assessing adhesion performance. Based on the sponsor's adhesion analysis, adhesion performance of the test product appears to be non-inferior to that of the RLD.

According to the sponsor's adhesion data, 38 out of 38 subjects with the test product had a score of 95 (>90 to 100% attached, same as the recommended score of 0), while 37 out of 38 subjects with the reference product had a score of 95. One subject had a score of 85 (>80 to 90% attached, consistent with a recommended score of 1) with the reference product. No patch had an unacceptable adhesion score.

According to the FDA statistical review, the 95% upper confidence bound (CB) for the adjusted mean difference (μ_T -1.25μ_R) was greater than zero (0.0025). **Thus, the test product was found to be inferior to the reference product.** Additionally, analysis based on the dichotomized (adhered / not adhered) endpoint showed that for the test product to be non-inferior to the reference product, a non-inferiority bound $\delta \geq 2.63$ percentage points would be required.

The FDA statistical review states that the sponsor's proposed statistical analysis is not acceptable. The sponsor's proposed statistical hypotheses are only appropriate when adhesion score is reversed. According to the reviewer, when using a scale going from 0 (best) to 4 (worst), the 95% Upper-Confidence Bound of the μ_T-1.25 μ_R must be used. When using a scale going from 4 (best) to 0 (worst), the 95% Lower-Confidence Bound of the μ_T-0.8 μ_R must be used. The sponsor however used the scale 0 (best) to 4 (worst) using the 95% Lower-Confidence Bound of the μ_T-0.8 μ_R. This is not acceptable.

Although from a clinical perspective, the sponsor's adhesion data appears to be adequate to the reference product, the clinical significance cannot be ascertained with any confidence based on

numerous factors, i.e. sample size and the subjective nature of the scoring. Therefore, the statistical findings must be upheld.

V. Comparative Review of Safety

A. Brief Statement of Conclusions

No significant safety concerns were identified in this study of the placebo system.

B. Description of Adverse Events

For Study #ORTH-0943, no serious adverse events were reported. There were 1208 AEs reported by 220 subjects over the course of the study. AEs were mild to moderate in severity.

Relationship	Test	Reference
Probably Related	533	544
Possibly Related	0	1

There were 533 AEs (application site erythema, pruritus, pain, irritation, and skin laceration) considered probably related to the test product. There were 544 similar AEs considered probably related to the RLD. There was one additional AE considered possibly related to the RLD. There were no deaths or serious or life threatening adverse events associated with study drug administration reported for this study

For Study #ORTH-09198, No serious adverse events were reported. There were eighty-five (85) AE's reported by thirty-one (31) subjects over the course of the study, AE's were mild to moderate in severity.

Relationship	Test	Reference
Total	38	45
Definitely Related	21	23
Probably Related	2	6
Possibly Related	12	9
Unlikely Related	3	3
Unrelated	0	4

Thirty-eight (38) mild AE's were experienced after the test patch application. Forty-two (42) mild and three (3) moderate AE's were experienced after the RLD application. Twenty-one (21) AE's (Erythema, Mild Itching In or Around Patch Site, Tenderness in Breast, Late Period) were considered definitely related to the test patch application. Two (2) AE's (Loss of Appetite, Tenderness in Breast) were considered probably related to the RLD. Twelve (12) AE's (Headache, Loss of Appetite, Nausea, Drowsiness, Sleepiness, Swelling in Lower Legs) were considered possibly related to the test patch application . Three (3) AE's (Lower Back Pain, Constipation, Headache) were considered unlikely related to the test patch.

Twenty-three (23) AE's (Erythema, Vomiting, Late Period, Itching In Vaginal Area, Tenderness in Breast, Extended Period, Itching In or Around Patch Site, Dizziness) were considered

definitely related to the RLD. Six (6) AE's (Emotional, Nausea, Vomiting, Headache, Period In Advance) were considered probably related to the RLD. Nine (9) AE's (Sleepiness, Urinalysis Ketone, Nausea, Headache, Rhinitis, Acne) were considered possibly related to the RLD. Three (3) AE's (Rhinitis, Nausea) were considered unlikely related to the RLD. Four (4) AE's (Urinalysis Leukocytes, Urinalysis WBC, Urinalysis Epithelial, Urinalysis Bacteria) were considered unrelated to the RLD.

In addition, two (2) AEs (Scratch on Abdomen) occurred prior to either patch application and were considered unrelated to the study drugs. There were two (2) moderate AE's (Vomiting) one considered definitely and one probably related, and one (1) mild AE (Vomiting) considered probably related to the RLD. Four (4) AE's (Urinalysis: Bacterial, Epithelial, Leukocytes, and WBC) were considered unrelated and one (1) AE (Urinalysis Ketone) was considered possibly related to the RLD. Two (2) mild AE's (Itching: around and in the patch) were considered definitely related, and one (1) moderate AE (Itching in Vaginal Area) was considered definitely related to the to the RLD.

VI. Relevant Findings From Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

Inspection of Cetero Research, Miami was conducted on 7/1-21/2011. Form FDA-483 was issued at the end of the inspection. The following observations were noted:

2. The investigation was not conducted in accordance with the investigational plan. The clinic staff involved in adhesion and irritation scoring was to be blinded to the randomization scheme at the time of evaluation and scoring. The document on file disclosed that in several instances during Period 2, the irritation evaluator also conducted the last adhesion assessment at the 16 hour interval post patch application. Irritation evaluations were to be conducted at 30 and 60 minute time points post patch removal after completion of the 16 hour adhesion period. The physical appearance of both study test articles is clearly distinctive. Therefore, blinding of the evaluator could have been compromised.

In the written response, Cetero acknowledged the deficiency. They stated they will use different evaluators for assessing adhesion and irritation for similar future studies.

Although the firm did not adhere to the study protocol, the OSI reviewer is of the opinion that maintaining blinding during the patch adhesion assessment was not possible. Lack of blinding during irritation evaluation is not likely to have significant impact on the study outcome, because the results of irritation scoring for Test and Reference drug patches did not differ significantly.

Final classification: Cetero Research, Miami, FL (VAI)

VIII. Conclusion and Recommendation

A. Conclusion

The data submitted to ANDA 200910, for irritation, sensitization and adhesion of Mylan's Norelgestromin/Ethinyl Estradiol Transdermal System are adequate to demonstrate that it is no more irritating than the RLD and does not have a greater potential to cause sensitization than that expected with use of the reference listed drug (RLD), Ortho Evra®. However, **the study failed to demonstrate that its adhesion performance is no worse than that of the RLD**.

B. Recommendation

This application **is not** recommended for approval from a clinical bioequivalence standpoint.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200910 APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 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:

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 adhesion study (**ORTH-09198)**, your product was statistically significantly less adhesive than the reference product .

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: Guidance

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: 0.02 mg/24 hr; 0.15 mg/24 hr
   Subjects: Healthy nonpregnant females, general population, who are candidates for hormonal contraception.
   Additional comments: Specific recommendations are provided below.

---

2. Type of study: Skin Irritation and Sensitization Study
   Design: Randomized, evaluator-blinded, in vivo within-subject repeat test
   Strength: 0.02 mg/24 hr; 0.15 mg/24 hr (Dose: One-half of a 0.02 mg/24 hr; 0.15 mg/24 hr patch)
   Subjects: Healthy nonpregnant females, general population, who are candidates for hormonal contraception.
   Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Ethinyl Estradiol and Norelgestromin in plasma (PK study only)

Bioequivalence based on (90% CI): Ethinyl Estradiol and Norelgestromin (PK study only)

Waiver request of in vivo testing: Not Applicable.

Dissolution test method and sampling times: Please note that a **Dissolution Method Database** is available to the public at the Office of Generic Drugs (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 modified release products, dissolution profiles on 12 dosage units each of test and reference products generated in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Multipoint dissolution profiles should be obtained using a discriminating agitation speed. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 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 PK bioequivalence and adhesion study:

1. Females should not be pregnant. Due to an increased myocardial risk primarily in smokers, non-smoking subjects who have previously used hormonal contraceptives without complications should be enrolled. Also, females weighing less than 90 kg and not exceeding 35 years of age should be considered since older women may be at a higher risk of drug-related adverse events (AEs). Blood pressure (BP) within 140/80 mm Hg limit should be an inclusion criterion.

2. Criteria should also be developed to discontinue subjects that reach a pre-defined maximum BP throughout the study.

3. The patch should be applied to the abdomen in all subjects.

4. Adhesion performance of the intact test product and RLD patches must be formally evaluated and compared in the PK bioequivalence study or in a separate parallel or crossover adhesion study of single 7-day patch applications of the active test product versus the RLD. No patch reinforcement is allowed when the study is being used to establish adequate adhesion performance to support product approval. Adhesion scoring is to be performed at least daily. 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.

5. 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)

6. The Per-Protocol (PP) Population evaluation of the adhesion parameter should be defined per patch instead of per subject 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 7-day application.

7. The cumulative adhesion score and the time from application until patch detachment (i.e., duration of patch wear) should be calculated for the test product and RLD, and a statistical analysis of the comparative results should be performed. In addition, the following adhesion data should be provided for the test product and RLD:

   a. frequency table showing the number of patches with each adhesion score at each evaluation time point
   b. number of patches that are completely detached at each evaluation time

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 cumulative adhesion score for the test product minus 1.25 times the mean cumulative adhesion score for the RLD must be less than or equal to 0. For the adhesion evaluation, the Office of Generic Drugs (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 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 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 cumulative adhesion scores and also show no meaningful difference with regard to degree of detachment.

8. For the Adhesion Analysis, please provide a separate line listing for each individual test article per subject, per each visit (if data exist), using the following headings, if applicable:

    a. Subject identifier
    b. Treatment: test article (i.e., test product, RLD)
    c. Period (i.e., patch was applied during Period 1 or Period 2)
    d. Application Number: number of particular test article application (i.e., 1=first, 2=second)
    e. Location of Dose Administration: individual test article application site
    f. Number of days since baseline visit
    g. Application date and time
    h. Date and time of removal or complete detachment
    i. Duration of Treatment: time (hours) from individual test article application to removal or complete detachment
    j. Included in PP population for adhesion analysis (yes/no)
    k. Reason for exclusion from PP population for adhesion analysis
    l. Scoring date
    m. Adhesion scores
    n. Identity of the evaluator
    o. Was the patch reinforced with tape or overlay (yes/no)
    p. If patch was reinforced, time from patch application to reinforcement

Additional comments regarding the skin irritation and sensitization study:

1. The OGD recommends evaluating skin irritation and sensitization in a single study. To support approval, the test product must be no more irritating than the RLD and be no more sensitizing than 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. Safety concerns preclude the use of two whole, active, 0.02 mg/24 hr, 0.15 mg/24 hr ethinyl estradiol/norelgestromin patches on the same healthy subject during the 21-day skin irritation and sensitization study. The optimum design of this study will depend on the design of the test product patch. Since the RLD has a matrix design that can be safely cut in half, one half of the patch can be used for these studies. If the test product patch also has a design that can be cut to a smaller size, it should also be cut in half and one half of the test product patch applied simultaneously with one half of a RLD patch (to separate skin sites). It would not be acceptable to manufacture a separate batch of product in order to use a smaller patch in this study.

3. Cutting patches will change the shape and size of the patch and may alter the adhesive performance. Therefore, if partial patches are used for the skin irritation and sensitization study, the OGD recommends collecting adhesion data in the PK bioequivalence study to demonstrate that the test product adheres at least as well as the RLD for the 7 day duration of wear. To do so, no reinforcement may be applied to patches in the PK study. Alternatively, a separate single-application parallel or crossover design adhesion study may be conducted for the 7 day duration of wear, comparing the un-altered to be marketed test product and RLD.

4. If the test product patch has a reservoir design that cannot be cut in half, then, in order to avoid an unacceptable risk of serious adverse events, the study should be conducted using a parallel design with healthy subjects randomized to receive either the test product or RLD. The study should be powered to show that the test is no more irritating, no more sensitizing, and adheres at least as well as the RLD.

5. 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 when using one half patches, all test articles (i.e., one half of the 0.02 mg/24 hr; 0.15 mg/24 hr test product[1], one half of the 0.02 mg/24 hr; 0.15 mg/24 hr RLD, optional vehicle patch[2] and optional negative control[3]) are to be applied simultaneously to each subject to clean, dry, intact healthy skin at different sites on the buttock, abdomen, upper outer arm or torso, with sequential patch applications to the same skin sites weekly (i.e., every 7 days; the intended duration of wear) for a total of 21 consecutive days. Thus, it is recommended to apply the patches on Days 1, 8, and 15 to the same sites and to have each of them remain in place for 7 days (a total of 21 days altogether). The Day 15 patches would

[1] The test product evaluated should be the actual patches to be marketed. If the test product has a design that can be cut to a smaller size, the OGD recommends cutting them in half.
[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 ethinyl estradiol and norelgestromin.
[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.

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 when using one half patches consists of a single 48-hour application of one half of the 0.02 mg/24 hr; 0.15 mg/24 hr test product, one half of the 0.02 mg/24 hr; 0.15 mg/24 hr RLD, 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.

Adhesion should be evaluated prior to patch removal throughout the entire study period to ensure adequate skin contact for maximal induction of irritation and sensitization.

6. When evaluating the one half patches, an adequate number of subjects should be enrolled to ensure that at least 200 evaluable subjects are included in the PP population.

7. 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.

8. 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.

9. 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.

10. 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 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.

11. Inclusion Criteria (the sponsor may add additional criteria):

a. Healthy female subjects 18-35 years of age (inclusive) who are candidates for hormonal contraception.
b. Subjects who have previously used hormonal contraceptives without complications are the optimal candidates for this study.
c. Subject willing to stop using any current hormonal contraceptive method.
d. Subject had a tubal ligation OR throughout the study and for 7 days after completion of the study or premature discontinuation, agrees to abstain from sexual intercourse or use a reliable non-hormonal method of contraception (e.g., diaphragm with spermicide or condom with spermicide).
e. Negative pregnancy test on first dosing day, prior to application of patch.

12. Exclusion Criteria (the sponsor may add additional criteria):
    a. Subject is pregnant or lactating.
    b. Subject is a current smoker.
    c. Subject weighs 90 kg or more.
    d. Systolic blood pressure >140 mmHg at screening measured in supine position after 5 minutes rest; diastolic blood pressure >80 mmHg at screening measured in supine position after 5 minutes rest.
    e. Subject was previous user of RLD.
    f. Subject who is currently using any long-acting hormonal method of contraception (e.g., contraceptive rod implant such as Implanon™, hormonal IUD such as Mirena®, hormone injections such as Depo-Provera or depo-subQ Provera 104) or has used them within past 3 months.
    g. Subject who currently has any of the following conditions:
        1. Thrombophlebitis, thromboembolic disorders
        2. A past history of deep vein thrombophlebitis or thromboembolic disorders
        3. Cerebrovascular or coronary artery disease (current or past history)
        4. Valvular heart disease with complications
        5. Severe hypertension
        6. Diabetes with vascular involvement
        7. Headaches with focal neurological symptoms
        8. Major surgery with prolonged immobilization
        9. Known or suspected carcinoma of the breast or personal history of breast cancer
        10. Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
        11. Undiagnosed abnormal genital bleeding
        12. Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use
        13. Acute or chronic hepatocellular disease with abnormal liver function
        14. Hepatic adenomas or carcinomas
        15. 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 erythematous).

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 investigative site.
j. 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).
k. Within 72 hours prior to dosing, use of antihistamines or use of topical drugs at patch site.
l. 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.
m. Presence of open sores at the application site.

13. Criteria should also be developed to discontinue subjects that reach a pre-defined maximum BP throughout the study.

14. Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
    a. 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, adrenocortical steroids such as prednisone, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG), monoclonal antibodies, radiation therapy).
    b. Hormonal contraception other than test product and RLD (e.g., oral contraceptive pills, contraceptive vaginal ring such as NuvaRing®, contraceptive rod implant such as Implanon™, hormonal IUD such as Mirena®, hormone injections such as Depo-Provera or depo-subQ Provera 104).

15. Subjects should be informed that wearing patches cut in half will not protect them from pregnancy and they are especially at risk for pregnancy during the first week of the Induction Phase, after Day 7 of the rest period and during the entire Challenge Phase.

16. Subjects should receive the first patch within seven days after the first day of a menstrual period. Subjects currently taking hormonal contraceptives should switch to study drug on the day they are scheduled to start a new contraceptive cycle. This will minimize disruption of the menstrual cycle.

17. Subjects should be advised to expect menstrual bleeding after each patch is removed.

18. Following the Challenge Phase, if a subject wishes to use the contraceptive patch or resume oral contraceptives, she may apply a new (RLD) patch to a different site immediately or start

a new pill cycle, but she must also continue using non-hormonal contraception for 7 days after starting the new hormonal contraceptive cycle. Subjects who do not wish to use a hormonal contraceptive may experience vaginal bleeding or spotting after removal of the challenge patch.

19. During the induction phase, subjects should return for weekly visits on Days 8 and 15 for adhesion scoring, patch removal, irritation scoring, and patch replacement and on Day 22 for adhesion scoring, patch removal and irritation scoring. 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 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.

20. 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.

21. 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)

22. During both the Induction Phase and Challenge Phase, the skin reactions are to be evaluated and scored according to the following two scales[4]:

[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.

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).

23. 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 the first patch site should be carried forward for all remaining observations in the irritation analysis.

24. 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 completed 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. Whereas this study using partial patches can not be used for a definitive assessment of adhesion performance of the active product, criteria may be established for using tape or an overlay to reinforce any patches that are lifting during the irritation and sensitization study. 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.

Safety Data and Analyses

25. 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.

    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.

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
05/07/2013

JOHN R PETERS
05/09/2013

DALE P CONNER
05/14/2013

CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# _200910_____ **FIRM NAME** Mylan Pharmaceuticals Inc._____

DRUG NAME _Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/24 hr, 0.02 mg/24 hr_____

DOSAGE FORM __Transdermal Patch_____

Reference Listed Drug (RLD) _Ortho Evra® (0.15 mg/0.02 mg/day), NDA 021180_____

Requested by: ___Edward Washington_____ Date: _2/22/10_____
Regulatory Support Team, (HFD-615)

	Summary of Findings by Clinical Review Team
X	**Study meets statutory requirements** **The sponsor needs to submit additional data for the review. Please see comments to be conveyed to the sponsor for details.**
	Study does NOT meet statutory requirements
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: _X_ COMPLETE __INCOMPLETE

Reviewed by:

_____ Date: _____
Carol Y. Kim, Pharm.D.
Clinical Reviewer

_____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

Item Verified:	Irritation/ Sensitization #Orth-0943		Adhesion #Orth-09198		Comments
	YES	NO	YES	NO	
Protocol	X		X		
Summary of Study	X		X		
Clinical Site (s)	X		X		
Study Investigator (s)	X		X		
List of subjects included in PP/ (M)ITT populations per treatments	X			X	For study #Orth-09198, no adhesion data were submitted in .xpt file.
List of subjects excluded/ from PP/ (M)ITT per treatments	X			X	
Reasons for discontinuation from the study if discontinued	X		X		
Adverse Events	X		X		Submitted in .pdf file. Need data in .xpt file.
Concomitant Medications	X		X		Submitted in .pdf file. Need data in .xpt file.
Individual subject's scores/data per visit		X	X		For study #Orth-0943, other effects scores were not provided for each subject. Data for column "IND_C1" (other effects for the 1st site) is empty in "Ortho943irr.xpt".
Pre-screening of Patients	X		X		
IRB Approval	X		X		
Consent Forms	X		X		
Randomization Schedule	X		X		
Protocol Deviations	X		X		
Case Report Forms	X		X		
PD Data Disk (or Elec Subm)	X			X	For study #Orth-0943, no "other effects" scores were provided. For study #Orth-09198, no individual

					adhesion scores were provided in .xpt file. See comments below for details.
Financial Disclosure	X		X		
Study Results	X		X		
Clinical Raw Data/ Medical Records	X		X		
Composition	X		X		Test: 14 cm^2; RLD: 20 cm^2
BioStudy Lot Numbers	X		X		
Date of Manufacture	X		X		
Exp. Date of RLD	X		X		
Statistical Reports	X		X		
Defined BE endpoints		X		X	N/A
Summary results provided by the firm indicate no worse skin irritation, adhesion, and sensitization properties of the test product compared to that of the RLD	X		X		See comments below
Waiver requests for other strengths / supporting data		X		X	N/A

Comments <u>NOT</u> to be conveyed to the sponsor:

The sponsor submitted two separate studies: 1) a skin irritation/sensitization study (#Orth-0943) using one-half of the original size of patch delivering 0.15 mg norelgestromin/day and 0.02 mg estradiol/day and 2) an adhesion study (#Orth-09198) using a single patch (original size of patch) for 7 days. Adhesion performance was evaluated in study Orth-09198 only. Although frequency table for adhesion scores were provided for study #Orth-0943, overlay use was allowed to ensure adequate adhesion.

1. <u>Data presented for comparison of skin irritation potential between products are acceptable for filing.</u>

The sponsor evaluated skin irritation and sensitization potential of the test and reference products in 214 completed healthy female subjects. One-half of both active test and reference products were placed on their abdomen simultaneously for a total of 3 sequential applications of 7 day duration, giving a total induction phase of 21 days of continuous same-site exposure to each product. Local irritation was assessed after removal of each patch during the induction period. Following a 14-day rest period, a challenge patch of each product was applied for 48 hours at a naïve abdomen site. The application sites were assessed for potential sensitization reactions at approximately, 0.5, 24, 48, and

72 hours after challenge patch removal.

According to the sponsor's skin irritation analysis, the upper bound of the one-sided 95% CI for the mean irritation score of the test product minus 1.25 X the mean irritation score of the reference product was -0.1751 which shows that the skin irritation potential of the test product is no worse than that of the reference product. The sponsor's summary of cumulative mean irritation analysis is shown below.

14.3. Table 3- Primary Efficacy Analysis of Cumulative Irritation Scores

Clinical Site	Least-Squares Mean		μ_1-1.25μ_2[1]	Upper Bound of 95% Lower Confidence Region[2]	P-Value[3]
	Treatment A NEETS	Treatment B Ortho Evra®			
All[4]	0.8951	0.8781	-0.2025	-0.1751	< 0.0001
Fargo, ND	0.9196	0.8968	-0.2014	-0.1734	< 0.0001
East Grand Forks, MN	0.3347	0.4431	-0.2191	-0.0926	0.0135

[1] Estimated as Mylan's NEETS least-squares mean – 1.25 x Ortho Evra® least-squares mean.
[2] Upper one-sided 95% confidence bound on μ_1-1.25μ_2. A value ≤ 0 indicates Mylan's NEETS is non-inferior to Ortho Evra®.
[3] P-value for H0: μ_1-1.25μ_2 > 0, from two-way analysis of variance with factors of treatment and center. If the estimate of μ_1-1.25μ_2 ≤ 0, a p-value ≤ 0.100 indicates Mylan's NEETS is non-inferior to Ortho Evra®.
[4] As a result of the statistically significant clinical site by treatment interaction term (p-value < 0.1000), additional statistical analyses were performed individually for each clinical site.

14.1. Table 1- Frequency of Irritation Score Occurrence

Time after Initial Patch Application	Treatment A Mylan (Lot# R6A0014)					Treatment B Ortho Evra® (Lot # 7LM5212)				
Score	0	1	2	3	5	0	1	2	3	5
Day 8	36	163	16	1	0	30	172	13	1	0
Day 15	57	146	11	1	1	62	142	10	1	1
Day 22	32	166	16	1	1	40	158	16	1	1

Reviewer's Comment: *For calculation of the cumulative irritation score, the sponsor used the greater of the dermal response and other effects scores [e.g., dermal response of 2 + other effects of B (1)=actual score of 2] in the statistical analysis. The cumulative mean irritation score should be evaluated using the combined dermal response and "other effect" scores.*

2. Data presented for comparison of skin sensitization potential between products are acceptable for filing.

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. No re-challenge was performed.

Reviewer's Comment: *The sponsor did not provide a statistical summary of dermal response or other effects scores for the challenge patch application. Only individual dermal response scores were provided for the challenge patch application in the "orth0943irri.xpt" dataset. No other effect scores were provided for the challenge patch application.*

According to the irritation raw data listing under "16 appendices", two subjects (#31, 106) for the test product and three subjects (#31, 80, 106) for the reference product could be considered potentially sensitized. These subjects had a dermal response score of 2 at both 24 and 48 hours post challenge patch removal. Of these five subjects, four subjects had a dermal response no higher than a score of 1 during induction phase.

3. Data presented for comparative adhesion performance between the test and reference products are acceptable for filing.

In an open-label, single-dose, randomized, two-period, two-treatment, crossover study, adhesion performance of test and reference products was evaluated. Forty healthy female subjects received a single patch of either the test product or the RLD to the left or right lower abdomen for a 7 day wear period. No washout period was required for this study. The second patch was applied as soon as the first patch was removed according to the randomization sequence. No overlay was used. Adhesion was observed every 24 hours post dose for 7 days including 24, 48, 72, 96, 120, 144, and 168 hours following patch application.

The sponsor used a different adhesion scale for assessing adhesion performance. Based on the sponsor's adhesion analysis, adhesion performance of the test product appears to be non-inferior to that of the RLD.

The sponsor's summary of adhesion analysis is shown below.

Statistical Analysis of Adhesion

Least-Squares Mean		μ_1-0.8μ_2[1]	Lower Bound of 95% Confidence Region[2]	P-Value[3]
Treatment A Mylan	Treatment B Ortho Evra®			
95.00	94.96	19.03	18.97	< 0.0001

Source: Appendix 16.1.1

[1] Estimated as Mylan's NEETS least-squares mean – 0.8 x Ortho Evra® least-squares mean.

[2] Lower one-sided 95% confidence bound on μ_1-0.8μ_2. A value ≥ 0 indicates Mylan's NEETS is non-inferior to Ortho Evra®.

[3] P-value for H_0: μ_1-0.8μ_2 > 0, from two-way analysis of variance. If the estimate of μ_1-0.8μ_2 ≥ 0, a p-value ≤ 0.100 indicates Mylan's NEETS is non-inferior to Ortho Evra®.

Adhesion Results:

Mean (%CV) Adhesion Scores In Thirty-eight Healthy Adult Female Subjects Following A Single 0.15 mg/0.02 mg/day Dose Of Norelgestromin/Ethinyl Estradiol Transdermal System Worn for 7 Days PROTOCOL NUMBER ORTH-09198		
Hour	**Arithmetic Mean (%CV) A = Mylan**	**Arithmetic Mean (%CV) B = Ortho Evra®**
24	95.00 (0.0%)	95.00 (0.0%)
48	95.00 (0.0%)	95.00 (0.0%)
72	95.00 (0.0%)	95.00 (0.0%)
96	95.00 (0.0%)	94.74 (1.7%)
120	95.00 (0.0%)	95.00 (0.0%)
144	95.00 (0.0%)	95.00 (0.0%)
168	95.00 (0.0%)	95.00 (0.0%)
Cumulative Mean	95.00 (0.0%)	94.96 (0.2%)

Source: Appendix 16.1.1

Rating Scale for Assessing Patch Adhesion:

Adhesion	Score
>90% to ≤100%	95
>80% to 90%	85
>70% to 80%	75
>60% to 70%	65
>50% to 60%	55
>40% to 50%	45
>30% to 40%	35
>20% to 30%	25
>10% to 20%	15
0% (Falloff*) to 10%	5

Table 1 of HOUR by SCORE
Controlling for TREAT=A

HOUR	SCORE		
Frequency	85	95	Total
24	0	38	38
48	0	38	38
72	0	38	38
96	0	38	38
120	0	38	38
144	0	38	38
168	0	38	38
Total	0	266	266

Table 2 of HOUR by SCORE
Controlling for TREAT=B

HOUR	SCORE		
Frequency	85	95	Total
24	0	38	38
48	0	38	38
72	0	38	38
96	1	37	38
120	0	38	38
144	0	38	38
168	0	38	38
Total	1	265	266

The composition of the test product is shown below.

Table Ia: Pharmaceutical Function of Components, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Adhesive Matrix

Components	Pharmaceutical Function	% w/w	mg/ patch	Maximum Level listed in the FDA *IID*[1] (mg)	Quality Standards
Active Ingredients					
Norelgestromin	Active Ingredient	2.31	4.86	NA	(b) (4)
Ethinyl Estradiol, USP (b) (4)	Active Ingredient	0.25	0.53	NA	
Inactive Ingredients					
Polyisobutene Adhesive	(b) (4)				
Oleyl Alcohol, NF					
Dipropylene Glycol					
(b) (4) Mineral Oil, NF					
Crospovidone, NF					
(b) (4)					
Theoretical Total Matrix		100.00	210.00		

(b) (4)

Table Ib: Pharmaceutical Function of Components, Formula Justification with FDA Inactive Ingredient Database and Quality Standards for Other Components of Norelgestromin and Ethinyl Estradiol Transdermal System

Components	Pharmaceutical Function	mg/ patch	Maximum Level listed in the FDA *IID* [1] (mg)	Quality Standards
Polyethylene/ Polyester Film	(b) (4)			
Brown Ink				
Nonwoven Polyester				
Fluoropolymer Coated Polyester Film				

Table IIa: Quantitative Composition of Adhesive Matrix Components of Mylan's Norelgestromin and Ethinyl Estradiol Transdermal System

Components	% w/w	Basis Weight (g/m^2)[1]	mg/patch	kg per batch (360 m^2)
Active Ingredients				
Norelgestromin	2.31	3.47	4.86	1.249
Ethinyl Estradiol, USP (b) (4)	0.25	0.38	0.53	0.135
Inactive Ingredients				
Polyisobutene Adhesive	(b) (4)			
Oleyl Alcohol, NF				
Dipropylene Glycol				
(b) (4) Mineral Oil, NF				
Crospovidone, NF				
(b) (4)				
Total	**100.00**	**150.00**	**210.00**	**123.871**

Table IIb: Quantitative Composition of Components of Other Components of Norelgestromin and Ethinyl Estradiol Transdermal System

Components	Basis Weight (g/m^2)	mg/patch
Polyethylene/ Polyester Film	(b) (4)	
Brown Ink		
Nonwoven Polyester		
Fluoropolymer Coated Polyester Film		

Mylan's Norelgestromin and Ethinyl Estradiol Transdermal System – A 14.0 cm^2 patch that contains 4.86 mg of norelgestromin and 0.53 mg of ethinyl estradiol. It is a (b) (4) patch (b) (4) consisting of a peach-colored backing film (b) (4) printed with "Norelgestromin and Ethinyl Estradiol" in brown ink, an adhesive layer containing a non-woven polyester, (b) (4) (b) (4) release liner. Each individual patch is packaged (b) (4) protective (b) (4) pouch.

Comments to be conveyed to the sponsor:

Your skin irritation/sensitization study (orth-0943) and adhesion study (orth-09198) are acceptable for receiving your ANDA.

Please submit the following additional information for the review:

1. A frequency table for dermal response, "other effects" and combined scores (dermal response score plus other effects score) for test and reference product for each patch application day (e.g., day 8, 15, 22) during induction phase and for Day 38, 39, 30 and 41 during challenge phase is requested for the review.
2. The dataset "orth0943irr.xpt" included a column of "other effects" (i.e., IND_C1) but no scores were reported. Please explain the reason for the missing data.
3. Please provide dermal response score, "other effects" score, combination of dermal response and other effects scores in the primary dataset (SAS .xpt file).
4. Please submit adhesion data in SAS .xpt file. The dataset should include at least the following variables: subject, treatment, period, evaluator, included in the adhesion analysis (yes/no), reason for discontinuation or exclusion, adhesion scores at each adhesion assessment time points.
5. Please provide a list of concomitant medications used during the study and adverse events in SAS .xpt file.
6. In general, the data submission should include the following details in the primary dataset:

1) 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.

2) 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 or RLD)
   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. Per Protocol (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	RUA	21	2	Y	
101	1	01	54	YEARS	M	1	B	LUA	21	2	Y	
101	2	01	45	YEARS	M	2	A	RUA	21	2	Y	
101	2	01	45	YEARS	M	2	B	LUA	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 Draft dated 7/25/07.

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, E=test overlay, F=reference overlay
EXLOC: Location of Dose Administration (exposure): specific anatomical site of patch application, e.g., RUA=right upper arm, LUA=left upper arm
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: Per Protocol (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: Per Protocol (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 8 adhesion scoring due to AE that was not intolerable irritation, B=failed to complete Day 8 adhesion scoring due to lost to follow-up, C=failed to complete Day 8 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

3) For the Irritation, Sensitization and Adhesion 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, RLD)
   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 scores (e.g., Hours 0-7 days)
   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 each site
   r. Challenge “Other Effects” letter score for each 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	RUA	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 Draft dated 7/25/07.

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, E=test overlay, F=reference overlay
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., RUA=right upper arm, LUA=left upper arm
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. to Day 8)
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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200910	ORIG-1	MYLAN TECHNOLOGIES	ETHINYL ESTRADIOL;NORELGESTROMIN

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
04/12/2010

DENA R HIXON
04/12/2010
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200910

CHEMISTRY REVIEWS

(b) (4)

CHEMISTRY REVIEW

FINAL Version for DARRTS – 12/17/13
CMC is Adequate. EES, Labeling and Bio are Adequate.

Chemist/Guohua Li/12/17/13
Team Leader/Bhagwant Rege/12/17/13
DDD/Bing Cai/12/17/13
PM/Jasmeet Kalsi/12/17/13

ANDA 200910

CR #5

Norelgestromin and Ethinyl Estradiol Transdermal System
0.15 mg/24 hours and 0.02 mg/24 hours
(7-day patch)

Mylan Technologies Inc.

Guohua Li
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 200910

2. REVIEW #: 5

3. REVIEW DATE: 11/08/2013

4. REVIEWER: Guohua Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	December 31, 2009
Minor Amendment	March 17, 2010
Minor Amendment	September 24, 2010
Review #1	October 30, 2010
Minor Amendment (SD #11, #12)	July 29, 2011
Review #2	October 28, 2011
Minor Amendment	April 5, 2012
Review #3	May 7, 2012
Minor Amendment (SD #20)	July 30, 2012
Review #4	February 18, 2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment (SD #28)	August 20, 2013
Minor Amendments (SD #31, #32)	October 15, 2013
ECD (SD #34)	November 27, 2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Technologies Inc
Address:	110 Lake Street St. Albans, VT 05478
Representative:	S. Wayne Talton, VP, Regulatory Affairs 781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310

Telephone: 304-599-2595 ext. 6551
Fax: 802-527-8155

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Norelgestromin and ethinyl estradiol

9. LEGAL BASIS FOR SUBMISSION:

The basis for this ANDA submission is the RLD Ortho Evra® (NDA 21180) manufactured by Ortho-McNeil-Janssen Pharmaceuticals. The applicant has filed **paragraph IV** certification for the following U.S. Patents: 5,876,746 (expires on November 20, 2015) and 5,972,377 (expires on June 7, 2015). The applicant also certifies that there is no unexpired exclusivity.

10. PHARMACOLOGICAL CATEGORY: Contraceptive

11. DOSAGE FORM: Transdermal System

12. STRENGTH/POTENCY:

0.15 mg Norelgestromin and 0.02 mg Ethinyl Estradiol per 24 hours

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

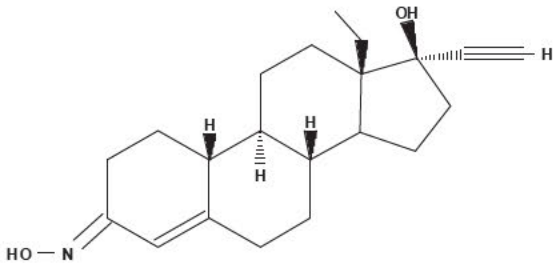
__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Norelgestromin

Chemical Name: (17α)-13-ethyl-17-hydroxy-18,19-dinorpregn-4-en-20yn-3-one-oxime
18,19-dinorpregn-4-en-20-yn-3-one, 13-ethyl-, 17-hydroxy, 3-oxime, (17α)-

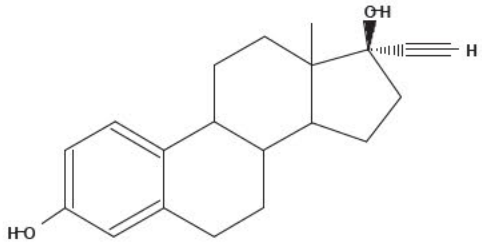
Chemical Structure:



Molecular Formula: $C_{21}H_{29}NO_2$
Molecular Weight: 327.47

Ethinyl Estradiol
Chemical Names: 19-Nor-17□-pregna-1,3,5(10)-trien-20-yne-3,17□-diol
17□-Ethynylestra-1,3,5(10)-triene-3,17□-diol
19-Norpregna-1,3,5(10)-trien-20-yne-3,17□-diol, (17□□-

Chemical Structure:



Molecular Formula: $C_{20}H_{24}O_2$
Molecular Weight: 296.41

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	12/12/2013	Guohua Li
	II			3	Adequate	12/17/2013	NAI by Guohua Li
	IV			1	Adequate	5/4/2012	S. Read
	IV			3	Adequate	4/25/2011	S. Read
11404	IV	Mylan		4	NA		Per CR #4
(b) (4)	IV	(b) (4)		4	NA		Per CR #4
	III			4	NA		Per CR #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 NA (There is enough data in the application, therefore the DMF did not need to be reviewed)

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

$ New submission dated 04/11/2013 (SD #19) is found adequate.
* New submission dated 11/25/2013 (SD #181) was NAI'ed with changes in holder of the DMF (API facilities will remain unchanged) and change in US agent name.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Tox Consult	OGD-2011-0517	(b) (4) in adhesive Conclusion: See DARRTS 11/21/11

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	10/10/13	
Methods Validation	NA		
Labeling	Adequate	11/12/2013	Imam Malik
Bioequivalence -dissolution -Bio portion	 Adequate Adequate	 11/11/2013 09/06/2013	Suman Dandamudi
Clinical	Inadequate	05/14/2013	Nicole Lee
EA	Categorical Exclusion Requested		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 200910

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC is adequate.

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)

The ethinyl estradiol is compendial. It is a white to creamy white, odorless, crystalline powder, which is insoluble in water, soluble in chloroform, alcohol, ether, vegetable oils, and in the solutions of alkali hydroxides.

The drug substance, norelgestromin is a white or almost white powder with very low aqueous solubility. It exists as a mixture of two geometrical isomers (anti and syn) which have the same activity and are present in the ratio of 1.3 to 1.5.

The drug product is a transdermal drug delivery system for contraception consisting of two drug substances (norelgestromin and ethinyl estradiol) and (b) (4) oleyl alcohol, in polyisobutylene adhesive matrix. The transdermal system contains 4.86 mg of norelgestromin and 0.53 mg ethinyl estradiol per 14 cm^2 patch, delivering 150 ug of norelgestromin and 20 ug of ethinyl estradiol per day over a 7 day period.

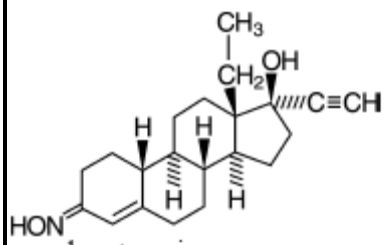
1. Description of How the Drug Product is Intended to be Used

Three active patches, one each, during first three weeks of a cycle designed to deliver to the systemic circulation 0.15 mg norelgestromin and 0.02 mg ethinyl estradiol daily. followed by a 'no-patch' week is the recommended regimen.

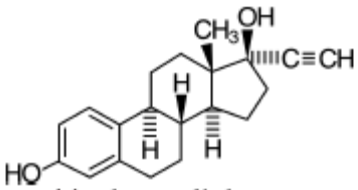
From Draft Labeling:

Norelgestromin and ethinyl estradiol transdermal systems are packaged with additional pieces of protective film above and below the system within each pouch. These pieces of protective film are removed and discarded at the time of use.

The structural formulas of the components are:



norelgestromin



ethinyl estradiol

Molecular weight, norelgestromin: 327.47

Molecular weight, ethinyl estradiol: 296.41

Chemical name for norelgestromin: 18, 19-dinorpregn-4-en-20-yn-3-one, 13-ethyl- 17-hydroxy-, 3-oxime, (17α)

Chemical name for ethinyl estradiol: 19-Norpregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol, (17α)

Special Precautions for Storage and Disposal

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

Store patches in their protective pouches. Apply to the skin immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

C. Basis for Approvability or Not-Approval Recommendation

CMC is adequate.

II. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200910 APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 h and 0.02 mg/24 h.

Sincerely yours,

Andre Raw, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemist/Guohua Li/12/17/13
Team Leader/Bhagwant Rege/12/17/13
DDD/Bing Cai/12/17/13
PM/Jasmeet Kalsi/12/17/13

CMC is adequate.

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
12/19/2013

JASMEET K KALSI
12/19/2013

BHAGWANT D REGE
12/19/2013

BING CAI
12/19/2013

ANDA 200910
CR #4

Norelgestromin and Ethinyl Estradiol Transdermal System
0.15 mg/24 hours and 0.02 mg/24 hours
(7-day patch)

Mylan Technologies Inc.

Shanaz Read
Chemistry Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 200910

2. REVIEW #: 4

3. REVIEW DATE: September 7, 2012, revised January, 18, 2013, Feb 5, 2013

4. REVIEWER: Shanaz Read

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Acknowledgement Letter	April 19, 2010
Original Submission	December 31, 2009
Minor Amendment	March 17, 2010
Minor Amendment	September 24, 2010
Review #1	October 30, 2010
Minor Amendment (SD #11, #12)	July 29, 2011
Review #2	October 28, 2011
Minor Amendment	April 5, 2012
Review #3	May 7, 2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	July 30, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Technologies Inc
Address:	110 Lake Street St. Albans, VT 05478
Representative:	S. Wayne Talton, VP, Regulatory Affairs 781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Telephone:	304-599-2595 ext. 6551
Fax:	802-527-8155

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: NA
   b) Non-Proprietary Name (USAN): Norelgestromin and ethinyl estradiol

9. LEGAL BASIS FOR SUBMISSION:
The basis for this ANDA submission is the RLD Ortho Evra® (NDA 21180) manufactured by Ortho-McNeil-Janssen Pharmaceuticals. The applicant has filed **paragraph IV** certification for the following U.S. Patents: 5,876,746 (expires on November 20, 2015) and 5,972,377 (expires on June 7, 2015). The applicant also certifies that there is no unexpired exclusivity.

10. PHARMACOLOGICAL CATEGORY: Contraceptive

11. DOSAGE FORM: Transdermal System

12. STRENGTH/POTENCY:
0.15 mg Norelgestromin and 0.02 mg Ethinyl Estradiol per 24 hours

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
____ SPOTS product – Form Completed

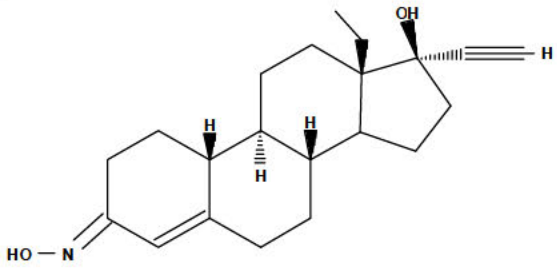
__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Norelgestromin

Chemical Name: (17α)-13-ethyl-17-hydroxy-18,19-dinorpregn-4-en-20yn-3-one-oxime
18,19-dinorpregn-4-en-20-yn-3-one, 13-ethyl-, 17-hydroxy, 3-oxime, (17α)-

Chemical Structure:

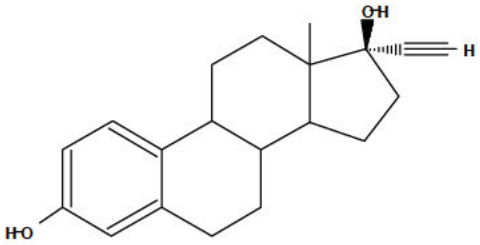


Molecular Formula: $C_{21}H_{29}NO_2$
Molecular Weight: 327.47

Ethinyl Estradiol

Chemical Names: 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17β-diol
17α-Ethynylestra-1,3,5(10)-triene-3,17β-diol
19-Norpregna-1,3,5(10)-trien-20-yne-3,17β-diol, (17α)-

Chemical Structure:



Molecular Formula: $C_{20}H_{24}O_2$
Molecular Weight: 296.41

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	5/7/2012	S. Read
	II			3	Adequate	06/14/2012	by S. Dhanesar
	IV			1	Adequate	5/4/2012	S. Read
	IV			3	Adequate	4/25/2011	S. Read
11404	IV	Mylan		4	NA		
(b) (4)	IV	(b) (4)		4	NA		
	III			4	NA		

[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 NA (There is enough data in the application, therefore the DMF did not need to be reviewed)

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Tox Consult	OGD-2011-0517	(b) (4) in adhesive Conclusion: See DARRTS 11/21/11

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	1/30/12	A. Inyard
Methods Validation	NA		
Labeling	Acceptable (Pending proprietary name review)	9/28/12	M. Imam
Bioequivalence	Pending		
EA	Categorical Exclusion Requested		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 200910

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable for CMC.

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)

The ethinyl estradiol is compendial. It is a white to creamy white, odorless, crystalline powder, which is insoluble in water, soluble in chloroform, alcohol, ether, vegetable oils, and in the solutions of alkali hydroxides.

The drug substance, norelgestromin is a white or almost white powder with very low aqueous solubility. It exists as a mixture of two geometrical isomers (anti and syn) which have the same activity and are present in the ratio of 1.3 to 1.5.

The drug product is a transdermal drug delivery system for contraception consisting of two drug substances (norelgestromin and ethinyl estradiol) and (b) (4) oleyl alcohol, in polyisobutylene adhesive matrix. The transdermal system contains 4.86 mg of norelgestromin and 0.53 mg ethinyl estradiol per 14 cm^2 patch, delivering 150 ug of norelgestromin and 20 ug of ethinyl estradiol per day over a 7 day period.

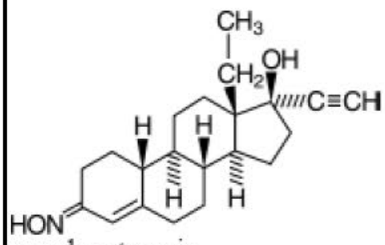
B. Description of How the Drug Product is Intended to be Used

Three active patches, one each, during first three weeks of a cycle designed to deliver to the systemic circulation 0.15 mg norelgestromin and 0.02 mg ethinyl estradiol daily. followed by a 'no-patch' week is the recommended regimen.

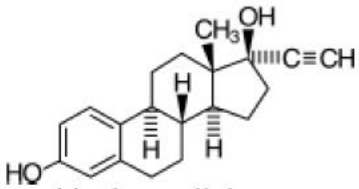
From Draft Labeling:

Norelgestromin and ethinyl estradiol transdermal systems are packaged with additional pieces of protective film above and below the system within each pouch. These pieces of protective film are removed and discarded at the time of use.

The structural formulas of the components are:



norelgestromin



ethinyl estradiol

Molecular weight, norelgestromin: 327.47

Molecular weight, ethinyl estradiol: 296.41

Chemical name for norelgestromin: 18, 19-dinorpregn-4-en-20-yn-3-one, 13-ethyl- 17-hydroxy-, 3-oxime, (17α)

Chemical name for ethinyl estradiol: 19-Norpregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol, (17α)

Special Precautions for Storage and Disposal

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

Store patches in their protective pouches. Apply to the skin immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

C. Basis for Approvability or Not-Approval Recommendation

Firm has to resolve the CMC issue described in the deficiency letter.

II. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200910 APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 h and 0.02 mg/24 h.

A. The deficiency presented below represents MINOR deficiency.

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". To ensure this, the ANDA applicant should provide information about the formulation performance to ensure that the sensitivity to in-use conditions like heat /hot water exposure 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 release data to the RLD at normal and "stress" situations: 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 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

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

cc: ANDA 200910
DIV FILE

Endorsements:

HFD-645/SRead/9/7/12, 1/18/13, 2/5/13

HFD-640/BRege/ 9/20/2012; 2/5/13

HFD-617/ T.Trang/ Echuh 10/5/12; TT 2/6/13

TYPE OF LETTER: Not Approvable. CMC is inadequate. Labeling and EES are AC. Pending Bio and proprietary name reviews.

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

/s/

SHAHNAZ T READ
02/08/2013

TRANG Q TRAN
02/08/2013

BHAGWANT D REGE
02/08/2013

BING CAI
02/18/2013

ANDA 200910
CR #3

Norelgestromin and Ethinyl Estradiol Transdermal System
0.15 mg/24 hours and 0.02 mg/24 hours
(7-day patch)

Mylan Technologies Inc.

Shanaz Read
Chemistry Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 200910

2. REVIEW #: 3

3. REVIEW DATE: May 7, 2012

4. REVIEWER: Shanaz Read

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Acknowledgement Letter	April 19, 2010
Original Submission	December 31, 2009
Minor Amendment	March 17, 2010
Minor Amendment	September 24, 2010
Review #1	October 30, 2010
Minor Amendment (SD #11, #12)	July 29, 2011
Review #2	October 28, 2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	April 5, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Technologies Inc
Address:	110 Lake Street St. Albans, VT 05478
Representative:	S. Wayne Talton, VP, Regulatory Affairs 781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Telephone:	304-599-2595 ext. 6551
Fax:	802-527-8155

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: NA
   b) Non-Proprietary Name (USAN): Norelgestromin and ethinyl estradiol

9. LEGAL BASIS FOR SUBMISSION:
The basis for this ANDA submission is the RLD Ortho Evra® (NDA 21180) manufactured by Ortho-McNeil-Janssen Pharmaceuticals. The applicant has filed **paragraph IV** certification for the following U.S. Patents: 5,876,746 (expires on November 20, 2015) and 5,972,377 (expires on June 7, 2015). The applicant also certifies that there is no unexpired exclusivity.

10. PHARMACOLOGICAL CATEGORY: Contraceptive

11. DOSAGE FORM: Transdermal System

12. STRENGTH/POTENCY:

0.15 mg Norelgestromin and 0.02 mg Ethinyl Estradiol per 24 hours

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

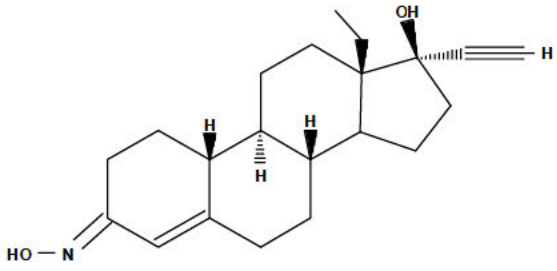
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Norelgestromin
Chemical Name: (17α)-13-ethyl-17-hydroxy-18,19-dinorpregn-4-en-20yn-3-one-oxime
18,19-dinorpregn-4-en-20-yn-3-one, 13-ethyl-, 17-hydroxy, 3-oxime, (17α)-

Chemical Structure:



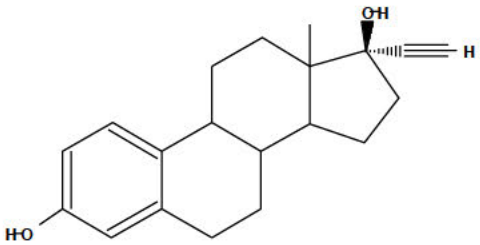
Molecular Formula: $C_{21}H_{29}NO_2$

Molecular Weight: 327.47

Ethinyl Estradiol

Chemical Names: 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17β-diol
17α-Ethynylestra-1,3,5(10)-triene-3,17β-diol
19-Norpregna-1,3,5(10)-trien-20-yne-3,17β-diol, (17α)-

Chemical Structure:



Molecular Formula: $C_{20}H_{24}O_2$
Molecular Weight: 296.41

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	5/7/2012	By S. Read
	II			3	Adequate	06/14/2012	by S. Dhanesar
	IV			1	Adequate	5/4/2012	
	IV			3	Adequate	04/25/2011	
11404	IV	Mylan		4	NA		
(b) (4)	IV	(b) (4)		4	NA		
	III			4	NA		

[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 NA (There is enough data in the application, therefore the DMF did not need to be reviewed)

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Tox Consult	OGD-2011-0517	(b) (4) in adhesive Conclusion: See DARRTS 11/21/11

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	1/30/12	A. Inyard
Methods Validation	NA		
Labeling	Acceptable	6/19/12	M. Imam
Bioequivalence	Pending		
EA	Categorical Exclusion Requested		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 200910

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable for CMC.

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)

The ethinyl estradiol is compendial. It is a white to creamy white, odorless, crystalline powder, which is insoluble in water, soluble in chloroform, alcohol, ether, vegetable oils, and in the solutions of alkali hydroxides.

The drug substance, norelgestromin is a white or almost white powder with very low aqueous solubility. It exists as a mixture of two geometrical isomers (anti and syn) which have the same activity and are present in the ratio of 1.3 to 1.5.

The drug product is a transdermal drug delivery system for contraception consisting of two drug substances (norelgestromin and ethinyl estradiol) and (b) (4) oleyl alcohol, in polyisobutylene adhesive matrix. The transdermal system contains 4.86 mg of norelgestromin and 0.53 mg ethinyl estradiol per 14 cm^2 patch, delivering 150 ug of norelgestromin and 20 ug of ethinyl estradiol per day over a 7 day period.

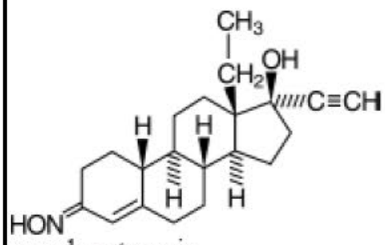
B. Description of How the Drug Product is Intended to be Used

Three active patches, one each, during first three weeks of a cycle designed to deliver to the systemic circulation 0.15 mg norelgestromin and 0.02 mg ethinyl estradiol daily. followed by a 'no-patch' week is the recommended regimen.

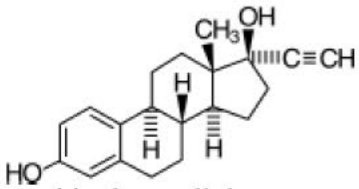
From Draft Labeling:

Norelgestromin and ethinyl estradiol transdermal systems are packaged with additional pieces of protective film above and below the system within each pouch. These pieces of protective film are removed and discarded at the time of use.

The structural formulas of the components are:



norelgestromin



ethinyl estradiol

Molecular weight, norelgestromin: 327.47

Molecular weight, ethinyl estradiol: 296.41

Chemical name for norelgestromin: 18, 19-dinorpregn-4-en-20-yn-3-one, 13-ethyl- 17-hydroxy-, 3-oxime, (17α)

Chemical name for ethinyl estradiol: 19-Norpregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol, (17α)

Special Precautions for Storage and Disposal

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

Store patches in their protective pouches. Apply to the skin immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

C. Basis for Approvability or Not-Approval Recommendation

Firm has to resolve CMC issues listed in the deficiency letter.

II. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200910 APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 h and 0.02 mg/24 h.

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)

2.

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

We encourage you to apply Quality by Design (QbD) principles to the pharmaceutical development of your future original ANDA product submissions. A risk-based, scientifically sound submission would be expected to include the following:

- Quality target product profile (QTPP)
- Critical quality attributes (CQAs) of the drug product
- Product design and understanding including identification of critical attributes of excipients, drug substance(s), and/or container closure systems
- Process design and understanding including identification of critical process parameters and in-process material attributes
- Control strategy and justification

An example illustrating QbD concepts can be found online at FDA's **Generic Drugs: Information for Industry** webpage: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf

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

cc: ANDA 200910
DIV FILE

Endorsements:

HFD-645/SRead/5/7/12

HFD-640/BRege/7/10/2012

HFD-617/TTran/7/16/12

TYPE OF LETTER: Not Approvable

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

/s/

SHAHNAZ T READ
07/19/2012

TRANG Q TRAN
07/19/2012

BHAGWANT D REGE
07/19/2012

ANDA 200910
CR #2

Norelgestromin and Ethinyl Estradiol Transdermal System
0.15 mg/24 hours and 0.02 mg/24 hours
(7-day patch)

Mylan Technologies Inc.

Shanaz Read
Chemistry Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 200910

2. REVIEW #: 1

3. REVIEW DATE: October 28, 2010

4. REVIEWER: Shanaz Read

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Acknowledgement Letter	April 19, 2010
Original Submission	December 31, 2009
Minor Amendment	March 17, 2010
Minor Amendment	September 24, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment (SD #11, #12)	July 29, 2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Technologies Inc
Address:	110 Lake Street St. Albans, VT 05478
Representative:	S. Wayne Talton, VP, Regulatory Affairs 781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Telephone:	304-599-2595 ext. 6551
Fax:	304-285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: NA
   b) Non-Proprietary Name (USAN): Norelgestromin and ethinyl estradiol

9. LEGAL BASIS FOR SUBMISSION:

The basis for this ANDA submission is the RLD Ortho Evra® (NDA 21180) manufactured by Ortho-McNeil-Janssen Pharmaceuticals. The applicant has filed **paragraph IV** certification for the following U.S. Patents: 5,876,746 (expires on November 20, 2015) and 5,972,377 (expires on June 7, 2015). The applicant also certifies that there is no unexpired exclusivity.

10. PHARMACOLOGICAL CATEGORY: Contraceptive

11. DOSAGE FORM: Transdermal System

12. STRENGTH/POTENCY:

0.15 mg Norelgestromin and 0.02 mg Ethinyl Estradiol per 24 hours

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

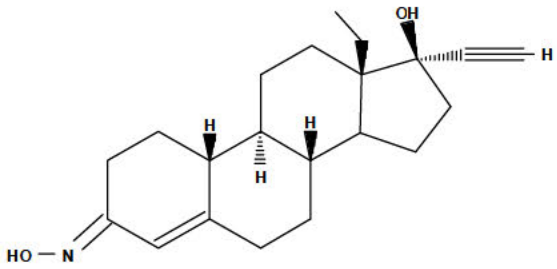
__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Norelgestromin

Chemical Name: (17α)-13-ethyl-17-hydroxy-18,19-dinorpregn-4-en-20yn-3-one-oxime
18,19-dinorpregn-4-en-20-yn-3-one, 13-ethyl-, 17-hydroxy, 3-oxime, (17α)-

Chemical Structure:

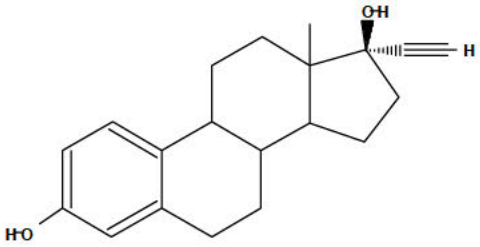


Molecular Formula: $C_{21}H_{29}NO_2$
Molecular Weight: 327.47

Ethinyl Estradiol

Chemical Names: 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17β-diol
17α-Ethynylestra-1,3,5(10)-triene-3,17β-diol
19-Norpregna-1,3,5(10)-trien-20-yne-3,17β-diol, (17α)-

Chemical Structure:



Molecular Formula: $C_{20}H_{24}O_2$
Molecular Weight: 296.41

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	4/25/2011	Last found adequate 4/25/11New information will be reviewed at next review cycle.
	II			3	Adequate	12/20/2010	by N. Takiar
	IV			1	Inadequate	10/26/2011	
	IV			3	Adequate	04/25/2011	
11404	IV	Mylan		4	NA		
(b) (4)	IV	(b) (4)		4	NA		
	III			4	NA		

[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 NA (There is enough data in the application, therefore the DMF did not need to be reviewed)

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Tox Consult	OGD-2011-0517	(b) (4) in adhesive Conclusion: See DARRTS 11/21/11

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending		
Methods Validation	NA		
Labeling	Deficiency	11/15/2011	C Hoppes
Bioequivalence	Pending		
EA	Categorical Exclusion Requested		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 200910

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable for CMC, minor amendment.

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)

The ethinyl estradiol is compendial. It is a white to creamy white, odorless, crystalline powder, which is insoluble in water, soluble in chloroform, alcohol, ether, vegetable oils, and in the solutions of alkali hydroxides.

The drug substance, norelgestromin is a white or almost white powder with very low aqueous solubility. It exists as a mixture of two geometrical isomers (anti and syn) which have the same activity and are present in the ratio of 1.3 to 1.5.

The drug product is a transdermal drug delivery system for contraception consisting of two drug substances (norelgestromin and ethinyl estradiol) and (b) (4) oleyl alcohol, in polyisobutylene adhesive matrix. The transdermal system contains 4.86 mg of norelgestromin and 0.53 mg ethinyl estradiol per 14 cm^2 patch, delivering 150 ug of norelgestromin and 20 ug of ethinyl estradiol per day over a 7 day period.

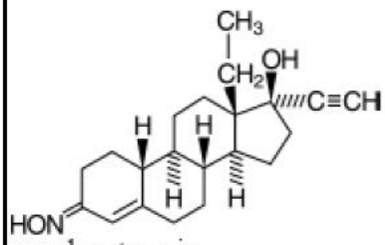
B. Description of How the Drug Product is Intended to be Used

Three active patches, one each, during first three weeks of a cycle designed to deliver to the systemic circulation 0.15 mg norelgestromin and 0.02 mg ethinyl estradiol daily. followed by a 'no-patch' week is the recommended regimen.

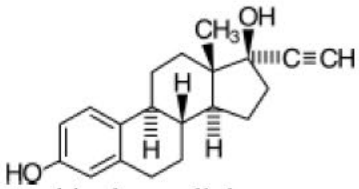
From Draft Labeling:

Norelgestromin and ethinyl estradiol transdermal systems are packaged with additional pieces of protective film above and below the system within each pouch. These pieces of protective film are removed and discarded at the time of use.

The structural formulas of the components are:



norelgestromin



ethinyl estradiol

Molecular weight, norelgestromin: 327.47

Molecular weight, ethinyl estradiol: 296.41

Chemical name for norelgestromin: 18, 19-dinorpregn-4-en-20-yn-3-one, 13-ethyl- 17-hydroxy-, 3-oxime, (17α)

Chemical name for ethinyl estradiol: 19-Norpregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol, (17α)

Special Precautions for Storage and Disposal

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

Store patches in their protective pouches. Apply to the skin immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

C. Basis for Approvability or Not-Approval Recommendation

Firm needs to resolve issues as described in the deficiency letter.

II. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200910

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 h and 0.02 mg/24 h

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

9. Please provide updated stability data for the exhibit batch(es).

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

cc: ANDA 200910
DIV FILE

Endorsements:

HFD-645/SRead/10/28/11, 12/14/11

HFD-620/BCai/

HFD-617/EChuh/ 11/28/11

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

/s/

SHAHNAZ T READ
12/19/2011

EUNJUNG E CHUH
12/20/2011

BING CAI
12/20/2011

ANDA 200910
CR #1

Norelgestromin and Ethinyl Estradiol Transdermal System
0.15 mg/24 hours and 0.02 mg/24 hours
(7-day patch)

Mylan Technologies Inc.

Shanaz Read
Chemistry Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 200910

2. REVIEW #: 1

3. REVIEW DATE: October 30, 2010

4. REVIEWER: Shanaz Read

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Acknowledgement Letter	April 19, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	December 31, 2009
Minor Amendment	March 17, 2010
Minor Amendment	September 24, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Technologies Inc
Address:	110 Lake Street St. Albans, VT 05478
Representative:	S. Wayne Talton, VP, Regulatory Affairs 781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Telephone:	304-599-2595 ext. 6551
Fax:	304-285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA

b) Non-Proprietary Name (USAN): Norelgestromin and ethinyl estradiol

9. LEGAL BASIS FOR SUBMISSION:

The basis for this ANDA submission is the RLD Ortho Evra® (NDA 21180) manufactured by Ortho-McNeil-Janssen Pharmaceuticals. The applicant has filed **paragraph IV** certification for the following U.S. Patents: 5,876,746 (expires on November 20, 2015) and 5,972,377 (expires on June 7, 2015). The applicant also certifies that there is no unexpired exclusivity.

10. PHARMACOLOGICAL CATEGORY: Contraceptive

11. DOSAGE FORM: Transdermal System

12. STRENGTH/POTENCY:

0.15 mg Norelgestromin and 0.02 mg Ethinyl Estradiol per 24 hours

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

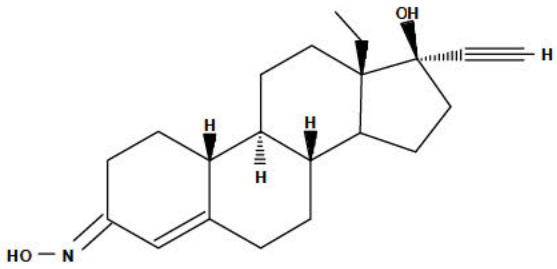
__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Norelgestromin

Chemical Name: (17α)-13-ethyl-17-hydroxy-18,19-dinorpregn-4-en-20yn-3-one-oxime
18,19-dinorpregn-4-en-20-yn-3-one, 13-ethyl-, 17-hydroxy, 3-oxime, (17α)-

Chemical Structure:

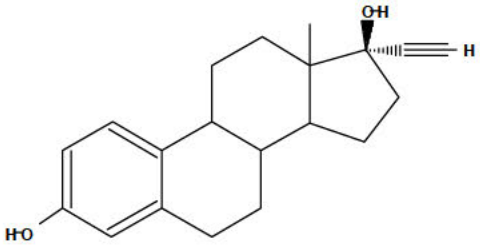


Molecular Formula: $C_{21}H_{29}NO_2$
Molecular Weight: 327.47

Ethinyl Estradiol

Chemical Names: 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17β-diol
17α-Ethynylestra-1,3,5(10)-triene-3,17β-diol
19-Norpregna-1,3,5(10)-trien-20-yne-3,17β-diol, (17α)-

Chemical Structure:



Molecular Formula: $C_{20}H_{24}O_2$
Molecular Weight: 296.41

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	10/18/2010	
	II			3	Adequate	12/20/2010	by N. Takiar
	IV			1	Inadequate	10/25/2010	
	IV			1	Adequate	11/1/2010	
11404	IV	Mylan		4	NA		
(b) (4)	IV	(b) (4)		4	NA		
	III			4	NA		

[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 NA (There is enough data in the application, therefore the DMF did not need to be reviewed)

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending		
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Pending		
EA	Categorical Exclusion Requested		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 200910

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable for CMC.

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)

The ethinyl estradiol is compendial. It is a white to creamy white, odorless, crystalline powder, which is insoluble in water, soluble in chloroform, alcohol, ether, vegetable oils, and in the solutions of alkali hydroxides.

The drug substance, norelgestromin is a white or almost white powder with very low aqueous solubility. It exists as a mixture of two geometrical isomers (anti and syn) which have the same activity and are present in the ratio of 1.3 to 1.5.

The drug product is a transdermal drug delivery system for contraception consisting of two drug substances (norelgestromin and ethinyl estradiol) and (b) (4) oleyl alcohol, in polyisobutylene adhesive matrix. The transdermal system contains 4.86 mg of norelgestromin and 0.53 mg ethinyl estradiol per 14 cm^2 patch, delivering 150 ug of norelgestromin and 20 ug of ethinyl estradiol per day over a 7 day period.

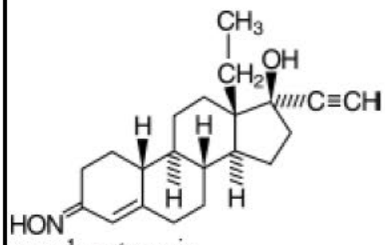
B. Description of How the Drug Product is Intended to be Used

Three active patches, one each, during first three weeks of a cycle designed to deliver to the systemic circulation 0.15 mg norelgestromin and 0.02 mg ethinyl estradiol daily. followed by a 'no-patch' week is the recommended regimen.

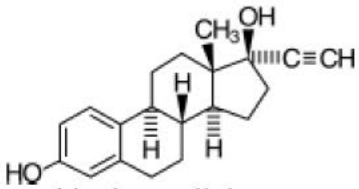
From Draft Labeling:

Norelgestromin and ethinyl estradiol transdermal systems are packaged with additional pieces of protective film above and below the system within each pouch. These pieces of protective film are removed and discarded at the time of use.

The structural formulas of the components are:



norelgestromin



ethinyl estradiol

Molecular weight, norelgestromin: 327.47

Molecular weight, ethinyl estradiol: 296.41

Chemical name for norelgestromin: 18, 19-dinorpregn-4-en-20-yn-3-one, 13-ethyl- 17-hydroxy-, 3-oxime, (17α)

Chemical name for ethinyl estradiol: 19-Norpregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol, (17α)

Special Precautions for Storage and Disposal

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

Store patches in their protective pouches. Apply to the skin immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

C. Basis for Approvability or Not-Approval Recommendation

Firm needs to resolve issues as described in the deficiency letter.

Following this page, 82 Pages Withheld in Full as (b)(4)

II. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200910

APPLICANT: Mylan Techonologies, Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 h and 0.02 mg/24 h.

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.
9.
10.

(b) (4)

11.

12.

13.

14.

15.

16.

17.

18.

19.

20.

21.

22.

23. (b) (4)

24.

25.

26.

27.

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

1. The labeling and bioequivalence portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate cover.

2. Please provide updated stability data for the exhibit batches.

3. (b) (4)

Sincerely yours,

{See appended electronic signature page}

Paul Schwartz, Ph.D
Acting Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 200910
DIV FILE

Endorsements:

HFD-645/SRead/10/30/10

HFD-620/BCai/

HFD-617/EChuh/ 4/29/2011

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

/s/

SHAHNAZ T READ
05/27/2011

EUNJUNG E CHUH
05/27/2011

BING CAI
05/27/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200910

PHARM/TOX REVIEWS

OGD request for P/T consult- Memo to the file

Date: 11/18/2011

ANDA #: 200910 Safety Amendment

Date of submission: 7/29/2011

Consult request by: OGD

Consult number: FRM-Consult – 01

Reviewer: Krishan L. Raheja, D. V. M., Ph.D.

Through: Alex Jordan, Ph.D. Expert P/T Reviewer

To: Shahnaz T Read

Sponsor: Mylan Technologies

Drug Product: Ethinyl Estradiol/Norelgestromin Transdermal System

Indication: Contraception

Date submitted for P/T Consult review: 10/31/2011

Desired Completion Date: 12/27/2011

Subject: Specification for (b) (4) in the (b) (4) set at (b) (4) ppm.

Background: (b) (4) It is an important industrial compound used in the production of medical adhesives found in various medical applications including transdermal drug product formulations.

Currently there is no entry for (b) (4) in the Inactive Ingredients Database nor is there any entry in the CFR for its approved use. However, a number of entries are present for polyisobutylene in these sources in which (b) (4) is likely to be present. In this regard, (b) (4) may be safely used and are approved for use in trandermal films and patches.

Purpose of the consult: The purpose of the P/T consult is to review the available safety information on (b) (4) to provide an assessment of its safety in the proposed

transdermal product. Sponsor has provided information on the safety of (b) (4) based on available published and unpublished information for P/T evaluation.

Preclinical toxicology: (b) (4) has been studied in a set of experiments including acute, subacute, subchronic and reproductive toxicity in various species via oral and inhalation routes of exposure. Additionally, mutagenic activity and clastogenic activity has been assessed in variety of in vitro and in vivo assays and in carcinogenicity studies in rats and mice by the inhalation administration. Sponsor has stated that summary reviews of toxicity have also been completed by the EPA, NTP, European Chemicals Bureau and the OECD.

NB: (b) (4) it is unclear to this reviewer how the oral toxicity studies were conducted. Similarly, it is not stated how the in vitro mutagenicity studies were conducted.

(b) (4)

Following this page, 2 Pages Withheld in Full as (b)(4)

(b) (4)

Sponsor's Conclusion: Based on the proposed specification of (b) (4) ppm for impurity (b) (4) in (b) (4) used in the manufacture of Mylan's Norelgestromin and Ethinyl Estradiol Transdermal System, the maximum potential exposure to (b) (4) is calculated to be (b) (4) per day under the worst assumption that all (b) (4) potentially in the raw material is present in the final product formulation and subject exposed to all of the (b) (4) during the first 24 hours of the 7-day application.

P/T comments: Mylan proposed limit specification for the impurity, (b) (4) of not more than (b) (4) ppm in the (b) (4) adhesive used in the manufacture of Mylan's Norelgestromin and Ethinyl Estradiol Transdermal System is based on the following calculations:

The Norelgestromin/Ethinyl Estradiol TDS is available in a single strength and contains a total of (b) (4) polyisobutylene adhesive. Based on a specification of NMT (b) (4) ppm for (b) (4) in (b) (4) adhesive raw material with solid content range of (b) (4)%, the maximum potential (b) (4) in finished transdermal product is (b) (4) Thus maximum exposure will be (b) (4)/24 hours if all (b) (4) is released during the first 24 hours after patch application. If however, it is released at a constant rate, the daily exposure will be (b) (4)/kg/day).

The above calculation does not take in to account that it is (b) (4) As such the daily exposure to (b) (4) may be lower than (b) (4) as calculated above.

P/T Recommendations: Preclinical toxicology of (b) (4) has been studied in acute, subacute, subchronic, chronic and reproductive toxicity in various animal species via oral and inhalation routes of exposure. (b) (4) mutagenic potential and clastogenic activity has been assessed in both in vitro and in vivo models and in two carcinogenicity trials in rodents following inhalation administration.

(b) (4)

Furthermore, although not mentioned, Ortho Evra (Norelgestromin 6 mg/EE 0.75 mg) approved under NDA 21-180 has polyisobutylene adhesive and has been used as a contraceptive without any significant toxicity.

Based on the information provided, Pharmacology/Toxicology considers that the sponsor's proposed specification for the impurity, (b) (4) of no more than (b) (4) ppm is safe as used in the Norelgestromin and Ethinyl Estradiol Transdermal System for the approved contraceptive indication and is acceptable from the P/T perspective.

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
11/21/2011

ALEXANDER W JORDAN
11/21/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200910

STATISTICAL REVIEWS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL ANALYSIS FOR

ADHESION WAIVER

AMENDMENT TO THE STATISTICAL REVIEW

CLINICAL STUDIES

ANDA/Serial Number:	200910
Drug Name:	Norelgestromin/Ethinyl Estradiol Transdermal System, 14 cm^2, 0.15mg/0.02 mg/day
Indication(s):	Prevention of pregnancy in women
Reference Listed Drug:	Ortho Evra®, 20 cm^2, 0.15mg/0.02 mg/day Janssen-Ortho, LLC
Applicant:	Mylan Technologies Inc.
Date(s):	February 3, 2014
Biometrics Division:	DBVI
Statistical Reviewer:	Vicki A. Lancaster, Ph.D., Generics Team, DBVI/OB/CDER
Concurring Reviewers:	Stella C. Grosser, Ph.D., Generics Team Leader, DBVI/OB/CDER
Medical Division:	Division of Clinical Reviewers OGD/OPS/CDER
Clinical Team:	Sarah Seung, Pharm.D., DCR/OGD/OPS/CDER
Keywords:	Estradiol, Crossover Design, Patch Adhesion

TABLE OF CONTENTS

List of Tables

1. Executive Summary

1.1 Conclusions and Recommendations

The adherence of the TEST product is 100% throughout the duration of wear for 100% of the patches. This statistical review and evaluation of the adhesion data submitted for ANDA 200910 support approval.

1.2 Brief Overview of the Clinical Study

The primary objective of this study was to evaluate the adhesion of Mylan's norelgestromin/ethinyl estradiol transdermal (NEETS) patch to Ortho Evra® patch manufactured by Janssen Ortho, LLC following a 7 day application of one Ortho Evra® or one Mylan NEETS patch for two treatment periods.

This was an open-label, single-dose, randomized, two-period, two-treatment, crossover study investigating the adhesive properties of Mylan's norelgestromin/ethinyl estradiol 0.15 mg/0.02 mg/day transdermal system to Ortho Evra® transdermal system, 0.15 mg/0.02 mg/day manufactured by Janssen Ortho, LLC for Ortho Women's Health & Urology. Forty (40) healthy female volunteers were enrolled in the study. Each subject wore each patch for 7 days. No washout period was required for this study. The second patch was applied as soon as possible after the first patch was removed. Adhesion was assessed every 24 hours the patch was worn. Each subject that completed the study had seven measurements taken 24, 48, 72, 96, 120, 144, and 168 hours after application.

Adhesion Scoring and Endpoint

For assessment of adhesion, Mylan employed a 10-point scale where a score of '95' indicated > 90% to ≤ 100% adhered to the skin, while a score of '5' meant the transdermal system was completely detached from the skin. The Mylan 10-point scale was converted to the FDA recommended scale prior to statistical analysis. The conversion template is provided in Table 1.

Table 1. FDA and Mylan Adhesion Scales

Mylan Adhesion Scale		Conversion to FDA adhesion scale
Adhesion: > 90% to ≤ 100%	95	0 (essentially no lift-off from the skin)
Adhesion: > 80% to ≤ 90%	85	1 (some edges only lifting off the skin)
Adhesion: > 70% to ≤ 80%	75	1
Adhesion: > 60% to ≤ 70%	65	2 (< ½ of the system lifting off the skin)
Adhesion: > 50% to ≤ 60%	55	2
Adhesion: > 40% to ≤ 50%	45	3 (> ½ the system lifting off the skin without falling off)
Adhesion: > 30% to ≤ 40%	35	3
Adhesion: > 20% to ≤ 30%	25	3
Adhesion: > 10% to ≤ 20%	15	3
Adhesion: > 0% to ≤ 10%	5	4 (patch completely off the skin)

Statistician Note: Conversion from the Mylan to the FDA scale does not impact the inferential analysis. All measurements except one indicated perfect adhesion throughout the duration of wear.

The endpoint is the mean adhesion score calculated as the sum of the observed scores divided by the total number of observations.

Patient Disposition

Forty subjects were planned for enrollment and 40 subjects were initially dosed in the study. Thirty-seven subjects completed the clinical portion of the study. The adhesion data for 38 of 40 subjects was used in the statistical analysis.

- Subject 09 voluntarily withdrew consent during Period II.
- Subject 11 was discontinued from the study during Period I due to non-compliance (exposed patch to excessive water).
- Subject 12 voluntarily withdrew consent during Period II, but had an adequate number of adhesion scores to be included in the statistical analysis as required by the protocol.

The adhesion per-protocol population included 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.

1.3 Statistical Issues

Table 2. Distribution of Adhesion Scores by Product over Time

Hour	Product	0	1	2	3	4
24	RLD	38	0	0	0	0
	TEST	38	0	0	0	0
48	RLD	38	0	0	0	0
	TEST	38	0	0	0	0
72	RLD	38	0	0	0	0
	TEST	38	0	0	0	0
96	RLD	37	1	0	0	0
	TEST	38	0	0	0	0
120	RLD	38	0	0	0	0
	TEST	38	0	0	0	0
144	RLD	38	0	0	0	0
	TEST	38	0	0	0	0
168	RLD	38	0	0	0	0
	TEST	38	0	0	0	0

The FDA recommended statistical analysis for adhesion data proposed in the *Draft Guidance on Estradiol* relies on the normal distribution for evaluating non-inferiority. The guidance recommends, "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." The guidance makes no provision for a scenario where the normality assumption does not hold and there is no between or within subject variability as is the case for the adhesion data from ANDA 200910. Table 2 summarizes the responses for the TEST and RLD over the duration of wear; all TEST measurements are 0 and there is only one non-zero RLD measurement. The distribution of the adhesion data from ANDA 200910 requires an alternative approach for making inferences.

The science staff in the Office of Generic Drugs, proposed an alternative approach for making inferences in their document *Waiver of Statistical Non-Inferiority Analysis for Highly Adhering Patch Drug Products* on February 10, 2014. In lieu of the FDA recommended approach, the data are summarized based on an approach described in the in the 2012 European Medicines Agency's (EMA) *Draft Guidance on Quality Transdermal Patches*. The EMA document 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."

The FDA has incorporated this idea in the waiver document. This document states that,

> "…, 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."

1.4 Statistical Analysis

For both the TEST and RLD products the mean adherence is greater than 90%. The adherence of the TEST product is 100% adherence throughout the duration of wear for 100% of the patches.

2. References

Food and Drug Administration Draft Guidance on Estradiol, November 2010.
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234962.pdf

European Medicines Agency Draft Guideline on Quality of Transdermal Patches, August 23, 2012.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/09/WC500132404.pdf

Waiver of Statistical Non-Inferiority Analysis for Highly Adhering Patch Drug Products, February 10, 2014.

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

/s/

STELLA C GROSSER
02/14/2014
document entered into DARRTS on behalf of Vicki Lancaster, stat reviewer

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

ANDA 200-910
Drug Product: Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day.
Sponsor: Mylan Pharmaceuticals Inc.
Drug Class: Combination Transdermal Contraceptive Patch.

Reference Listed Drug: Ortho-Evra® Transdermal System (Ortho McNeil Janssen Pharmaceuticals, Inc., NDA: 021-180, Approved 11/20/2001).

Approved Indication(s): ORTHO EVRA® is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.

Dosing Regimen: This system uses a 28-day (four-week) cycle. A new patch is applied each week for three weeks (21 total days). Week four is patch-free. Withdrawal bleeding is expected during week four. Every new patch should be applied on the same day of the week.

Submission dates: December 23, 2009.

Biometrics Division:	DB6
Statistical Reviewer:.	Mohamed Nagem, Ph.D.
Concurring Reviewers:	Stella Grosser, Ph.D., Team Leader
Medical Division:	Division of Clinical Review, OGD
Clinical Team:	Nicole Lee, Pharm. D.
Keywords:	Irritation, sensitization, norelgestromin, estradiol, Transdermal.

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Objectives of the studies (ORTH-0943 & ORTH-09198)

According to the sponsor, the primary objectives of this study #ORTHO-0943were to compare the cumulative irritation and sensitization potential of Mylan's norelgestromin/ethinyl estradiol transdermal system (0.15 mg/0.02 mg/day) to Ortho's Ortho Evra® (0.15 mg/0.02 mg/day) in two hundred (225) healthy subjects.

In addition, the sponsor (Mylan) also conducted study #ORTH-09198 for adhesion performance. The primary objective of this study was to compare the adhesive properties of test and reference patches following a single application in 40 healthy subjects.

Background

Norelgestromin (NGMN) is the active progestin largely responsible for the progestational activity that occurs in women following application of Ortho Evra®. Norelgestromin is also the primary active metabolite produced following oral administration of norgestimate (NGM). Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus, which increase the difficulty of sperm entry into the uterus, and changes in the endometrium, which may reduce the likelihood of implantation. Receptor and human sex hormone-binding globulin (SHBG) binding studies, as well as studies in animals and humans, have shown that both NGM and NGMN exhibit high progestational activity with minimal intrinsic androgenicity. Transdermally-administered norelgestromin, in combination with ethinyl estradiol (EE), does not counteract the estrogen-induced increases in SHBG, resulting in lower levels of free testosterone in serum compared to baseline.

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 and NGMN over a seven-day period, while oral contraceptives (containing NGM 250 μg / EE 35 μg) are administered on a daily basis.

Study: Study #ORTH-0943

Title: Comparative Evaluation of the Cumulative Irritation and Contact Sensitization Potential of the Test (Norelgestromin/Ethinyl Estradiol Transdermal System (NEETS) (0.15 mg/0.02 mg/day: Mylan) to the Reference (Ortho Evra® (0.15 mg/0.02 mg/day: Ortho)) in Healthy Female Volunteers.

Design of Study:

This was an open-label, multiple dose, randomized application site, two-treatment, three-phase, one-period study investigating the human dermal safety of Mylan's norelgestromin/ethinyl estradiol transdermal system (NEETS) (0.15 mg/0.02 mg/day) compared to Ortho's Ortho Evra® transdermal system (0.15 mg/0.02 mg/day).

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Inclusion Criteria: Subjects could participate if they met the following inclusion criteria:

1. Age: 18 to 35 years old.
2. Sex: Non-pregnant, non-lactating female.
   a. Women of childbearing potential who had a negative serum beta human chorionic gonadotropin (β-HCG) pregnancy tests performed within 28 days prior to the start of the study and prior to each transdermal system application. An additional serum (β-HCG) pregnancy test was performed upon completion of the study.
   b. Women of childbearing potential were required to practice abstinence or use an acceptable form of contraception from 7 days before dosing until 30 days post final patch removal. The subjects were notified that they were not protected from pregnancy during this study. This requirement was documented in the informed consent form. Acceptable forms of contraception included the following:
      i. barrier methods containing or used in conjunction with a spermicidal agent, or
      ii. surgical sterilization

   c. Women were not considered of childbearing potential if one of the following was reported and documented on the medical history:
      i. postmenopausal with spontaneous amenorrhea for at least one (1) year, or
      ii. bilateral oophorectomy with or without a hysterectomy and an absence of bleeding for at least 6 months, or
      iii. total hysterectomy and an absence of bleeding for at least 3 months
3. Weight: At least 48 kg (106 lbs) with all subjects having a Body Mass Index (BMI) less than or equal to 35 but greater than or equal to 19.
4. All subjects were judged by the principal or sub-investigator physician listed on the Form FDA 1572 as normal and healthy during a pre-study medical evaluation performed within 28 days of the initial dose of study medication which included:
   a. a normal or non-clinically significant physical examination, including vitals signs
   b. within normal limits or non-clinically significant laboratory evaluation results for the following tests
      i. 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
      ii. Hematology: Platelet Count, Leukocyte Count with Differential, Hemoglobin, Hematocrit, Red Blood Cell Count
      iii. Urinalysis: Appearance, Specific Gravity, Protein, pH, Microscopic Examination (performed based on clinical judgment)
      iv. Additional tests may have been performed, if necessary
   c. negative Hepatitis B and Hepatitis C tests,
   d. negative HIV test,
   e. normal or non-clinically significant 12-lead ECG
   f. negative urine drug screen for all of the following compounds: amphetamines, barbiturates, benzodiazepines, cannabinoid, cocaine, methadone, opiates, and phencyclidine
   g. if warranted, tests for sexually transmitted diseases (STD) may have been performed at the discretion of the Principal Investigator or responsible physician.

5. The pre-study physical examination included breast and pelvic exams including a Pap smear performed as follows:
   a. The breast examination must be preformed within 28 days of the initial dose administration.
   b. A pelvic exam including a Pap smear was required on subjects if one had not been performed within the 6 months prior to dosing. Subjects provided written documentation of normal results from their physician.

Exclusion Criteria: Subjects could not be enrolled if they met any of the following exclusion criteria:

1. Institutionalized
2. History of skin diseases (eczema, psoriasis, atopic dermatitis).
3. Social Habits:
   a. Use of any tobacco-containing products within 1 year of the start of the study.
   b. Any recent, significant change in dietary or exercise habits.
   c. A positive test for any drug included in the urine drug screen.
   d. History of drug and/or alcohol abuse.
4. Medications:
   a. Use of any prescription or over-the-counter (OTC) systemic or topical analgesics or antihistamines within 72 hours of initial patch application or use of systemic or topical corticosteroids within 3 weeks of initial patch application.
   b. A depot injection or implant of any drug within 3 months prior to administration of study medication.
   c. Use of any medication or herbal products known to inhibit CYP3A4 enzyme activity within 7 days prior to the initial dose of study medication
5. Diseases:
   a. 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 Sub-Investigator.
   b. Acute illness at the time of either the pre-study medical evaluation or dosing.
   c. History of severe allergic reaction.
   d. Thrombotic disorders, especially thrombophlebitis or pulmonary embolism.
   e. Coronary artery or cerebrovascular disease.
   f. Liver or kidney dysfunction/disorders.
   g. Gall bladder disease.
   h. Fibrocystic disease or breast nodules.
   i. Family history of breast cancer (direct genetic link, i.e. mother, sister, etc.).
   j. Diabetes or any other endocrinological disease.
   k. Estrogen-dependent neoplasia.
   l. Cervical dysplasia.
6. Subjects who had an acute illness at the time of either the screening evaluation or patch application(s).
7. Damaged skin in or around test sites that included sunburn, uneven skin tones, tattoos, scars, or other disfigurations of the test site.

8. Donation or loss of a significant volume of blood or plasma (>450 mL) within 28 days prior to the initial dose of study medication.
9. Subjects who had received an investigational drug within 30 days prior to the initial patch application and/or participated in any transdermal system or patch study for irritation or sensitization within the last 4 weeks.
10. Sunbathing or the use of tanning salons for 7 days prior to transdermal system application.
11. Use of perfumes, body lotions, or oils within 7 days prior to transdermal system application.
12. Allergy or hypersensitivity to tapes or adhesives (ex. Band-aids, medical tape), isopropyl alcohol, progestins, estrogens, other hormonal products, or to any other component of product.
13. Consumption of grapefruit or grapefruit-containing products within 7 days of drug administration.

Study Conduct:

Treatments included patch applications once a week for three weeks. Subjects received one half patch of Mylan's norelgestromin/ethinyl estradiol transdermal system and one half patch of Ortho's Ortho Evra® transdermal system simultaneously once a week for three weeks. A 14-day rest phase followed with a subsequent 48-hour challenge phase. The challenge phase was followed by a 3 day observation and irritation evaluation. Within two weeks afterwards subjects had a post study clinical and laboratory evaluation to assess their health condition after drug administration. Patches were applied to test sites on the abdomen according to the application site randomization. The edges of the patches were marked with a surgical marker to ensure patch reapplication at the same site. Within 60 minutes prior to the first application and following the 30 minute irritation evaluation for all other applications, the test sites were wiped gently three times with a warm water washcloth, then lightly patted dry with a soft towel. The skin was completely dry before any patches were applied.

(a) Induction/Irritation Period:

The patches were removed 168 hours + 2 hours after application. Patch applications were made once weekly for 21 days. The three applications (per transdermal system) performed during this three-week phase were designated Applications 1 through 3, respectively. The appropriate transdermal system was re-applied to the identical site until after the third 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 the 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 appropriately documented and diagrammed. All other treatment applications continued as scheduled. If a subject developed a reaction of 3 or greater, according to the irritation rating scale found in Appendix 3 of the protocol (Appendix 16.1.1), the subject did not have any further transdermal systems applied to the same application site during the Induction phase of the study. The original application site continued to be evaluated until a reaction score of 0 was achieved. This score was recorded separately. In this case, any reapplications for Induction were made at a designated alternate site and appropriately documented and diagrammed. All other treatment applications continued as scheduled.

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

(b) Rest Phase:
A rest period (no patch applications) of 14 days followed Induction application 3.

(c) Sensitization Evaluation-Challenge Phase:
Following the Rest Phase, a Challenge application of one half patch of 0.15 mg/0.02 mg/day norelgestromin/ethinyl estradiol transdermal system (Mylan) and one half patch of 0.15 mg/ 0.02 mg/day Ortho Evra® transdermal system simultaneously applied to a clean, dry area of the skin on the abdomen (naïve site) according to the application site randomization. Transdermal systems were removed at 48 hours (+ 2 hours) after application. Irritation was assessed at 0.5, 24, 48, and 72 hours after removal of the Transdermal system, according to the irritation rating scale.

Outcome Variables

Induction/Irritation Skin Reaction Evaluations

During the Induction/Irritation Period, the test sites were evaluated at visits 2-10, 30 minutes after patch removal. Subjects who missed one of the Induction/Irritation visits 2-10 returned for a make-up visit for evaluation. Irritation, including superficial effects, was measured using an eight-point numeric and six-point alphabetic scale.

Irritation scale: Dermal Response (per key on Irritation Raw Data Listing):

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

Effects on superficial layers of the skin:

0(A)	Slight glazed appearance
1(B)	Marked glazing
2(C)	Glazing with peeling and cracking
3(F)	Glazing with fissures
3(G)	Film of dried serous exudates covering all or part of the patch site
3(H)	Small petechial erosions and/or scabs

In the Irritation and Sensitization analyses, the letter Scores were converted to numeric Scores as follows: A=0; B=1; C=2; F through I =3). The combined Score equaled the sum of the numerical Score "dermal response" and Letter Score.

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Primary Endpoint:

Irritation: The primary endpoint for Statistical Analysis of Dermal Irritation is the mean Irritation Score, that is, (cumulative Irritation Score)/3, since there are 3 Irritation scores measured at three different visits.

Contact Sensitization: The primary endpoint for Statistical Analysis of contact Sensitization is the dichotomized (Sensitized / Not Sensitized) Dermal response at the end of the challenge phase (Day 41 or 40 Days from baseline). A subject was classified as Sensitized if the dermal response (total of numeric score + letter score) was greater than or equal to a Score of 2.

Statistical Analysis Methods

Analysis Populations:

Evaluable population (EP): This population was based on individual patches and should only include those patches for subjects:

- Who met inclusion/exclusion criteria,
- Did not violate protocol,
- For whom no Patch was detached for longer than 24 hours,
- Who were within the visit window (± 4 hours), and completed the study,
- Did not take any prohibited concomitant medications or,
- Have any other significant protocol violations.

The determination of Non-inferiority was assessed using the evaluable population (EP).

Analysis of Cumulative Irritation (Induction/Cumulative Irritation Phase):

The primary analysis to evaluate irritation is to compare the mean Irritation Scores of the Test Product to that of the Reference product at the end of the Induction/Cumulative Irritation phase.

The Non-inferiority analyses were based on the estimated ratio of the least squares means (of the mean irritation scores) of the Test Product and the Reference product along with its 90% confidence interval. If the 95% Upper confidence bound for the quantity $\mu_T - 1.25\mu_R$ is less than or equal to zero, we can conclude that the Test Product is Non-inferior to the Reference product. An ANOVA model where treatment was a fixed effect and subject was a random effect was used for Non-inferiority analyses. The SAS® (Version 9.1) PROC MIXED statements used are as follows:

```
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;
```

Analysis of Contact Sensitization (Challenge Phase):

The sponsor did not perform a statistical analysis for contact Sensitization, but only argued that no evidence of sensitization reaction was observed.

Remark: This reviewer analyzed the dichotomized (Sensitized / Not Sensitized) Dermal response at the end of the challenge phase (Day 41). A subject was classified as Sensitized if the dermal response was greater than or equal to a Score of 2.

To assess the Non-inferiority of the Test product to Reference product, a 95% upper confidence bound for the difference of the proportions, $p_t - p_r$, was calculated, based on results published by McNemar.

Let p_t = Sensitization rate of the Test product, p_r = Sensitization rate of the Reference product.
Let n = number of subjects, b = number of subjects Sensitized to the Test product but not to the Reference product, and c = number of subjects Sensitized to the Reference product but not to the Test product.

The difference $p_t - p_r$ may be estimated by the quantity $(b - c)/n$.
A 95% upper confidence bound 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 on page 117 of Statistical Methods for Rates and Proportions (second edition, 1981) by Joseph L. Fleiss.
For any given Non-inferiority bound δ, the null hypothesis H_0 may be rejected if the 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. Specification of the appropriate non-inferiority bound δ is a policy decision by the Office of Generic Drugs.

Statistical Analysis Results

A total of 225 subjects was enrolled in the study. Of these, 216 subjects completed the Induction Cumulative Irritation Phase and entered the challenge phase. For potential contact sensitization, at the end of the Challenge phase only 214 subjects completed the study and were qualified to be included in the evaluable population analysis.

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Table 1 - Population distributions

Population	**Cumulative Irritation (N = 225)**
Subjects Enrolled	225 (100%)
Patients Excluded from Evaluable Population (EP)	9 (4%)
Total Patients in the Evaluable Population (EP)	216 (96%)

Demographic characteristics:
The population at baseline consisted of 204 subjects who are white, 1 subject who is Asian, 7 subjects who are black and 4 subjects of other ethnicity.

Table 2 - Demographic characteristics (Enrolled subjects)

Age	
Max	35
Mean (std)	24 (5)
Min	18
Race	
Caucasian	204 (94.4%)
Asian	1 (0.5%)
Black	7 (3.2%)
Others	4 (1.9%)
Gender	
Male	0
Female	216 (100%)

Non-Inferiority Analyses: The Test product was found to be Non-inferior to the Reference product for the mean irritation score (primary endpoint). Therefore, the Irritation property of the Test product is no worse than that of the Reference product. The 95% upper confidence bounds for $\mu_T - 1.25\mu_R$ were calculated using PROC MIXED in SAS version 9.1. Table 3 summarizes the Non-inferiority analyses. Cumulative Irritation score results are similar to those of the Mean Irritation score as expected, since, the Mean Irritation score = Cumulative Irritation score/3.

For the test product to pass the Non-inferiority test, the upper confidence bound for the quantity $p_t - p_r$ needs to be ≤0.46% and 2.6% at Day 22 for a cut off point of 2 and 3 respectively.

Table 3- Non-inferiority Analyses -- PP population

Parameter	Test LS Mean	Reference LS Mean	95% Upper Bound of μ_T-1.25 x μ_R	Passed	p-value (μ_T- μ_R)
Mean Irritation Score	0.89	0.87	-0.17	Yes	0.260
Cumulative Irritation Score	2.67	2.62	-0.52	Yes	0.260
Irritation		Reference			
Dichotomized Irritation Score at Day 22 (Score ≥ 3)		Not Irritating	Irritating		
Test	Not Irritating	215	0		
	Irritating	0	1		

95% Upper bound (U*)	0.46%		
Parameter		Reference	
Dichotomized Irritation Score at Day 22 (Score ≥ 2)		Not Irritating	Irritating
Test	Not Irritating	195	4
	Irritating	4	13
95% Upper bound (U*)	2.62%		

U^* is the upper limit of the 90% confidence interval for $\mu_v - 1.25\mu_c$.

Table 4- Frequency of Irritation score (PP)

Frequency of Irritation Score per Patch Per Observation (EPP)							
Product/Score	0	1	2	3	4	5	Total Per Treatment
Test	125	477	43	1	0	2	648 (216x3)
Reference	132	474	39	1	0	2	648 (216x3)
Frequency of Maximum Irritation Score per Patch Per Subject (PP)							
Product/Score	0	1	2	3	4	5	Total Per Treatment
Test	13	170	31	1	0	1	216
Reference	10	176	28	1	0	1	216

Irritation Score		Score					
		0	1	2	3	4	5
Score at visit 1	Test	36	163	16	1	0	0
	Reference	30	172	13	1	0	0
Score at visit 2	Test	57	147	11	0	0	1
	Reference	62	143	10	0	0	1
Score at visit 3	Test	32	167	16	0	0	1
	Reference	40	159	16	0	0	1

Frequency of discontinued Patches

	Days From Baseline			
Patch	*7*	*14*	*21*	*Total*
Test				*0*
Reference	*11*			*11*
Total	*11*			***11***

Three of these 11 subjects were included in the Primary analyses (Subjects No 180, 202 and 222)

Non-inferiority analyses for Sensitization:

The primary endpoint for Statistical Analysis of contact Sensitization was defined by this reviewer as the dichotomized (Sensitized / Not Sensitized) Dermal response at the end of the challenge phase (Day 41). A subject was classified as Sensitized if the dermal response Score was greater than or equal to 2. No subject was Sensitized on Day 41, and only 1 subject on Day 40 was Sensitized (Vehicle Patch.)

Using Fleiss's confidence bound formula (see **Analysis of Contact Sensitization (Challenge Phase)** above) the Test product was found to be statistically better than or Non-inferior to the Reference product for the response rate, provided the Non-inferiority margin is set no lower than 0.77 percentage points for Day 40 and Day 41 respectively. The contact Sensitization property

of the Test product is better or no worse than that of the Reference product, since the upper bound of the 90% confidence interval of the difference is relatively small (0.77%).

Table 5 Contact Sensitization analyses

Parameter	Reference		
Sensitization at Day 41 (Score ≥ 2)		Sensitized	not Sensitized
Test	Sensitized	1	0
	not Sensitized	1	211
95% Upper Confidence bound (U*)	0.77 percentage points		
Parameter	Reference		
Sensitization at Day 40 (Score ≥ 2)		Sensitized	not Sensitized
Test	Sensitized	1	0
	not Sensitized	1	211
95% Upper Confidence bound (U*)	0.77 percentage points		

U* is the upper limit of the 90% confidence interval for $p_t - p_r$.

Because of the very low counts of sensitized subjects, there may be concerns about the accuracy of Fleiss's approximation and therefore the statistical test.

Table 6- Frequency of Sensitization score per patch per observation (PP)

Frequency of Sensitization score per patch per observation						
	Score					
Patch	**0**	**1**	**2**	**3**	**4**	Total
Test	526	305	25	0	0	856 (214x4)
Reference	549	280	27	0	0	856 (104x4)
Frequency of Maximum Sensitization score per Patch Per Subject (PP)						
Patch / Score	**0**	**1**	**2**	**3**	**4**	**Total**
Test	15	179	20			214
Reference	20	173	21			214

Subjects with Score of 2 Or higher in the challenge phase							
Subject /Patch	Induction phase			Challenge Phase			
	Day 8	Day 15	Day 22	Day 38	Day 39	Day 40	Day 41
31 / Test	1	1	1	2	2	2	1
31 / Reference	1	1	1	1	2	2	1
80 / Reference	1	1	1	1	2	2	2
106 / Test	1	0	2	2	2	2	2
106/ Reference	1	1	1	2	2	2	2

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Comments on the Sponsor's Analyses

According to the sponsor, 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. No re-challenge was performed.

Reviewer Comment:

The FDA's reviewer analysis (as shown in Table 6), confirmed that two subjects (#31, 106) were potentially sensitized to both the Test product and the Reference Patch. One additional subject (#80) was potentially sensitized to the reference product. Subjects 80 and 106 had a dermal response score of 2 or more at both 48 and 72 hours post challenge patch removal while subject 31 had a dermal response score of 2 at both 24 and 48 hours post challenge patch removal. Of these five patches, four had a dermal response no higher than a score of 1 during the induction phase. Subject 106 had a dermal score of 2 for the Test product on day 22 of the irritation phase.

Adhesion Study (Protocol #: ORTH-09198):

Title: Adhesion Evaluation Study of Norelgestromin/Ethinyl Estradiol Transdermal System (NEETS) Patch (0.15 mg/0.02 mg/day; Mylan) and Active Wear of Ortho Evra® Patch (0.15 mg/0.02 mg/day; Ortho- McNeil-Jannsen) in Normal Healthy Female Volunteers.

Objective: The primary objective of this study was to evaluate the adhesion of Mylan's norelgestromin/ethinyl estradiol transdermal (NEETS) patch to Ortho Evra® patch manufactured by Janssen Ortho, LLC following a 7 day application of one Ortho Evra® or one Mylan NEETS patch for two treatment periods.

Study Design:
According to the sponsor, this was an open-label, single-dose, randomized, two-period, two-treatment, crossover study investigating the adhesive properties of Mylan's norelgestromin/ethinyl estradiol 0.15 mg/0.02 mg/day transdermal system to Ortho Evra® transdermal system, 0.15 mg/0.02 mg/day manufactured by Janssen Ortho, LLC for Ortho Women's Health & Urology. Forty (40) healthy female volunteers were enrolled in the study and 37 subjects completed the study. The adhesion data for 38 subjects was used in the statistical analysis. Each subject wore each patch for 7 days. No washout period was required for this study. The second patch was applied as soon as possible after the first patch was removed. Adhesion was assessed every 24 hours the patch was worn.

Study Population: Same inclusion/exclusion criteria as protocol #ORTH-0943 (Irritation/Sensitization Study)

Procedures/Observations: Subjects were to wear one Ortho Evra® patch or one Mylan Neets patch with the treatments applied to the subject's right or left lower abdomen in a randomized fashion. Each subject wore each patch for 7 days. No washout period was required for this study. The second patch was applied as soon as possible after the first patch was removed. Adhesion

was assessed every 24 hours the patch was worn. All subjects returned to the clinical facility on Days 2 (24 hours), Day 3 (48 hours) Day 4 (72 hours) Day 5 (96 hours), Day 6 (120 hours) and Day 7 (144 hours) after patch application for patch adhesion evaluation. On Day 8 (168 hours) of Period 1 the patch was removed and another patch was applied (according to the randomization scheme). It was placed on the opposite side (right or left) of the abdomen from the previous patch. On Day 8 of Period 2, following removal of the patch, the End of Study Procedures were initiated. The following products were administered:

Treatment A: Norelgestromin/Ethinyl Estradiol Transdermal System, 14 cm^2, 0.15 mg/0.02 mg/day, Mylan Technologies Inc. (Mylan), Lot #R6A0014

Treatment B: Ortho Evra®, 20 cm^2, 0.15 mg/0.02 mg/day, Janssen Ortho, LLC, Lot # 7LM5212

Clinical reviewer's comments: *The sponsor used a different adhesion scale for assessing adhesion performance than that recommended by the OGD. The adhesion scale recommended by OGD is the following:*

Table –A

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)

Adhesion: *The primary analysis to evaluate the Mean Adhesion Score of the 7 post-baseline assessments (7 evaluations at 24, 48, 72, 96, 120, 144 and 168 hours) was to compare the Mean Adhesion Score of the Test and Reference products.*

Additional analyses were based on a secondary endpoint defined as the dichotomized (Adhered / Not Adhered) Adhesion Score at the end of the Adhesion study. A Patch was classified as Adhered if the Adhesion Score was less than or equal to a Score of 1.

- The Test product was to be considered better or Non-inferior to the Reference product if the upper limit of the 90% confidence interval for the quantity $\mu_T - 1.25\mu_R$ was less than or equal to zero.
- The least square means of the Test and Reference products were calculated, along with the 90% confidence interval for $\mu_T - 1.25\mu_R$. The SAS® (Version 9.1) PROC MIXED statements used are as follows:

```
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;
```

- The dichotomized (Adhered / Not Adhered) Adhesion Score was analyzed using the 95% upper confidence bound based on McNemar's results (Fleiss, 1981), as defined in the previous section "Analysis of Contact Sensitization"

Adhesion Analyses Results:

A total of 38 subjects completed the Adhesion study and were included in the PP population. The Test product was found to be inferior or worse than the Reference product for the Mean Adhesion Score (primary endpoint). That is, the Adhesion property of the Test product is worse than that of the Reference product. Additionally, analysis based on the dichotomized (Adhered / Not Adhered) endpoint showed that for the Test product to be Non-inferior to the Reference product, a Non-inferiority bound $\delta \geq 2.63$ percentage points would be required. Table 7 summarizes the Non-inferiority analyses.

It should be noted and emphasized that the Mean Adhesions Score of the Test product is zero(μ_T =0): i.e., all the Test's patches have essentially no lift off the skin) and is less than that of the Reference product (μ_R = 0.0038, where subject No 18 has an Adhesion Score of 1 at 96 hour), and therefore, according to the sponsor's data, we observed a better property as measured by the point estimate for the Test product than the Reference product. Clinical decision should be assessed with medical judgment as well as statistics.

Population	**Adhesion (N = 40)**
Subjects Enrolled	40 (100%)
Patients Excluded from Evaluable Population (EP)	2 (5%)
Total Patients in the Evaluable Population (EP)	38 (95%)

Table 7 –Adhesion analyses results (Non-inferiority) –PP population

Parameter	Test LS Mean	Reference LS Mean	95% Upper Bound of μT-1.25 x μR	Pass The Non-Inferiority Test?	p-value (μT-μR)
Mean Adhesion Score	0.0000	0.0038	0.0025	No	0.324
Cumulative Adhesion Score	0.000	0.026	0.02	No	0.324
Sponsor Adhesion score					
Mean Percentage Adhesion	95.00	94.96	-23.63	Yes	<.0001
Cumulative Percentage Adhesion	665.00	664.74	-165.42	Yes	<.0001
Dichotomized score (≤ 1)					
Dichotomized score (≤ 1)			Reference		
Adhesion (Score at Day 8)			Adhered	not Adhered	
Test		Adhered	38	0	
		not Adhered	0	0	
95% Upper bound (U*)	2.63%				**1.00**

U^* is the upper limit of the 90% confidence interval for $\mu_T - 1.25\mu_R$.
U^{**} is the 95% upper confidence bound for p_T-p_R.

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Table 8-Frequency of Adhesion score (PP)

Frequency of Adhesion score per Patch Per Observation (PP)						
	Score					
Patch	**0**	**1**	**2**	**3**	**4**	**Total**
Test	266					266 (38x7)
Reference *	265	1				266 (38x7)
Frequency of Maximum Adhesion Score per Patch Per Subject (PP)						
Product/Score	0	1	2	3	4	Total Per Treatment
Test	38					38
Reference *	37	1				38

*: Subject No 18 in the Reference product at visit 96 Hours

Adhesion Scores							
Hours	Adhesion Score Evaluation Day		0	Score 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

Comments on sponsor Adhesion Analyses:

The sponsor stated in their study report (page 18 of the Clinical review) that a one-sided hypothesis test was used to determine if the adhesion score of Mylan's NEETS was equivalent to or better than the Ortho Evra® (for the reference product). For the mean adhesion scores, the null and alternative hypotheses were: H0: $\mu 1/\mu 2 < 0.8$ and H1: $\mu 1/\mu 2 < 0.8$, which (assuming $\mu 2 > 0$) can be written as: H0: $\mu 1 - 0.8\mu 2 < 0$ and H1: $\mu 1 - 0.8\mu 2 > 0$, where $\mu 1$ is the mean adhesion score for the test product and $\mu 2$ is the mean adhesion score for the reference product. The null hypothesis H0 was rejected when the lower limit of the 90% confidence interval (that is the 95% lower confidence bound) for the quantity $\mu 1 - 0.8\mu 2$ was ≥ 0.

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

The sponsor's proposed statistical analysis is not acceptable. The OGD's recommended method is described on page 13 of this review. The sponsor's proposed statistical hypotheses are only appropriate when adhesion score is reversed, as described in the table below.

Reversed System Adherence	
Score	**Definitions**
4	≥90% adhered (essentially no lift off the skin)
3	≥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)
1	>0% to <50% adhered but not detached (more than half of the system lifting off the skin without falling off)
0	0% adhered-test system detached (test system completely off the skin)

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Conclusions:

Study #: ORTH-0943:

Irritation: The Test product was found to be Non-inferior to the Reference product for the mean irritation score (primary endpoint). Therefore, the Irritation property of the Test product is no worse than that of the Reference product.

Sensitization: Based on Fleiss's 95% upper confidence bound for the difference in Sensitization rates, the Test product rate may exceed the Reference Product rate by at most 0.77 percentage points based on the dermal response at both Day 40 and 41. The Test product was found to be statistically better or Non-inferior to the Reference product for the response rate, provided the Non-inferiority margin is set no lower than 0.77 percentage points for Day 41.

Study #: ORTH-09198:

Adhesion: The Test product was not found to be Non-inferior to the Reference product for the Mean Adhesion Score (primary endpoint), treating the Mean Adhesion Score as a continuous variable. However, the observed mean Adhesion score of the Test product in this study is better than that of the Reference product (see Table 7), indicating better adhesion property.

For the additional dichotomized endpoint, where a patch was classified as adhered if the adhesion score at the end of the study was 0 or 1, the 95% upper confidence bounds for the difference in the Adhesion rates of the Test and the Reference Products (p_T - p_R) is 2.63%. This upper confidence bound may be compared to any appropriate Non-inferiority bound δ that may be set by the Office of Generic Drugs. Clinical decision should be assessed with medical judgment as well as statistics.

_____
Mohamed Nagem, Ph.D.
Mathematical Statistician, DB6/OB

_____
Stella C. Grosser, Ph.D.
Mathematical Statistician,
Team Leader, DB6/OB

_____
Stella G. Machado, Ph.D.
Director, DB6/OB

cc: Original ANDA 2020-26, John Peters, Nicole Lee, Nitin K. Patel, OGD.

Stella Machado, Stella C. Grosser, Mohamed Nagem, DB6/OB/OTS

This review includes 17 pages.

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

/s/

MOHAMED O NAGEM

05/16/2013

The last table page 10, the title of the table should read: " "Frequency of discontinued Patches' .

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

ANDA 200-910
Drug Product: Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day.
Sponsor: Mylan Pharmaceuticals Inc.
Drug Class: Combination Transdermal Contraceptive Patch.

Reference Listed Drug: Ortho-Evra® Transdermal System (Ortho McNeil Janssen Pharmaceuticals, Inc., NDA: 021-180, Approved 11/20/2001).

Approved Indication(s): ORTHO EVRA® is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.

Dosing Regimen: This system uses a 28-day (four-week) cycle. A new patch is applied each week for three weeks (21 total days). Week four is patch-free. Withdrawal bleeding is expected during week four. Every new patch should be applied on the same day of the week.

Submission dates: December 23, 2009.

Biometrics Division:	DB6
Statistical Reviewer:.	Mohamed Nagem, Ph.D.
Concurring Reviewers:	Stella Grosser, Ph.D., Team Leader
Medical Division:	Division of Clinical Review, OGD
Clinical Team:	Nicole Lee, Pharm. D.
Keywords:	Irritation, sensitization, norelgestromin, estradiol, Transdermal.

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Objectives of the studies (ORTH-0943 & ORTH-09198)

According to the sponsor, the primary objectives of this study #ORTHO-0943were to compare the cumulative irritation and sensitization potential of Mylan's norelgestromin/ethinyl estradiol transdermal system (0.15 mg/0.02 mg/day) to Ortho's Ortho Evra® (0.15 mg/0.02 mg/day) in two hundred (225) healthy subjects.

In addition, the sponsor (Mylan) also conducted study #ORTH-09198 for adhesion performance. The primary objective of this study was to compare the adhesive properties of test and reference patches following a single application in 40 healthy subjects.

Background

Norelgestromin (NGMN) is the active progestin largely responsible for the progestational activity that occurs in women following application of Ortho Evra®. Norelgestromin is also the primary active metabolite produced following oral administration of norgestimate (NGM). Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus, which increase the difficulty of sperm entry into the uterus, and changes in the endometrium, which may reduce the likelihood of implantation. Receptor and human sex hormone-binding globulin (SHBG) binding studies, as well as studies in animals and humans, have shown that both NGM and NGMN exhibit high progestational activity with minimal intrinsic androgenicity. Transdermally-administered norelgestromin, in combination with ethinyl estradiol (EE), does not counteract the estrogen-induced increases in SHBG, resulting in lower levels of free testosterone in serum compared to baseline.

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 and NGMN over a seven-day period, while oral contraceptives (containing NGM 250 μg / EE 35 μg) are administered on a daily basis.

Study: Study #ORTH-0943

Title: Comparative Evaluation of the Cumulative Irritation and Contact Sensitization Potential of the Test (Norelgestromin/Ethinyl Estradiol Transdermal System (NEETS) (0.15 mg/0.02 mg/day: Mylan) to the Reference (Ortho Evra® (0.15 mg/0.02 mg/day: Ortho)) in Healthy Female Volunteers.

Design of Study:

This was an open-label, multiple dose, randomized application site, two-treatment, three-phase, one-period study investigating the human dermal safety of Mylan's norelgestromin/ethinyl estradiol transdermal system (NEETS) (0.15 mg/0.02 mg/day) compared to Ortho's Ortho Evra® transdermal system (0.15 mg/0.02 mg/day).

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Inclusion Criteria: Subjects could participate if they met the following inclusion criteria:

1. Age: 18 to 35 years old.
2. Sex: Non-pregnant, non-lactating female.
   a. Women of childbearing potential who had a negative serum beta human chorionic gonadotropin (β-HCG) pregnancy tests performed within 28 days prior to the start of the study and prior to each transdermal system application. An additional serum (β-HCG) pregnancy test was performed upon completion of the study.
   b. Women of childbearing potential were required to practice abstinence or use an acceptable form of contraception from 7 days before dosing until 30 days post final patch removal. The subjects were notified that they were not protected from pregnancy during this study. This requirement was documented in the informed consent form. Acceptable forms of contraception included the following:
      i. barrier methods containing or used in conjunction with a spermicidal agent, or
      ii. surgical sterilization

   c. Women were not considered of childbearing potential if one of the following was reported and documented on the medical history:
      i. postmenopausal with spontaneous amenorrhea for at least one (1) year, or
      ii. bilateral oophorectomy with or without a hysterectomy and an absence of bleeding for at least 6 months, or
      iii. total hysterectomy and an absence of bleeding for at least 3 months
3. Weight: At least 48 kg (106 lbs) with all subjects having a Body Mass Index (BMI) less than or equal to 35 but greater than or equal to 19.
4. All subjects were judged by the principal or sub-investigator physician listed on the Form FDA 1572 as normal and healthy during a pre-study medical evaluation performed within 28 days of the initial dose of study medication which included:
   a. a normal or non-clinically significant physical examination, including vitals signs
   b. within normal limits or non-clinically significant laboratory evaluation results for the following tests
      i. 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
      ii. Hematology: Platelet Count, Leukocyte Count with Differential, Hemoglobin, Hematocrit, Red Blood Cell Count
      iii. Urinalysis: Appearance, Specific Gravity, Protein, pH, Microscopic Examination (performed based on clinical judgment)
      iv. Additional tests may have been performed, if necessary
   c. negative Hepatitis B and Hepatitis C tests,
   d. negative HIV test,
   e. normal or non-clinically significant 12-lead ECG
   f. negative urine drug screen for all of the following compounds: amphetamines, barbiturates, benzodiazepines, cannabinoid, cocaine, methadone, opiates, and phencyclidine
   g. if warranted, tests for sexually transmitted diseases (STD) may have been performed at the discretion of the Principal Investigator or responsible physician.

5. The pre-study physical examination included breast and pelvic exams including a Pap smear performed as follows:
   a. The breast examination must be preformed within 28 days of the initial dose administration.
   b. A pelvic exam including a Pap smear was required on subjects if one had not been performed within the 6 months prior to dosing. Subjects provided written documentation of normal results from their physician.

Exclusion Criteria: Subjects could not be enrolled if they met any of the following exclusion criteria:

1. Institutionalized
2. History of skin diseases (eczema, psoriasis, atopic dermatitis).
3. Social Habits:
   a. Use of any tobacco-containing products within 1 year of the start of the study.
   b. Any recent, significant change in dietary or exercise habits.
   c. A positive test for any drug included in the urine drug screen.
   d. History of drug and/or alcohol abuse.
4. Medications:
   a. Use of any prescription or over-the-counter (OTC) systemic or topical analgesics or antihistamines within 72 hours of initial patch application or use of systemic or topical corticosteroids within 3 weeks of initial patch application.
   b. A depot injection or implant of any drug within 3 months prior to administration of study medication.
   c. Use of any medication or herbal products known to inhibit CYP3A4 enzyme activity within 7 days prior to the initial dose of study medication
5. Diseases:
   a. 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 Sub-Investigator.
   b. Acute illness at the time of either the pre-study medical evaluation or dosing.
   c. History of severe allergic reaction.
   d. Thrombotic disorders, especially thrombophlebitis or pulmonary embolism.
   e. Coronary artery or cerebrovascular disease.
   f. Liver or kidney dysfunction/disorders.
   g. Gall bladder disease.
   h. Fibrocystic disease or breast nodules.
   i. Family history of breast cancer (direct genetic link, i.e. mother, sister, etc.).
   j. Diabetes or any other endocrinological disease.
   k. Estrogen-dependent neoplasia.
   l. Cervical dysplasia.
6. Subjects who had an acute illness at the time of either the screening evaluation or patch application(s).
7. Damaged skin in or around test sites that included sunburn, uneven skin tones, tattoos, scars, or other disfigurations of the test site.

8. Donation or loss of a significant volume of blood or plasma (>450 mL) within 28 days prior to the initial dose of study medication.
9. Subjects who had received an investigational drug within 30 days prior to the initial patch application and/or participated in any transdermal system or patch study for irritation or sensitization within the last 4 weeks.
10. Sunbathing or the use of tanning salons for 7 days prior to transdermal system application.
11. Use of perfumes, body lotions, or oils within 7 days prior to transdermal system application.
12. Allergy or hypersensitivity to tapes or adhesives (ex. Band-aids, medical tape), isopropyl alcohol, progestins, estrogens, other hormonal products, or to any other component of product.
13. Consumption of grapefruit or grapefruit-containing products within 7 days of drug administration.

Study Conduct:

Treatments included patch applications once a week for three weeks. Subjects received one half patch of Mylan's norelgestromin/ethinyl estradiol transdermal system and one half patch of Ortho's Ortho Evra® transdermal system simultaneously once a week for three weeks. A 14-day rest phase followed with a subsequent 48-hour challenge phase. The challenge phase was followed by a 3 day observation and irritation evaluation. Within two weeks afterwards subjects had a post study clinical and laboratory evaluation to assess their health condition after drug administration. Patches were applied to test sites on the abdomen according to the application site randomization. The edges of the patches were marked with a surgical marker to ensure patch reapplication at the same site. Within 60 minutes prior to the first application and following the 30 minute irritation evaluation for all other applications, the test sites were wiped gently three times with a warm water washcloth, then lightly patted dry with a soft towel. The skin was completely dry before any patches were applied.

(a) Induction/Irritation Period:

The patches were removed 168 hours + 2 hours after application. Patch applications were made once weekly for 21 days. The three applications (per transdermal system) performed during this three-week phase were designated Applications 1 through 3, respectively. The appropriate transdermal system was re-applied to the identical site until after the third 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 the 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 appropriately documented and diagrammed. All other treatment applications continued as scheduled. If a subject developed a reaction of 3 or greater, according to the irritation rating scale found in Appendix 3 of the protocol (Appendix 16.1.1), the subject did not have any further transdermal systems applied to the same application site during the Induction phase of the study. The original application site continued to be evaluated until a reaction score of 0 was achieved. This score was recorded separately. In this case, any reapplications for Induction were made at a designated alternate site and appropriately documented and diagrammed. All other treatment applications continued as scheduled.

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

(b) Rest Phase:
A rest period (no patch applications) of 14 days followed Induction application 3.

(c) Sensitization Evaluation-Challenge Phase:
Following the Rest Phase, a Challenge application of one half patch of 0.15 mg/0.02 mg/day norelgestromin/ethinyl estradiol transdermal system (Mylan) and one half patch of 0.15 mg/ 0.02 mg/day Ortho Evra® transdermal system simultaneously applied to a clean, dry area of the skin on the abdomen (naïve site) according to the application site randomization. Transdermal systems were removed at 48 hours (+ 2 hours) after application. Irritation was assessed at 0.5, 24, 48, and 72 hours after removal of the Transdermal system, according to the irritation rating scale.

Outcome Variables

Induction/Irritation Skin Reaction Evaluations

During the Induction/Irritation Period, the test sites were evaluated at visits 2-10, 30 minutes after patch removal. Subjects who missed one of the Induction/Irritation visits 2-10 returned for a make-up visit for evaluation. Irritation, including superficial effects, was measured using an eight-point numeric and six-point alphabetic scale.

Irritation scale: Dermal Response (per key on Irritation Raw Data Listing):

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

Effects on superficial layers of the skin:

0(A)	Slight glazed appearance
1(B)	Marked glazing
2(C)	Glazing with peeling and cracking
3(F)	Glazing with fissures
3(G)	Film of dried serous exudates covering all or part of the patch site
3(H)	Small petechial erosions and/or scabs

In the Irritation and Sensitization analyses, the letter Scores were converted to numeric Scores as follows: A=0; B=1; C=2; F through I =3). The combined Score equaled the sum of the numerical Score "dermal response" and Letter Score.

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Primary Endpoint:

Irritation: The primary endpoint for Statistical Analysis of Dermal Irritation is the mean Irritation Score, that is, (cumulative Irritation Score)/3, since there are 3 Irritation scores measured at three different visits.

Contact Sensitization: The primary endpoint for Statistical Analysis of contact Sensitization is the dichotomized (Sensitized / Not Sensitized) Dermal response at the end of the challenge phase (Day 41 or 40 Days from baseline). A subject was classified as Sensitized if the dermal response (total of numeric score + letter score) was greater than or equal to a Score of 2.

Statistical Analysis Methods

Analysis Populations:

Evaluable population (EP): This population was based on individual patches and should only include those patches for subjects:

- Who met inclusion/exclusion criteria,
- Did not violate protocol,
- For whom no Patch was detached for longer than 24 hours,
- Who were within the visit window (± 4 hours), and completed the study,
- Did not take any prohibited concomitant medications or,
- Have any other significant protocol violations.

The determination of Non-inferiority was assessed using the evaluable population (EP).

Analysis of Cumulative Irritation (Induction/Cumulative Irritation Phase):

The primary analysis to evaluate irritation is to compare the mean Irritation Scores of the Test Product to that of the Reference product at the end of the Induction/Cumulative Irritation phase.

The Non-inferiority analyses were based on the estimated ratio of the least squares means (of the mean irritation scores) of the Test Product and the Reference product along with its 90% confidence interval. If the 95% Upper confidence bound for the quantity $\mu_T - 1.25\mu_R$ is less than or equal to zero, we can conclude that the Test Product is Non-inferior to the Reference product. An ANOVA model where treatment was a fixed effect and subject was a random effect was used for Non-inferiority analyses. The SAS® (Version 9.1) PROC MIXED statements used are as follows:

```
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;
```

Analysis of Contact Sensitization (Challenge Phase):

The sponsor did not perform a statistical analysis for contact Sensitization, but only argued that no evidence of sensitization reaction was observed.

Remark: This reviewer analyzed the dichotomized (Sensitized / Not Sensitized) Dermal response at the end of the challenge phase (Day 41). A subject was classified as Sensitized if the dermal response was greater than or equal to a Score of 2.

To assess the Non-inferiority of the Test product to Reference product, a 95% upper confidence bound for the difference of the proportions, $p_t - p_r$, was calculated, based on results published by McNemar.

Let p_t = Sensitization rate of the Test product, p_r = Sensitization rate of the Reference product.
Let n = number of subjects, b = number of subjects Sensitized to the Test product but not to the Reference product, and c = number of subjects Sensitized to the Reference product but not to the Test product.

The difference $p_t - p_r$ may be estimated by the quantity $(b - c)/n$.
A 95% upper confidence bound 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 on page 117 of Statistical Methods for Rates and Proportions (second edition, 1981) by Joseph L. Fleiss.
For any given Non-inferiority bound δ, the null hypothesis H_0 may be rejected if the 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. Specification of the appropriate non-inferiority bound δ is a policy decision by the Office of Generic Drugs.

Statistical Analysis Results

A total of 225 subjects was enrolled in the study. Of these, 216 subjects completed the Induction Cumulative Irritation Phase and entered the challenge phase. For potential contact sensitization, at the end of the Challenge phase only 214 subjects completed the study and were qualified to be included in the evaluable population analysis.

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Table 1 - Population distributions

Population	**Cumulative Irritation (N = 225)**
Subjects Enrolled	225 (100%)
Patients Excluded from Evaluable Population (EP)	9 (4%)
Total Patients in the Evaluable Population (EP)	216 (96%)

Demographic characteristics:
The population at baseline consisted of 204 subjects who are white, 1 subject who is Asian, 7 subjects who are black and 4 subjects of other ethnicity.

Table 2 - Demographic characteristics (Enrolled subjects)

Age	
Max	35
Mean (std)	24 (5)
Min	18
Race	
Caucasian	204 (94.4%)
Asian	1 (0.5%)
Black	7 (3.2%)
Others	4 (1.9%)
Gender	
Male	0
Female	216 (100%)

Non-Inferiority Analyses: The Test product was found to be Non-inferior to the Reference product for the mean irritation score (primary endpoint). Therefore, the Irritation property of the Test product is no worse than that of the Reference product. The 95% upper confidence bounds for $\mu_T - 1.25\mu_R$ were calculated using PROC MIXED in SAS version 9.1. Table 3 summarizes the Non-inferiority analyses. Cumulative Irritation score results are similar to those of the Mean Irritation score as expected, since, the Mean Irritation score = Cumulative Irritation score/3.

For the test product to pass the Non-inferiority test, the upper confidence bound for the quantity $p_t - p_r$ needs to be ≤0.46% and 2.6% at Day 22 for a cut off point of 2 and 3 respectively.

Table 3- Non-inferiority Analyses -- PP population

Parameter	Test LS Mean	Reference LS Mean	95% Upper Bound of μ_T-1.25 x μ_R	Passed	p-value (μ_T- μ_R)
Mean Irritation Score	0.89	0.87	-0.17	Yes	0.260
Cumulative Irritation Score	2.67	2.62	-0.52	Yes	0.260
Irritation		Reference			
Dichotomized Irritation Score at Day 22 (Score ≥ 3)		Not Irritating	Irritating		
Test	Not Irritating	215	0		
	Irritating	0	1		

95% Upper bound (U*)	0.46%		
Parameter		Reference	
Dichotomized Irritation Score at Day 22 (Score ≥ 2)		Not Irritating	Irritating
Test	Not Irritating	195	4
	Irritating	4	13
95% Upper bound (U*)	2.62%		

U^* is the upper limit of the 90% confidence interval for $\mu_v - 1.25\mu_c$.

Table 4- Frequency of Irritation score (PP)

Frequency of Irritation Score per Patch Per Observation (EPP)							
Product/Score	0	1	2	3	4	5	Total Per Treatment
Test	125	477	43	1	0	2	648 (216x3)
Reference	132	474	39	1	0	2	648 (216x3)
Frequency of Maximum Irritation Score per Patch Per Subject (PP)							
Product/Score	0	1	2	3	4	5	Total Per Treatment
Test	13	170	31	1	0	1	216
Reference	10	176	28	1	0	1	216

Irritation Score		Score					
		0	1	2	3	4	5
Score at visit 1	Test	36	163	16	1	0	0
	Reference	30	172	13	1	0	0
Score at visit 2	Test	57	147	11	0	0	1
	Reference	62	143	10	0	0	1
Score at visit 3	Test	32	167	16	0	0	1
	Reference	40	159	16	0	0	1

Frequency of Patch discontinuation due to high Irritation Score

	Days From Baseline			
Patch	*7*	*14*	*21*	*Total*
Test				*0*
Reference	*11*			*11*
Total	*11*			***11***

Three of these 11 subjects were included in the Primary analyses (Subjects No 180, 202 and 222)

Non-inferiority analyses for Sensitization:

The primary endpoint for Statistical Analysis of contact Sensitization was defined by this reviewer as the dichotomized (Sensitized / Not Sensitized) Dermal response at the end of the challenge phase (Day 41). A subject was classified as Sensitized if the dermal response Score was greater than or equal to 2. No subject was Sensitized on Day 41, and only 1 subject on Day 40 was Sensitized (Vehicle Patch.)

Using Fleiss's confidence bound formula (see **Analysis of Contact Sensitization (Challenge Phase)** above) the Test product was found to be statistically better than or Non-inferior to the Reference product for the response rate, provided the Non-inferiority margin is set no lower than 0.77 percentage points for Day 40 and Day 41 respectively. The contact Sensitization property

of the Test product is better or no worse than that of the Reference product, since the upper bound of the 90% confidence interval of the difference is relatively small (0.77%).

Table 5 Contact Sensitization analyses

Parameter	Reference		
Sensitization at Day 41 (Score ≥ 2)		Sensitized	not Sensitized
Test	Sensitized	1	0
	not Sensitized	1	211
95% Upper Confidence bound (U*)	0.77 percentage points		
Parameter	Reference		
Sensitization at Day 40 (Score ≥ 2)		Sensitized	not Sensitized
Test	Sensitized	1	0
	not Sensitized	1	211
95% Upper Confidence bound (U*)	0.77 percentage points		

U* is the upper limit of the 90% confidence interval for $p_t - p_r$.

Because of the very low counts of sensitized subjects, there may be concerns about the accuracy of Fleiss's approximation and therefore the statistical test.

Table 6- Frequency of Sensitization score per patch per observation (PP)

Frequency of Sensitization score per patch per observation						
	Score					
Patch	**0**	**1**	**2**	**3**	**4**	Total
Test	526	305	25	0	0	856 (214x4)
Reference	549	280	27	0	0	856 (104x4)
Frequency of Maximum Sensitization score per Patch Per Subject (PP)						
Patch / Score	**0**	**1**	**2**	**3**	**4**	**Total**
Test	15	179	20			214
Reference	20	173	21			214

Subjects with Score of 2 Or higher in the challenge phase							
Subject /Patch	Induction phase			Challenge Phase			
	Day 8	Day 15	Day 22	Day 38	Day 39	Day 40	Day 41
31 / Test	1	1	1	2	2	2	1
31 / Reference	1	1	1	1	2	2	1
80 / Reference	1	1	1	1	2	2	2
106 / Test	1	0	2	2	2	2	2
106/ Reference	1	1	1	2	2	2	2

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Comments on the Sponsor's Analyses

According to the sponsor, 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. No re-challenge was performed.

Reviewer Comment:

The FDA's reviewer analysis (as shown in Table 6), confirmed that two subjects (#31, 106) were potentially sensitized to both the Test product and the Reference Patch. One additional subject (#80) was potentially sensitized to the reference product. Subjects 80 and 106 had a dermal response score of 2 or more at both 48 and 72 hours post challenge patch removal while subject 31 had a dermal response score of 2 at both 24 and 48 hours post challenge patch removal. Of these five patches, four had a dermal response no higher than a score of 1 during the induction phase. Subject 106 had a dermal score of 2 for the Test product on day 22 of the irritation phase.

Adhesion Study (Protocol #: ORTH-09198):

Title: Adhesion Evaluation Study of Norelgestromin/Ethinyl Estradiol Transdermal System (NEETS) Patch (0.15 mg/0.02 mg/day; Mylan) and Active Wear of Ortho Evra® Patch (0.15 mg/0.02 mg/day; Ortho- McNeil-Jannsen) in Normal Healthy Female Volunteers.

Objective: The primary objective of this study was to evaluate the adhesion of Mylan's norelgestromin/ethinyl estradiol transdermal (NEETS) patch to Ortho Evra® patch manufactured by Janssen Ortho, LLC following a 7 day application of one Ortho Evra® or one Mylan NEETS patch for two treatment periods.

Study Design:
According to the sponsor, this was an open-label, single-dose, randomized, two-period, two-treatment, crossover study investigating the adhesive properties of Mylan's norelgestromin/ethinyl estradiol 0.15 mg/0.02 mg/day transdermal system to Ortho Evra® transdermal system, 0.15 mg/0.02 mg/day manufactured by Janssen Ortho, LLC for Ortho Women's Health & Urology. Forty (40) healthy female volunteers were enrolled in the study and 37 subjects completed the study. The adhesion data for 38 subjects was used in the statistical analysis. Each subject wore each patch for 7 days. No washout period was required for this study. The second patch was applied as soon as possible after the first patch was removed. Adhesion was assessed every 24 hours the patch was worn.

Study Population: Same inclusion/exclusion criteria as protocol #ORTH-0943 (Irritation/Sensitization Study)

Procedures/Observations: Subjects were to wear one Ortho Evra® patch or one Mylan Neets patch with the treatments applied to the subject's right or left lower abdomen in a randomized fashion. Each subject wore each patch for 7 days. No washout period was required for this study. The second patch was applied as soon as possible after the first patch was removed. Adhesion

was assessed every 24 hours the patch was worn. All subjects returned to the clinical facility on Days 2 (24 hours), Day 3 (48 hours) Day 4 (72 hours) Day 5 (96 hours), Day 6 (120 hours) and Day 7 (144 hours) after patch application for patch adhesion evaluation. On Day 8 (168 hours) of Period 1 the patch was removed and another patch was applied (according to the randomization scheme). It was placed on the opposite side (right or left) of the abdomen from the previous patch. On Day 8 of Period 2, following removal of the patch, the End of Study Procedures were initiated. The following products were administered:

Treatment A: Norelgestromin/Ethinyl Estradiol Transdermal System, 14 cm^2, 0.15 mg/0.02 mg/day, Mylan Technologies Inc. (Mylan), Lot #R6A0014

Treatment B: Ortho Evra®, 20 cm^2, 0.15 mg/0.02 mg/day, Janssen Ortho, LLC, Lot # 7LM5212

Clinical reviewer's comments: *The sponsor used a different adhesion scale for assessing adhesion performance than that recommended by the OGD. The adhesion scale recommended by OGD is the following:*

Table –A

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)

Adhesion: *The primary analysis to evaluate the Mean Adhesion Score of the 7 post-baseline assessments (7 evaluations at 24, 48, 72, 96, 120, 144 and 168 hours) was to compare the Mean Adhesion Score of the Test and Reference products.*

Additional analyses were based on a secondary endpoint defined as the dichotomized (Adhered / Not Adhered) Adhesion Score at the end of the Adhesion study. A Patch was classified as Adhered if the Adhesion Score was less than or equal to a Score of 1.

- The Test product was to be considered better or Non-inferior to the Reference product if the upper limit of the 90% confidence interval for the quantity $\mu_T - 1.25\mu_R$ was less than or equal to zero.
- The least square means of the Test and Reference products were calculated, along with the 90% confidence interval for $\mu_T - 1.25\mu_R$. The SAS® (Version 9.1) PROC MIXED statements used are as follows:

```
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;
```

- The dichotomized (Adhered / Not Adhered) Adhesion Score was analyzed using the 95% upper confidence bound based on McNemar's results (Fleiss, 1981), as defined in the previous section "Analysis of Contact Sensitization"

Adhesion Analyses Results:

A total of 38 subjects completed the Adhesion study and were included in the PP population. The Test product was found to be inferior or worse than the Reference product for the Mean Adhesion Score (primary endpoint). That is, the Adhesion property of the Test product is worse than that of the Reference product. Additionally, analysis based on the dichotomized (Adhered / Not Adhered) endpoint showed that for the Test product to be Non-inferior to the Reference product, a Non-inferiority bound $\delta \geq 2.63$ percentage points would be required. Table 7 summarizes the Non-inferiority analyses.

It should be noted and emphasized that the Mean Adhesions Score of the Test product is zero(μ_T =0): i.e., all the Test's patches have essentially no lift off the skin) and is less than that of the Reference product (μ_R = 0.0038, where subject No 18 has an Adhesion Score of 1 at 96 hour), and therefore, according to the sponsor's data, we observed a better property as measured by the point estimate for the Test product than the Reference product. Clinical decision should be assessed with medical judgment as well as statistics.

Population	**Adhesion (N = 40)**
Subjects Enrolled	40 (100%)
Patients Excluded from Evaluable Population (EP)	2 (5%)
Total Patients in the Evaluable Population (EP)	38 (95%)

Table 7 –Adhesion analyses results (Non-inferiority) –PP population

Parameter	Test LS Mean	Reference LS Mean	95% Upper Bound of μT-1.25 x μR	Pass The Non-Inferiority Test?	p-value (μT-μR)
Mean Adhesion Score	0.0000	0.0038	0.0025	No	0.324
Cumulative Adhesion Score	0.000	0.026	0.02	No	0.324
Sponsor Adhesion score					
Mean Percentage Adhesion	95.00	94.96	-23.63	Yes	<.0001
Cumulative Percentage Adhesion	665.00	664.74	-165.42	Yes	<.0001
Dichotomized score (≤ 1)					
Dichotomized score (≤ 1)			Reference		
Adhesion (Score at Day 8)			Adhered	not Adhered	
Test		Adhered	38	0	
		not Adhered	0	0	
95% Upper bound (U*)	2.63%				**1.00**

U^* is the upper limit of the 90% confidence interval for $\mu_T - 1.25\mu_R$.
U^{**} is the 95% upper confidence bound for p_T-p_R.

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Table 8-Frequency of Adhesion score (PP)

Frequency of Adhesion score per Patch Per Observation (PP)						
	Score					
Patch	**0**	**1**	**2**	**3**	**4**	**Total**
Test	266					266 (38x7)
Reference *	265	1				266 (38x7)
Frequency of Maximum Adhesion Score per Patch Per Subject (PP)						
Product/Score	0	1	2	3	4	Total Per Treatment
Test	38					38
Reference *	37	1				38

*: Subject No 18 in the Reference product at visit 96 Hours

Adhesion Scores							
Hours	Adhesion Score Evaluation Day		0	Score 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

Comments on sponsor Adhesion Analyses:

The sponsor stated in their study report (page 18 of the Clinical review) that a one-sided hypothesis test was used to determine if the adhesion score of Mylan's NEETS was equivalent to or better than the Ortho Evra® (for the reference product). For the mean adhesion scores, the null and alternative hypotheses were: H0: $\mu 1/\mu 2 < 0.8$ and H1: $\mu 1/\mu 2 < 0.8$, which (assuming $\mu 2 > 0$) can be written as: H0: $\mu 1 - 0.8\mu 2 < 0$ and H1: $\mu 1 - 0.8\mu 2 > 0$, where $\mu 1$ is the mean adhesion score for the test product and $\mu 2$ is the mean adhesion score for the reference product. The null hypothesis H0 was rejected when the lower limit of the 90% confidence interval (that is the 95% lower confidence bound) for the quantity $\mu 1 - 0.8\mu 2$ was ≥ 0.

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

The sponsor's proposed statistical analysis is not acceptable. The OGD's recommended method is described on page 13 of this review. The sponsor's proposed statistical hypotheses are only appropriate when adhesion score is reversed, as described in the table below.

Reversed System Adherence	
Score	**Definitions**
4	≥90% adhered (essentially no lift off the skin)
3	≥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)
1	>0% to <50% adhered but not detached (more than half of the system lifting off the skin without falling off)
0	0% adhered-test system detached (test system completely off the skin)

ANDA 200-910 Norelgestromin/Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day (Mylan Pharmaceuticals Inc.), 02/28/2013.

Conclusions:

Study #: ORTH-0943:

Irritation: The Test product was found to be Non-inferior to the Reference product for the mean irritation score (primary endpoint). Therefore, the Irritation property of the Test product is no worse than that of the Reference product.

Sensitization: Based on Fleiss's 95% upper confidence bound for the difference in Sensitization rates, the Test product rate may exceed the Reference Product rate by at most 0.77 percentage points based on the dermal response at both Day 40 and 41. The Test product was found to be statistically better or Non-inferior to the Reference product for the response rate, provided the Non-inferiority margin is set no lower than 0.77 percentage points for Day 41.

Study #: ORTH-09198:

Adhesion: The Test product was not found to be Non-inferior to the Reference product for the Mean Adhesion Score (primary endpoint), treating the Mean Adhesion Score as a continuous variable. However, the observed mean Adhesion score of the Test product in this study is better than that of the Reference product (see Table 7), indicating better adhesion property.

For the additional dichotomized endpoint, where a patch was classified as adhered if the adhesion score at the end of the study was 0 or 1, the 95% upper confidence bounds for the difference in the Adhesion rates of the Test and the Reference Products (p_T - p_R) is 2.63%. This upper confidence bound may be compared to any appropriate Non-inferiority bound δ that may be set by the Office of Generic Drugs. Clinical decision should be assessed with medical judgment as well as statistics.

_____
Mohamed Nagem, Ph.D.
Mathematical Statistician, DB6/OB

_____
Stella C. Grosser, Ph.D.
Mathematical Statistician,
Team Leader, DB6/OB

_____
Stella G. Machado, Ph.D.
Director, DB6/OB

cc: Original ANDA 2020-26, John Peters, Nicole Lee, Nitin K. Patel, OGD.

Stella Machado, Stella C. Grosser, Mohamed Nagem, DB6/OB/OTS

This review includes 17 pages.

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

/s/

MOHAMED O NAGEM
03/18/2013

STELLA C GROSSER
04/05/2013

STELLA G MACHADO
04/05/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200910

BIOEQUIVALENCE REVIEWS

ADDENDUM TO DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	200910		
Drug Product Name	Norelgestromin and Ethinyl Estradiol Transdermal Patch		
Strength(s)	4.86 mg/0.53 mg/Patch (0.15 mg/0.02 mg/24 hrs)		
Applicant Name	Mylan Technologies Inc.		
Address	110 Lake St. St. Albans, VT 05478		
Applicant's Point of Contact	Joseph J. Sobecki		
Contact's Telephone Number	304- 599- 2595, ext 6429		
Contact's Fax Number	304- 285- 6407		
Original Submission Date(s)	December 31, 2009 October 8, 2010 (Dissolution Amendment) August 20, 2013 October 11, 2013 (Dissolution Amendment)		
Submission Date(s) of Amendment(s) Under Review	N/A		
Reviewer	Suman Dandamudi, Ph.D.		
Study Number (s)	ORTH-0942	ORTH-0943	ORTH-09198
Study Type (s)	Fasting	Cumulative Irritation and Sensitization	Adhesion
Strength (s)	4.86 mg/0.53 mg/Patch	4.86 mg/0.53 mg/Patch	4.86 mg/0.53 mg/Patch
Clinical Site	Cetero Research		
Clinical Site Address	625 Demers Avenue, East Grand Forks, MN 56721 USA		
Analytical Site	Mylan Pharmaceuticals Inc.		
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Road, Morgantown, WV 26505		
OVERALL REVIEW RESULT	**ADEQUATE**		
OSI REPORT RESULT	**ADEQUATE**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 8, 28, 31	**DISSOUTION**	**4.86 mg/0.53 mg/Patch**	**ADEQUATE**
1, 28	**FASTING STUDY**	**0.15 mg/0.02 mg/day**	**ADEQUATE**

This review addendum is to document to file the withdrawal of the consult request previously sent to the Science Staff, and to confirm that the bioequivalence and dissolution portions of the current ANDA are **adequate**. Please see attached for additional information related to the pending consult request and its withdrawal of the pending consult request to the Science Staff[1].

The adequacy and completeness of the BE and dissolution portions have been previously documented in the following two reviews:

DARRTS: DANDAMUDI, SUMAN 09/06/2013 N/A 09/06/2013 REV-BIOEQ-21(Primary Review) Original-1 (Not Applicable) Archive

DARRTS: DANDAMUDI, SUMAN 11/11/2013 N/A 11/11/2013 REV-BIOEQ-02(Dissolution Review) Original-1 (Not Applicable) Archive

The application is **adequate** with no deficiencies**.**

[1] DARRTS: DANDAMUDI, SUMAN 02/04/2014 N/A 02/04/2014 FRM-ADMIN-01(Memorandum to File) Original-1 (Not Applicable) Archive

ADDENDUM TO CONSULT REQUEST TO DIVISION OF RESEARCH AND STANDARDS, OGD	
To:	Robert Lionberger, Ph.D., Acting Director for Regulatory Science, Division of Research and Standards, Office of Generic Drugs
From:	Suman Dandamudi, Reviewer, Team 8, Division of Bioequivalence I, Office of Generic Drugs
Through:	Hoainhon Nguyen, Deputy Director, Division of Bioequivalence I (DBI), Office of Generic Drugs
Re:	**WITHDRAWAL OF CONSULT REQUEST**: For ANDA 200910 (Mylan's Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch) (See the original consult request attached)

Withdrawal of Consult Request:
Since determination of the appropriateness of the current RLD labeling with respect to the therapeutic equivalence rating determination for ANDA 200910 (once approved), is not a bioequivalence issue, but rather a pharmaceutical equivalence and labeling issue, DBI withdraws its pending consult request to the Science Staff (Division of Research and Standards, OGD) (See the content of the consult request attached).

DBI confirms that both the bioequivalence (BE) and dissolution testing portions of the ANDA are **adequate**, and the Division has no further question at this time. The adequacy and completeness of the BE and dissolution portions have been previously documented in the following two reviews:

DARRTS, DANDAMUDI, SUMAN, REV-BIOEQ-21(Primary Review), Submit/Final Date 09/06/2013

DARRTS, DANDAMUDI, SUMAN, REV-BIOEQ-02(Dissolution Review), Submit/Final Date 11/11/2013

ATTACHMENT I: PENDING CONSULT REQUEST	
To:	Robert Lionberger, Ph.D., Acting Director for Regulatory Science, Division of Research and Standards, Office of Generic Drugs
From:	Suman Dandamudi, Reviewer, Team 8, Division of Bioequivalence I, Office of Generic Drugs
Through:	Hoainhon Nguyen, Deputy Director, Division of Bioequivalence I (DBI), Office of Generic Drugs
Re:	Request opinion on the appropriateness of the change in the labeling (from "rate of drug release" to "amount of drug content") of the reference product, Ortho-McNeil's Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch, with respect to determination of the therapeutic equivalence for a generic product, Mylan's Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch (ANDA 200910)

Introduction:

Mylan Technologies submitted ANDA 200910 which contains the results of three studies, (1) a fasting bioequivalence (BE) study with a pharmacokinetic (PK) endpoint, comparing the test product Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch to the corresponding reference product, Ortho-McNeil's Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch; (2) Adhesion study (Orth-Cln-09198); and (3) Sensitization/Irritation study (Orth-Cln-0943). The Division of Bioequivalence reviews the BE study, and the Division of Clinical Review reviews the adhesion and sensitization/irritation studies.

The Division of Bioequivalence found the fasting BE study to be acceptable[2].

Based on the OCP recommendation[3], the potency of Ortho-McNeil's Ortho Evra® should be expressed as the **"amount of drug content"** instead of **"rate of drug release"** in the Orange Book, unlike other transdermal drug products approved to date (Please see the email communication attached). Since generic drug products generally have different drug release mechanism, they may contain different amounts of drug content and still can be bioequivalent to the respective reference products in the rate and extent of absorption. Specifically, Mylan's Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch (ANDA 200910) contains different amounts of drug content, compared with Ortho-McNeil's Ortho Evra® patch, but it is bioequivalent to this reference listed drug (RLD) product. However, with the RLD labeling expressed in the amount of drug content and the "strength" of this RLD product listed in the Orange Book in the drug content amount that is different from Mylan's product, the Division of Bioequivalence is concerned that the therapeutic equivalence rating of Mylan's product, once approved, cannot be made appropriately in the Orange Book. Additional details of the issue related to the labeling recommendation by the OCP are below.

[2] DARRTS for ANDA 200910: DANDAMUDI, SUMAN 06/11/2013 N/A 06/11/2013 REV-BIOEQ-21(Primary Review) Original-1 (Not Applicable) Archive
[3] DARRTS for NDA 021180: WILLIAMSON, ZETA-MAE C 05/17/2006 N/A 05/17/2006 REV-RPM-05(General Review) Supplement-20 (Labeling) Archive

Labeling of the RLD vs. Labeling of Mylan's Product:

- The test product is a 14 cm^2 square patch with round corners that contains 4.86 mg norelgestromin and 0.53 mg ethinyl estradiol. Whereas, the RLD product, Ortho Evra® is a transdermal patch with a contact surface area of 20 cm^2 containing 6 mg norelgestromin and 0.75 mg ethinyl estradiol. Even though there are differences in the amounts of the active ingredients in the patch, both the generic and RLD products are designed to deliver to the systemic circulation, 0.15 mg norelgestromin and 0.02 mg ethinyl estradiol daily.

- Based on the review of the controlled correspondence 07-0512[4], the following are the general considerations for Transdermal Drug Delivery Systems: "*Transdermal products are considered as extended release drug products. The strength of a transdermal product is related to the amount of active ingredient that is delivered into the blood stream over a defined period of time, and not to amount of active ingredient initially in the patch. The amount of active ingredient in the generic product may differ from the amount of active ingredient in the RLD as long as the amount of the active ingredient absorbed into the blood stream in both products is equivalent. The difference in the amount of the active ingredient in the proposed generic compared to the RLD would have to be justified, regardless of equivalent pharmacokinetic and bioequivalence data".*

- Although there are differences in the formulation design and amounts of the active ingredients in the patch between the test and reference products, the fasting BE study (ORTH-0942) revealed that the 90% confidence intervals are with in the acceptance range of 80% and 125% for LnAUC0-t, LnAUCi and LnCmax. Thus the study demonstrated bioequivalence between the test and reference products[2].

- Currently, in the Orange Book, the strength of the RLD product (Ortho Evra®) is listed as 0.75 mg/6 mg (total amount of drug content) rather than 0.02 mg/0.15 mg/24 hrs (rate of drug release)[5].

- The above potency change in the Orange Book was made based on the recommendation by Office of Clinical Pharmacology (See below for email communication with Office of Clinical Pharmacology (OCP)) to reflect the current RLD labeling[6].

- In 2006, the reference drug product labeling has been revised to omit the "rate of drug release". From both the carton and pouch labeling, the following text has been deleted: **"releases 150 g of norelgestromin and 20 g of ethinyl estradiol to the blood stream for 24 hours"**[3]. The current RLD labeling states the following under Description section: ***"ORTHO EVRA is a combination transdermal contraceptive system with a contact surface area of 20 cm2. It contains 6 mg NGMN and 0.75 mg EE".***

---

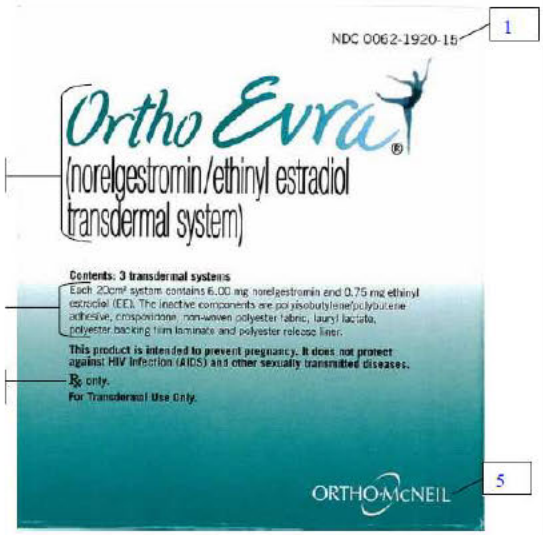
[4] V:\firmsam\Mylan\Controls\070512C0407.doc
[5] Online-Orange Book (2013). http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm (Last accessed: 12/19/2013)
[6] http://dailymed nlm nih.gov/dailymed/lookup.cfm?setid=f8e8a69e-a018-469a-af56-e20f61fe4e06 (Last accessed: 12/19/2013)

- Therefore, both the generic and innovator's carton labeling now contains information only on the "total drug content" and not "release rate" (See below).

Comparison of Carton Labeling between the Generic and Innovator Products[7]

Innovator's Carton

Front of Carton



Mylan's Draft Carton (b) (4)

(b) (4)

- In spite of the same release rate (0.15 mg/0.02 mg/24 hrs), the RLD and Mylan's products are not "equivalent" with respect to their amount-per-patch strengths as stated in the respective labels. The DBI requests the Division of Research and Standards (DRS) opinion on the appropriateness of the RLD labeling, and whether the RLD labeling should be changed to allow accurate therapeutic equivalence (TE) comparison between this innovator product and all generic versions of Norelgestromin and Ethinyl Estradiol Transdermal Patch as well as their subsequent TE rating in the Orange Book.

- Additionally, if DRS agree that the RLD labeling should be revised, please advice on the process by which such revision can take place.

[7] DARRTS for ANDA 200910: Firm's submission: 1 0000 12/31/2009 12/31/2009 New/ANDA Original-1 (Not Applicable) View EDR. Module 1.14.3. Listed Drug Labeling

Current Orange Book Listing of the RLD Product:

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N021180		Yes	ETHINYL ESTRADIOL; NORELGESTROMIN	FILM, EXTENDED RELEASE;TRANSDERMAL	0.75MG;6MG	ORTHO EVRA	JANSSEN PHARMS

Additional Information:

Section I: OGD History of this Drug Product

Currently there are no approved generic products of Norelgestromin and Ethinyl Estradiol Transdermal Film Extended Release listed in the Orange Book[5].

(b) (4)

Section II: Drug Product Information[5,6]

Test Product	Norelgestromin and Ethinyl Estradiol Transdermal Film Extended Release, 4.86 mg/0.53 mg (0.15 mg/0.02 mg/day)
Reference Product	Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal Film Extended Release, 6 mg/0.75 mg (0.15 mg/0.02 mg/day)
RLD Manufacturer	Ortho-McNeil Pharmaceutical, Inc.
NDA No.	021180
RLD Approval Date	November 20, 2001
Indication	Ortho Evra® is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception

PK/PD Information[6]

Bioavailability	Following a single application of the drug product, both Norelgestromin (NGMN) and Ethinyl Estradiol (EE) reach a plateau by approximately 48 hours. Pooled data from the 3 clinical studies have demonstrated that steady state is reached within 2 weeks of application. Absorption of NGMN and EE following application of ORTHO EVRA® to the buttock, upper outer arm, abdomen and upper torso (excluding breast) was examined. While absorption from the abdomen was slightly lower than from other sites, absorption from these anatomic sites was considered to be therapeutically equivalent. The absorption of NGMN and EE following application of ORTHO EVRA® was studied under conditions encountered in a health club (sauna, whirlpool and treadmill) and in a cold water bath. The results indicated that for NGMN there were no significant treatment effects on Css or AUC when compared to normal wear. For EE, increased exposures were observed due to sauna, whirlpool and treadmill. There was no significant effect of cold water on these parameters. Results from a study of consecutive ORTHO EVRA® wear for 7 days and 10 days indicated that serum concentrations of NGMN and EE dropped slightly during the first 6 hours after the patch replacement, and recovered within 12 hours. By Day 10 of patch administration, both NGMN and EE concentrations had decreased by approximately 25% when compared to Day 7 concentrations.
Food Effect	N/A
Tmax	48 hours
Metabolism	Since ORTHO EVRA® is applied transdermally, first-pass metabolism (via the gastrointestinal tract and/or liver) of NGMN and EE that would be expected with oral administration is avoided. Hepatic metabolism of NGMN occurs and metabolites include norgestrel (active) and various hydroxylated and conjugated metabolites. Ethinyl estradiol is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.
Excretion	Ethinyl estradiol is excreted in the urine primarily as glucuronide conjugates. The metabolites of NGMN and EE are eliminated by renal and fecal pathways.
Half-life	Half-lives of NGMN and EE are approximately 28 hours and 17 hours respectively.
Dosage and Administration	This system uses a 28-day (four-week) cycle. A new patch is applied each week for three weeks (21 total days). Week Four is patch-free. Every new patch should be applied on the same day of the week. This day is known as the "Patch Change Day." For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time. The ORTHO EVRA® patch should not be cut, damaged or altered in any way. If the ORTHO EVRA® patch is cut, damaged or altered in size, contraceptive efficacy may be impaired. On the day after Week Four ends a new four-week cycle is started by

	applying a new patch. Under no circumstances should there be more than a seven-day patch-free interval between dosing cycles.
Maximum Daily Dose	1 patch/week
Drug Specific Issues (if any)	**Black Box Warning:** **Cigarette Smoking and Serious Cardiovascular Risks:** Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, hormonal contraceptives, including ORTHO EVRA®, should not be used by women who are over 35 years of age and smoke. **Risk of Venous Thromboembolism:** The risk of venous thromboembolism (VTE) among women aged 15–44 who used the ORTHO EVRA® patch compared to women who used several different oral contraceptives was assessed in five U.S. epidemiologic studies using electronic healthcare claims data. The relative risk estimates ranged from 1.2 to 2.2; one of the studies found a statistically significant increased relative risk of VTE for current users of ORTHO EVRA®. **Pharmacokinetic Profile of Ethinyl Estradiol:** The pharmacokinetic (PK) profile for the ORTHO EVRA® patch is different from the PK profile for oral contraceptives in that it has higher steady state concentrations and lower peak concentrations. Area under the time-concentration curve (AUC) and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using ORTHO EVRA® compared with women using an oral contraceptive containing 35 mcg of EE. In contrast, peak concentrations for EE are approximately 25% lower in women using ORTHO EVRA®. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using ORTHO EVRA® compared with women using oral contraceptives containing 30–35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including venous thromboembolism.

Attachment:

E-mail Communication Regarding the Ortho Evra® Potency Change in Orange Book

---

From: Nguyen, Hoainhon T
Sent: Thursday, July 05, 2012 12:52 PM
To: Imam, Malik; Parise, Cecelia M; Conner, Dale P; Dandamudi, Suman; Smith, Glen J; Read, Shanaz; Tran, Trang
Cc: Ramson, Teresa; Nguyen, Hoainhon T
Subject: RE: Ortho Evra and Orange Book potency change

Unless I read the proposed labeling for ANDA 200910 incorrectly, this generic product does not contain the same total drug content, i.e., 0.53 mg EE/4.86 mg NGMN, versus 0.75 mg EE/6.00 mg NGMN in the RLD (Ortho Evra) product. With "different" strength(s), ANDA 200910 may have a problem referencing Ortho Evra? For transdermal patch products in general, it is not the total drug content that matters, but it is the rate that the drug is released from the patch. From the email exchange between Mary Ann and OCP below, it is not clear why the OCP recommended the change in the potency expression to the total drug content from the rate (which was originally approved for the NDA labeling).

Thanks,
Hoai

From: Imam, Malik
Sent: Thursday, July 05, 2012 11:35 AM
To: Parise, Cecelia M; Conner, Dale P; Nguyen, Hoainhon T; Dandamudi, Suman; Smith, Glen J; Read, Shanaz; Tran, Trang
Subject: RE: Ortho Evra and Orange Book potency change

For 200910 the rate is not mentioned on the box only the total drug content, so it should not be a problem.

Thanks,
Malik

From: Parise, Cecelia M
Sent: Thursday, July 05, 2012 9:14 AM
To: Conner, Dale P; Nguyen, Hoainhon T; Dandamudi, Suman; Smith, Glen J; Read, Shanaz; Imam, Malik; Tran, Trang
Subject: FW: Ortho Evra and Orange Book potency change

Folks,

Is this going to be a problem for ANDA 200910?

Thanks,

Cecelia

From: Holovac, Mary Ann
Sent: Thursday, July 05, 2012 8:53 AM
To: CDER-Orange Book Staff
Cc: Shimer, Martin; Parise, Cecelia M
Subject: FW: Ortho Evra and Orange Book potency change

For next update please make the following change to the potency display:

NDA 21180 Ortho Evra (EE + Norelgestromin)

FROM 0.02mg/24hr; 0.15mg/24hr TO 0.75mg; 6mg

Please note this is not a new potency but a change in potency display as the rate per hour was dropped from the labeling in 2005. The new potency will reflect the total drug content of the product.
(ANDA issues??)

Mary Ann

From: Yu, Chongwoo
Sent: Thursday, July 05, 2012 7:13 AM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

Mary Ann,

Thanks for your note and sorry for my late reply.
I was out of my office on Tuesday.

This is not for a new potency.
It is a labeling change of an existing product.

It is a long story but in simple terms, any reference of 0.02mg/24hr;0.15mg/24hr was removed from the product label sometime in 2006 and we would like to have the Orange Book reflect that.

I hope this answers your question. Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: Holovac, Mary Ann
Sent: Monday, July 02, 2012 3:38 PM
To: Yu, Chongwoo
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

First I would like to confirm that this is a labeling change of an existing product and not a new potency. Most transdermal products are listed in the orange book as dose per time period so this is an odd type of change that could possibly present challenges for the generics. What prompted this change?
Thanks.

From: Yu, Chongwoo
Sent: Monday, July 02, 2012 3:00 PM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

Yes… but the orange book still has the nominal delivery rate (0.02MG/24HR;0.15MG/24HR) on it which we would also like to correct to the total drug content.

Can you please give us a hand on this and let me know what is involved in this process? Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: Holovac, Mary Ann
Sent: Monday, July 02, 2012 2:48 PM
To: Yu, Chongwoo
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

Hi,
I'm back in the office, was on leave.
Looking at the latest labeling on the drugs@fda website it appears the product is now labeled with total drug content vs a dosage per hour?
Mary Ann

From: Yu, Chongwoo
Sent: Thursday, June 28, 2012 6:16 PM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book
Importance: High

Mary Ann,

Can you please give us a hand on this?
Your help is greatly appreciated. Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: Yu, Chongwoo
Sent: Friday, June 15, 2012 9:46 AM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

Mary Ann,

I am the current Clinical Pharmacology reviewer of Ortho Evra and just want to follow up with the email below as we have not heard back from you. Your help and input would be greatly appreciated. Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: Kim, Myong-Jin
Sent: Thursday, June 07, 2012 12:15 PM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Yu, Chongwoo; Tran, Doanh
Subject: Ortho Evra and Orange Book

Hi Mary Ann,

I left you a voice message regarding Ortho Evra and Orange Book yesterday afternoon.

Currently, the Orange Book lists Ortho Evra's strength as 0.02mg/24hr;0.15mg/24hr. However, any reference of 0.02mg/24hr;0.15mg/24hr was removed from the product label sometime in 2006 and we would like to have the Orange Book reflect that.

So, my question to you is what is involved to revise the Orange Book and how soon does it get updated? Once the ClinPharm team comes up with our proposed strength for this product and convey this to your group, does the Orange Book get updated soon (daily, weekly, monthly)? Do we work with you directly or someone from your group?

Thanks in advance,

MJ

Clinical Pharmacology Team Leader
Office of Clinical Pharmacology

ATTACHMENT II: DISCUSSION BETWEEN OGD AND OND CONCERNING THE ISSUES RELATED TO THE CURRENT RLD LABELING

From: Nguyen, Hoainhon T
To: Chuh, Esther; West, Robert L
Cc: Patel, Nitin K. (CDER/OGD); Dandamudi, Suman; Conner, Dale P; Basi, Surjit; Parise, Cecelia M; Imam, Malik;
Nguyen, Hoainhon T
Subject: RE: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System) - consult to science team
Date: Friday, January 31, 2014 12:17:00 PM
Attachments: RE Ortho Evra Delivery Rate - Implications on Current Supplement and ANDA 200910.msg

Esther,

Please see the email attached for the update on the latest discussion/decision related to Ortho Evra and the approval of ANDA 200910. Based on the unresolved deficiencies related to the pending supplement of the RLD application (NDA 21180), it is not certain how they would affect the decision of approval of the ANDA.

However, DBI would like to clarify the following:
1. Currently, there is NO bioequivalence issue related to this ANDA. We sent a consult to the Science Staff about the discrepancy between the RLD and ANDA labeling just to make sure the issue is addressed, as it appeared to us, at the time we completed our BE review, that no one from OGD/OND seemed to be concerned with this discrepancy.
2. The issue is actually a pharmaceutical equivalence and labeling issue to be addressed at the Office level by disciplines other than bioequivalence.
3. DBI will withdraw the consult sent to the Science Staff to make it clear that the pending issue is not a bioequivalence issue.

We will provide any technical assistance needed in this matter, but DBI cannot address the pharmaceutical equivalence/labeling issue at hand.

Thanks,
Hoai

From: Chuh, Esther
Sent: Friday, January 31, 2014 11:41 AM
To: Nguyen, Hoainhon T; West, Robert L
Cc: Patel, Nitin K. (CDER/OGD); Dandamudi, Suman; Conner, Dale P; Basi, Surjit; Parise, Cecelia M;
Imam, Malik
Subject: RE: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System) - consult to science team
Hello Hoai,
I would like to follow up on the meeting held on Tuesday on the labeling issue.
I am interested in knowing how this will impact the timeline for the approval of the ANDA.
Thank you,
Esther
From: Nguyen, Hoainhon T
Sent: Thursday, January 23, 2014 12:50 PM
To: Chuh, Esther; West, Robert L
Cc: Patel, Nitin K. (CDER/OGD); Lionberger, Robert; Dandamudi, Suman; Conner, Dale P; Basi, Surjit;

Nguyen, Hoainhon T; Parise, Cecelia M; Imam, Malik
Subject: RE: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System) - consult to science team

Esther,

There is a meeting on the labeling issue for this drug product next Tuesday. Please see attached. With respect to the awareness of the labeling group on this issue, please see my email attached, which showed that Malik from the labeling group was in the email conversation. Cecelia first raised the issue in 2012, and Mary Ann from the Orange Book (OB) was aware of the impact on ANDAs as well. However, it is not clear what has been done since that time. Recently DBI was wrapping up its BE/dissolution review and found out that the OB had changed the strength of the RLD to be expressed in amount and not rate, so it consulted the Science Staff to make sure that this issue is being addressed. DBI was not aware of any target approval for this drug product at any time during our review.

Thanks,
Hoai

From: Chuh, Esther
Sent: Thursday, January 23, 2014 11:55 AM
To: Nguyen, Hoainhon T; West, Robert L
Cc: Patel, Nitin K. (CDER/OGD); Lionberger, Robert; Dandamudi, Suman; Conner, Dale P; Basi, Surjit
Subject: RE: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System) - consult to science team

Hi Hoai,

Does this consult have any impact on the bio review that is currently acceptable? I am trying to find out how this newly identified issue will impact the review time line for the approval of the ANDA (currently – we are targeting for approval in Feb).
For my understanding, what is the bio involvement with this labeling issue? Is labeling aware of this? I am thinking revision to labeling may be needed based on the outcome of the consult.
Thank you,
Esther

From: Nguyen, Hoainhon T
Sent: Friday, January 17, 2014 12:36 PM
To: West, Robert L; Chuh, Esther
Cc: Patel, Nitin K. (CDER/OGD); Lionberger, Robert; Dandamudi, Suman; Nguyen, Hoainhon T; Conner,
Dale P
Subject: RE: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System) - consult to science team

Bob,
As of yesterday, we understand that Rob's group and a working group in OND are currently working on resolving the labeling issue related to this drug product. Without the labeling issue (related to using rate vs. amount to express product strengths) being clarified, there may be a problem with approval of generic products.
Thanks,
Hoai

From: West, Robert L
Sent: Friday, January 17, 2014 11:32 AM
To: Chuh, Esther
Cc: Patel, Nitin K. (CDER/OGD); Nguyen, Hoainhon T; Lionberger, Robert
Subject: FW: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System) - consult to science team

Esther/Nitin:
I missed much of the discussion a few weeks ago between OGD and Mylan. Mylan is referring to a meeting held on September 24, 2013 with the agency and to recent telephone conversations that included Cook regarding the alternative statistical analysis issue.
I also see that DBE recently issued a consult to the OGD Science Team.
Can I have an interim update on where we currently are?
Thank you,
Bob

From: Wayne.Talton@mylanlabs.com [mailto:Wayne.Talton@mylanlabs.com]
Sent: Friday, January 17, 2014 8:38 AM
To: West, Robert L
Subject: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System)

Hi Bob
As we discussed this morning, I am providing you with some summary background information on a key first generic product, Norelgestromin and Ethinyl Estradiol Transdermal System (ANDA 200910), which has been pending approval at the Agency following 48 months of review. No generic alternative currently exists for this important women's health product and patients pay an average of $80 or more per monthly prescription of Ortho-Evra according to IMS. There are no legal barriers preventing Mylan from launching our product immediately upon ANDA approval.
Product: Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 hours and 0.02 mg/24 hours
ANDA Number: 200910
RLD: Ortho Evra
Original Submission Date: December 31, 2009
Time in Review: 48 months
Regulatory Status: Complete Response Amendment Submitted August 20, 2013; Labeling Amendment Submitted September 18, 2013 (due to RLD Update); Drug Release Amendment Submitted October 11, 2013.
Legal Status: PIV filed with no suit. The first to file applicant withdrew their ANDA per FDA's PIV List
so Mylan's product represents a First Generic
FDA Feedback on the Regulatory Status: Application pending review however our request for expedited review has been granted.
Commercial Readiness: Mylan has product readily available in our distribution center for immediate distribution upon the receipt of approval.
Primary Issue Rate Limiting for Approval: Mylan proposed an alternative statistical analysis (to evaluate irritation/adhesion) from that published in the bioequivalence guidance since the model does not work well when both the test and reference product perform wells. We met with the Agency on this matter on September 24, 2013 and they acknowledged the issue.
I look forward to receiving further on the approval status of our application.
Wayne
Mylan
304.554.6551

From: Strasinger, Caroline
Sent: Thursday, January 30, 2014 11:52 AM
To: Joffe, Hylton; Bina, Christine; Soule, Lisa; Duffy, Eric P; Ghosh, Tapash; Kitchens, Kelly;

Jennings, Kerri-Ann; Williamson, Charlene; Yu, Chongwoo; Davis, Daniel; Abraham, Ciby
Cc: Ghosh, Priyanka *; Newman, Bryan *; Dandamudi, Suman; Kim, Myong-Jin; Gassman, Audrey; Li, Guohua; Braddy, April; Nguyen, Hoainhon T; Cai, Bing; Rege, Bhagwant; Li, Xihao; Ahn, Hae Young; Bashaw, Edward D; Conner, Dale P; Stier, Ethan; Lionberger, Robert; Huang, Yih Chain
Subject: RE: Ortho Evra Delivery Rate - Implications on Current Supplement and ANDA 200910

Hello,
I believe the meeting was productive in the very least at orientating everyone with all the moving parts between the two applications. At this time our rough plan is as follows:
1) As MJ pointed out, Jansen did not perform an actual irritation/sensitization study and that was one of the CR items in the first CR letter. The company instead attempted to justify the lack of study with adverse events table and a paragraph. We sent a consult to Clin/pharm for their comments on the justification, and I believe this will result in a second CR letter.

> a. All other PIB adhesive change products (e.g. Nicoderm) have performed irritation/sensitization studies as part of their BE study, and I believe it is what is required to establish BE of a generic transdermal product, so it isn't an unreasonable claim, despite their argument that very few irritations showed up in the AE.
> b. We offered at least once (maybe more) to review their BE protocol, this offer was captured in the Advice Letter (04/23/2013) in Darrts. They obviously never took us up on that offer, had they, we would have advised them to perform an irritation study among other things (we now know they didn't because they had already conducted the studies in 2008). I plan to put a memo in Darrts regarding this bullet point this week.

2) With a CR on lack of irritation/sensitization study, we will also tie in the request for the strength to be presented as a rate and that this rate should be supported with PK data from a new study which should include an IV infusion arm in order to obtain a clearance with the current validated analytical methods. Additionally, residual drug analysis will need to be performed on the used samples to further support the rate.

> a. This step still needs work, and will need some collaborative language I am sure, but that is the rough idea.
> b. We all agree that the Orange Book/strength will have to change and we all agree that that change should not just revert back to 20/150

3) What to do with Mylan's generic product is still a bit of a gray area, I believe (and OGD correct me if I am not summarizing correctly)

> a. The labels don't match, but should it be determined the Mylan product can still be approved (with slightly different labels?), the Orange Book will halt them because there would have to be 2 different listings of strength in the Orange Book, which will cause prescriber confusion and would be precedence setting (in a bad way)
> b. With a CR issued to Janssen, I believe a company has 1 year to respond so it could be at least a year before we could get the Orange Book changed, however, this doesn't stop Mylan from wondering why it doesn't just get changed back to 20/150.

Everyone who attended via donut fueled presence or via phone please feel free to adjust, add or comment on the above summary. And thank you again to all who participated and who are continuing to work on this tricky situation.
Caroline

From: Joffe, Hylton
Sent: Thursday, January 30, 2014 7:51 AM
To: Bina, Christine; Strasinger, Caroline; Soule, Lisa; Duffy, Eric P; Ghosh, Tapash; Kitchens, Kelly; Jennings, Kerri-Ann;
Williamson, Charlene; Yu, Chongwoo; Davis, Daniel; Abraham, Ciby
Cc: Ghosh, Priyanka *; Newman, Bryan *; Dandamudi, Suman; Kim, Myong-Jin; Gassman, Audrey; Li, Guohua; Braddy,
April; Nguyen, Hoainhon T; Cai, Bing; Rege, Bhagwant; Li, Xihao; Ahn, Hae Young; Bashaw, Edward D; Conner, Dale P;
Stier, Ethan; Lionberger, Robert; Huang, Yih Chain
Subject: RE: Ortho Evra Delivery Rate - Implications on Current Supplement and ANDA 200910
Sorry I had to leave before the meeting ended. Did we reach alignment on the path forward?
Hylton

From: Bina, Christine
Sent: Wednesday, January 29, 2014 5:23 PM
To: Strasinger, Caroline; Soule, Lisa; Duffy, Eric P; Ghosh, Tapash; Kitchens, Kelly; Jennings, Kerri-Ann; Williamson,
Charlene; Yu, Chongwoo; Davis, Daniel; Abraham, Ciby
Cc: Ghosh, Priyanka *; Newman, Bryan *; Dandamudi, Suman; Kim, Myong-Jin; Gassman, Audrey; Joffe, Hylton; Li,
Guohua; Braddy, April; Nguyen, Hoainhon T; Cai, Bing; Rege, Bhagwant; Li, Xihao; Ahn, Hae Young; Bashaw, Edward D;
Conner, Dale P; Stier, Ethan; Lionberger, Robert; Huang, Yih Chain
Subject: RE: Ortho Evra Delivery Rate - Implications on Current Supplement and ANDA 200910

Just as a follow up to yesterday's meeting the medical necessity determination has been completed and Ortho Evra was found to be not medically necessary noting there are many effective alternative choices for contraception. Additionally, DSS has not yet been notified by the company of a shortage.
Thanks,
Christine

-----Original Appointment-----
From: Strasinger, Caroline
Sent: Friday, January 17, 2014 12:13 PM
To: Strasinger, Caroline; Soule, Lisa; Duffy, Eric P; Ghosh, Tapash; Kitchens, Kelly; Jennings, Kerri-Ann;
Williamson, Charlene; Yu, Chongwoo; Davis, Daniel; Abraham, Ciby; Bina, Christine
Cc: Ghosh, Priyanka *; Newman, Bryan *; Dandamudi, Suman; Kim, Myong-Jin; Gassman, Audrey; Joffe, Hylton;
Li, Guohua; Braddy, April; Nguyen, Hoainhon T; Cai, Bing; Rege, Bhagwant; Li, Xihao; Ahn, Hae Young; Bashaw,
Edward D; Conner, Dale P; Stier, Ethan; Lionberger, Robert; Huang, Yih Chain
Subject: Ortho Evra Delivery Rate - Implications on Current Supplement and ANDA 200910
When: Tuesday, January 28, 2014 9:00 AM-10:30 AM (UTC-05:00) Eastern Time (US & Canada).
Where: CDER WO 1537 conf rm Bldg21 - AR

Updated with Call-in, Adobe Connect, and Preliminary Information:

Additional information will be presented at the meeting but I wanted to provide this preliminary Slide Deck in
advance:

Call-In Information:
Number: 877-693-8068
Participant Passcode: 22442381
Please use the following link to access slides that will be discussed during the meeting:
https://collaboration.fda.gov/transdermalwg/
<< File: OE.ppt >> << File: OE CR letter.pdf >>

This meeting is being held to discuss the delivery rate of Ortho Evra. Ortho Evra is facing a drug shortage if we do not approve the current supplement for adhesive change. With our original CR the question of delivery rate and strength presentation has resurfaced. Additionally, Mylan is seeking approval for a generic product and a request/consultation to change the orange book back to the original strength presentation is currently in progress from OGD.

With that said, I have information to share regarding the delivery rate of Ortho Evra from the Mylan application which indicates that the J&J in vivo delivery rate of OE of 20/150 ug/day is wrong (most on this email are well aware of that fact), however, now we have some potential PK proof and actual estimates that the delivery rate is more along the lines of (b) (4) ug/day, albeit from a generic application that we can't share with the innovator.

This meeting is being held to strategize our next move on OE and then briefly the implications on the Generic. It appears Mylan has successfully matched OE but at a roughly 3 times the delivery of what J&J says their rate is.

It is confusing, I know. I will provide slides (and call-in information/adobe connect) at a later date that may help with clarity, but at this time I just wanted to get it on the calendar. I have included a large group of OCP, OND, ONDQA, and OGD, however, please forward the invite to those who may also need the information or be part of the discussion.

Thank you,
Caroline

Outcome Page

ANDA: 200910

Productivity

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
21688	12/31/2009	Other (REGULAR)	Addendum	0	0
				Total:	0

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

/s/

SUMAN DANDAMUDI
02/04/2014

UTPAL M MUNSHI
02/04/2014

HOAINHON N CARAMENICO
02/05/2014

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/05/2014

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	200910		
Drug Product Name	Norelgestromin and Ethinyl Estradiol Transdermal Patch		
Strength (s)	4.86 mg/0.53 mg/Patch (release rate 0.15 mg/0.02 mg/24 hrs)		
Applicant Name	Mylan Technologies Inc.		
Applicant Address	110 Lake St. St. Albans, VT 05478		
Applicant's Point of Contact	Joseph J. Sobecki		
Telephone Number	304- 599- 2595, ext 6429		
Fax Number	304- 285- 6407		
Original Submission Date(s)	December 31, 2009 October 8, 2010 (Dissolution Amendment) August 20, 2013		
Submission Date(s) of Amendment(s) Under Review	October 11, 2013		
Reviewer	Suman Dandamudi, Ph.D.		
Study Number (s)	ORTH-0942	ORTH-0943	ORTH-09198
Strength(s)	Fasting	Cumulative Irritation and Sensitization	Adhesion
Study Type (s)	4.86 mg/0.53 mg/Patch	4.86 mg/0.53 mg/Patch	4.86 mg/0.53 mg/Patch
Clinical Site	Cetero Research		
Clinical Site Address	625 Demers Avenue, East Grand Forks, MN 56721 USA		
Analytical Site	Mylan Pharmaceuticals Inc.		
Analytical Address	Bioanalytical Department 3711 Collins Ferry Road, Morgantown, WV 26505		
Dissolution Method	**Correct (Firm Proposed Method)**		
OVERALL REVIEW RESULT	**ADEQUATE**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 8, 28, 31	**Dissolution**	**4.86 mg/0.53 mg/Patch**	**ADEQUATE**

REVIEW OF A DISSOLUTION AMENDMENT

1 Executive Summary

Mylan Technologies Inc. submitted its responses to the dissolution deficiency comments made by the Division of Bioequivalence I (DBI) in the letter dated October 3, 2013 **[DARRTS: YOON, MARTIN 10/03/2013 FAX 10/03/2013 COR-ANDADE-01(Bio Incomplete Deficiencies) Original-1 (Not Applicable) Archive].** The submission references NDA 021180, Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch from Ortho-McNeil Pharmaceutical, Inc.

In the original application, the firm submitted the results of a fasting bioequivalence (BE) study with a pharmacokinetic (PK) endpoint, comparing it's test product Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch (release rate 0.15 mg/0.02 mg/24 hrs) to the corresponding reference product, Ortho-McNeil's Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch (release rate 0.15 mg/0.02 mg/24 hrs). In the review of the amendment dated August 20, 2013, the fasting BE study was found acceptable based on the adequate responses for the objectionable OSI findings at the analytical site[1].

In the original submission, the firm also submitted comparative dissolution testing data using both the FDA-recommended and in-house dissolution methods. Based on the dissolution data submitted, the firm's proposed method was considered most suitable for the test product. However, the dissolution testing using the firm's proposed method was found inadequate as the sampling time points employed are insufficient. In the amendment (dated 8/20/2013), the firm submitted the repeated dissolution testing data using their proposed method but with additional sampling time points. The dissolution testing using firm's proposed method was found acceptable. However, the firm's proposed specifications for both norelgestromin and ethinyl estradiol are too liberal for its test product. Based on the data submitted, the firm was asked to acknowledge the following FDA-recommended specifications which are more appropriate for the test product.

Norelgestromin: 0.5 hrs- NMT (b) (4)%, 2 hrs- (b) (4)%, 8 hrs- (b) (4)%, 20 hrs- NLT (b) (4)%

Ethinyl Estradiol: 0.5 hrs- NMT (b) (4)%, 2 hrs- (b) (4)%, 8 hrs- (b) (4)%, 20 hrs- NLT (b) (4)%

In the current submission, the firm accepted the FDA-recommended specifications for ethinyl estradiol and proposes a slight revision in the dissolution specifications for norelgestromin at 2 and 8 hours

[1] DARRTS for ANDA 200910: DANDAMUDI, SUMAN 09/06/2013 N/A 09/06/2013 REV-BIOEQ-21(Primary Review) Original-1 (Not Applicable) Archive

Parameter	DBI Proposal	Mylan Proposal
Norelgestromin		
0.5 hour	NMT (b) (4)%	NMT (b) (4)%
2 hour	(b) (4)%	(b) (4)%
8 hour	%	%
20 hour	NLT (b) (4)%	NLT (b) (4)%
24 hour	N/A	N/A

Based on additional dissolution data submitted for additional batches of test product, the Division of Bioequivalence I (DBI) agrees with the proposed changes of the specifications Thus, the dissolution testing is now acceptable.

The dissolution testing of the application is **adequate** with no deficiencies.

2 Table of Contents

3 Background

1. Mylan Technologies Inc. has submitted ANDA 200910 for its product, Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch (release rate 0.15 mg/0.02 mg/24 hrs). The submission references NDA 021180, Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch (release rate 0.15 mg/0.02 mg/24 hrs) from Ortho-McNeil Pharmaceutical, Inc.

2. The firm conducted comparative dissolution testing using both the FDA-recommended and in-house dissolution methods. The firm's proposed method gave profiles with more gradual slopes, compared with the FDA method, for both the test and reference products, and therefore, demonstrated superiority. However, the firm's dissolution testing was found inadequate due to insufficient sampling time points used in characterizing the more gradual release profiles, The firm was asked to conduct additional dissolution testing using its proposed method with the time points of 0.5, 2, 6, 8, 14, 20 and 24 hours]. In the current amendment, the firm submitted repeated dissolution testing data using in-house method.

3. In the amendment (dated 8/20/2013), the firm submitted dissolution testing data using its proposed method but with additional sampling time points. The dissolution testing was found acceptable. However, the firm was asked to acknowledge the more appropriate specifications for its test product.

4. In the current amendment, the firm is proposing changes to the dissolution specifications for its Norelgestromin component.

4 Submission Summary

4.1 Review of Current Dissolution Amendment

Deficiency 1: *The dissolution testing using your proposed method in 0.25% Tween 20 in water is acceptable. However, your proposed specifications are not acceptable. Based on the data submitted, the DBI has recommended more appropriate specifications for the test product. Please acknowledge your acceptance of the following method and specifications:*

The dissolution testing should be conducted in 900 mL of 0.25% Tween 20 at 32ºC[2] *±0.5ºC, using USP apparatus V (paddle over disk) at 50 rpm. The test product should meet the following specifications:*

[2] In the deficiency letter sent to the firm on 10/13/2013, there is an inadvertent error regarding the temperature. The temperature was listed as (b)(4)ºC instead of 32ºC. The firm through email correspondence confirmed with the DBI the temperature at which dissolution testing has to be performed (See appendix, for email communication)

Norelgestromin: 0.5 hrs- NMT (b)(4)%, 2 hrs- (b)(4)%, 8 hrs- (b)(4)%, 20 hrs- NLT (b)(4)%
Ethinyl Estradiol: 0.5 hrs- NMT (b)(4)%, 2 hrs- (b)(4)%, 8 hrs- (b)(4)%, 20 hrs- NLT (b)(4)%

Firm's Response: Mylan has reviewed the drug limits recommended by the Division of Bioequivalence I (DBI) for our Norelgestromin and Ethinyl Estradiol Transdermal System. Based on this review, Mylan agrees with the DB I limits for Ethinyl Estradiol, and the limits of 0.5 hr- NMT (b)(4)%, and 20 hrs – NLT (b)(4)% for Norelgestromin. Mylan also agrees with narrowing the range for the Norelgestromin limit at 8 hours from (b)(4)% (i.e. (b)(4)% as originally proposed by Mylan) to a (b)(4)% range. However, Mylan proposes to center this narrowed range based on the Norelgestromin data currently available for this product. Likewise, Mylan proposes to center the Norelgestromin limit at 2 hours based on the currently available data.

A summary of Mylan's proposal is shown in Table 1. A summary of the initial drug release data for Norelgestromin and Ethinyl Estradiol Transdermal System is shown in Table 2.

Table 1- Proposal for Drug Release Limits

(b) (4)

Table 2-Initial Drug Release Data for Norelgestromin and Ethinyl Estradiol Transdermal System (Based on 11 Test Batches)

	Norelgestromin (% label)	Ethinyl Estradiol (% label)
Lot #	(b) (4)	
R6A0014		
R6A0039		
R6A0040		
6E0013		
6C0138		

6C0139	(b) (4)
6C0140	
6D0083	
6D0084	
6D0085	
6D0151	
Range	
Range Center	

Mylan acknowledges that test method recommended by DBI, and the dissolution method utilized by Mylan is the same one as recommended by the Agency.

Reviewer's Comments:

- DB has previously accepted the firm proposed method for its product and recommended the firm to acknowledge the following specifications[1]:

  Norelgestromin: 0.5 hrs- NMT (b) (4)%, 2 hrs- (b) (4)%, 8 hrs- (b) (4)%, 20 hrs- NLT (b) (4)%

  Ethinyl Estradiol: 0.5 hrs- NMT (b) (4)%, 2 hrs- (b) (4)%, 8 hrs- (b) (4)%, 20 hrs- NLT (b) (4)%

- In the current amendment dated October 11, 2013, the firm accepts the FDA-recommended specifications for ethinyl estradiol, however proposes a slight change in the dissolution specification from that recommended by DBI for norelgestromin.

- To justify the proposed specifications, the firm submitted **mean drug release data for 11 batches of the test product at the time points where the specifications were set.**

- Only for the time points of 2 hrs and 8 hrs, is the firm proposing a revision in the dissolution specifications for norelgestromin from (b) (4)% (2 hrs) and (b) (4)% (8 hrs) to (b) (4)% (2 hrs) and (b) (4)% (8 hrs). However, the firm agrees with the DBI in narrowing the specification range from (b) (4)% at 8 hrs.

- **The range of the mean dissolution data of 11 batches is (b) (4)% and (b) (4)% at the 2 hr and 8 hr time points respectively**. The reviewer agrees with the firm that the firm's revised specifications for 2 hr and 8 hr time points indeed centers the range of the dissolution data submitted for the 11 batches. Based on the dissolution data submitted, the revised specifications of (b) (4)% and (b) (4)% at the 2 hr and 8 hr time points respectively are more appropriate for the test product.

- The reviewer also verified the biolot (Lot No 6A0014) and confirmed that the dissolution data of biolot met the firm's revised proposed specifications (See appendix for biolot dissolution data).

- The firm's response is acceptable.

4.2 Deficiency Comment

None

4.3 Recommendations

1. The firm's *in vitro* dissolution testing is acceptable. The dissolution testing should be conducted using the following method:

   The dissolution testing should be conducted in 900 mL of 0.25% Tween 20 at 32°C±0.5°C, using USP apparatus V (paddle over disk) at 50 rpm. The test product should meet the following specifications:

   Norelgestromin: 0.5 hrs- NMT (b)(4)%, 2 hrs- (b)(4)%, 8 hrs- (b)(4)%, 20 hrs- NLT (b)(4)%
   Ethinyl Estradiol: 0.5 hrs- NMT (b)(4)%, 2 hrs- (b)(4)%, 8 hrs- (b)(4)%, 20 hrs- NLT (b)(4)%

4.4 Comments for Other OGD Disciplines

Discipline	Comment
None	

5 Appendix

5.1 Dissolution Testing Data of the Biolot[3] (Original Submission)

Dissolution Conditions	**Apparatus:**	USP – V(Paddle over disk)
	Sinker:	No
	Speed of Rotation:	50 rpm
	Medium:	0.25% Tween 20 in water
	Volume:	900 mL
	Temperature:	32°C ± 0.5 °C
Firm's Proposed Specifications	Ethinyl Estradiol: [redacted] (b) (4) Norelgestromin:	
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 & Form	No. of Dosage Units		Collection Times (hrs) Norelgestromin (b) (4)				Study Report Location
N/A	Nov 2009	Norelgestromin/Ethinyl Estradiol Transdermal System 14 cm^2 Batch # R6A0014 Mfg date: May 2009	4.86 mg	12	Mean	9	22	54	97	3.2.P.5.4 Batch Analysis
					Range	[redacted] (b) (4)				
					%CV	3.4	4.8	2.6	0.8	
	Dec 2009	Ortho Evra® Transdermal System 20 cm^2 Batch # 8HM6015P1 Exp. Date: July 2010	6.00 mg	12	Mean	9	26	63	97	
					Range	[redacted] (b) (4)				
					%CV	5.7	3.4	2.9	1.1	

[3] DARRTS FOR ANDA 200910: DANDAMUDI, SUMAN 06/11/2013 N/A 06/11/2013 REV-BIOEQ-21(Primary Review) Original-1 (Not Applicable) Archive

Dissolution Conditions	**Apparatus:**	USP – V(Paddle over disk)
	Sinker:	No
	Speed of Rotation:	50 rpm
	Medium:	0.25% Tween 20 in water
	Volume:	900 mL
	Temperature:	32°C ± 0.5 °C
Firm's Proposed Specifications	Ethinyl Estradiol: [redacted] (b) (4) Norelgestromin:	
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 & Form**	**No. of Dosage Units**		**Collection Times (hrs)**				**Study Report Location**
						Ethinyl Estradiol				
						[redacted] (b) (4)				
N/A	Nov 2009	Norelgestromin/Ethinyl Estradiol Transdermal System 14 cm^2 Batch # R6A0014 Mfg date: May 2009	0.53 mg	12	Mean	11	27	60	97	3.2.P.5.4 Batch Analysis
					Range	[redacted] (b) (4)				
					%CV	2.9	3.5	2.7	0.8	
	Dec 2009	Ortho Evra® Transdermal System 20 cm^2 Batch # 8HM6015P1 Exp. Date: July 2010	0.75 mg	12	Mean	11	29	65	98	
					Range	[redacted] (b) (4)				
					%CV	3.5	3.1	2.7	1.0	

5.2 E-mail Communication between Reviewer and Bio-PM for firm's clarification on Temperature for Dissolution Testing

(NOT TO BE RELEASED UNDER FOIA)

From: Dandamudi, Suman
Sent: Tuesday, October 08, 2013 10:40 AM
To: Yoon, Martin
Cc: Braddy, April
Subject: RE: Norelgestromin and Ethinyl Estradiol Transdermal System ANDA 200910

Hello Martin,

Regarding the specifications, its not an error. Based on the data submitted we asked to firm acknowledge the more appropriate FDA specifications. Therefore 20 hrs-NLT (b)(4)% is right.

Regarding the temperature, its an inadvertent error in the letter. The temperature should be 32°C and not (b)(4)C.

Thanks,
Suman

From: Braddy, April
Sent: Tuesday, October 08, 2013 10:14 AM
To: Dandamudi, Suman
Cc: Yoon, Martin; Braddy, April
Subject: RE: Norelgestromin and Ethinyl Estradiol Transdermal System ANDA 200910

Suman:

Please address Martin's e-mail.

Sincerely,

April

From: Yoon, Martin
Sent: Tuesday, October 08, 2013 8:07 AM
To: Dandamudi, Suman; Braddy, April
Subject: FW: Norelgestromin and Ethinyl Estradiol Transdermal System ANDA 200910

Hi Suman,

I received two inquiries from the RPM for ANDA 200910. Mylan is seeking clarification to bio dissolution deficiency letter submitted 10/3/2013 (attached).

1. Mylan believe that there is a typographical error as the limits for both Norelgestromin and Ethinyl Estradiol for the last time point are listed as "20 hrs-

NLT (b)(4)%" and believe they should read "(b)(4) hrs- NLT (b)(4)%". Please confirm that this is a typographical error and not a change that FDA is requesting.

2. Confirmation for Mylan that the temperature listed on page 2 for the drug release test should be 32 degrees instead of (b)(4) degrees.

Thank you,

Martin Yoon, Pharm.D.
LT, U.S. Public Health Service
Bio Project Manager, Branch 8
Division of Bioequivalence I
FDA/CDER/OGD

From: Chuh, Esther
Sent: Monday, October 07, 2013 4:57 PM
To: Yoon, Martin
Subject: FW: Norelgestromin and Ethinyl Estradiol Transdermal System ANDA 200910

Hi Martin,

Below is another inquiry from Mylan.

Thank you,
Esther

From: Juliane.Foley@mylanlabs.com [mailto:Juliane.Foley@mylanlabs.com]
Sent: Monday, October 07, 2013 4:55 PM
To: Chuh, Esther
Cc: (b) (4)
(b) (4)
Subject: Fw: Norelgestromin and Ethinyl Estradiol Transdermal System ANDA 200910

Esther,

Can you also please get confirmation for us that the temperature listed on page 2 for the drug release test should be 32 degrees instead of (b)(4) degrees.

thanks

Juliane

Juliane M. Foley, MSA, RAC
Director, Regulatory Affairs
Mylan Technologies Inc
110 Lake St.
St. Albans VT 05478
802-527-9345

juliane.foley@mylan.com
----- Forwarded by Juliane Foley/STALBANS/MYLAN on 10/07/2013 04:52 PM -----

From: Juliane Foley/STALBANS/MYLAN
To: "Chuh, Esther" <Esther.Chuh@fda.hhs.gov>
Cc: (b) (4)
Date: 10/04/2013 04:56 PM
Subject: Norelgestromin and Ethinyl Estradiol Transdermal System ANDA 200910

Hi Esther.

Mylan would like to seek clarification on the drug release specifications listed on page 2 of the attached Agency Bioequivalence communication received today.

We believe that there is a typographical error as the limits for both Norelgestromin and Ethinyl Estradiol for the last time point are listed as "20 hrs- NLT (b) (4)%" and we believe they should read "(b) (4) hrs- NLT (b) (4)%".

Can you please confirm that this is a typographical error and not a change that FDA is requesting.

thanks

Juliane

Juliane M. Foley, MSA, RAC
Director, Regulatory Affairs
Mylan Technologies Inc
110 Lake St.
St. Albans VT 05478
802-527-9345
juliane.foley@mylan.com

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200910

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch

The Division of Bioequivalence I (DBI) has completed the review of the dissolution portion of your submission acknowledged on the cover page and has no further questions at this time.

We agree with your proposed revisions of the FDA-recommended specifications at the 2-hour and 8-hour time points, based on the dissolution data of additional 11 fresh test batches. We acknowledge that you will conduct dissolution testing for the test product using the following dissolution method and specifications:

The dissolution testing should be conducted in 900 mL of 0.25% Tween 20 at 32ºC±0.5ºC, using USP apparatus V (paddle over disk) at 50 rpm. The test product should meet the following specifications:

Norelgestromin: 0.5 hrs - NMT (b)(4)%, 2 hrs - (b)(4)%, 8 hrs - (b)(4)%, 20 hrs - NLT (b)(4)%

Ethinyl Estradiol: 0.5 hrs - NMT (b)(4)%, 2 hrs - (b)(4)%, 8 hrs - (b)(4)%, 20 hrs - NLT (b)(4)%

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

6 Outcome Page

ANDA: 200910

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
21064	10/11/2013	Other (REGULAR)	Dissolution 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/

SUMAN DANDAMUDI
11/08/2013

APRIL C BRADDY
11/08/2013

HOAINHON N CARAMENICO on behalf of DALE P CONNER
11/11/2013

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	200910		
Drug Product Name	Norelgestromin and Ethinyl Estradiol Transdermal Patch		
Strength(s)	4.86 mg/0.53 mg/Patch		
Applicant Name	Mylan Technologies Inc.		
Address	110 Lake St. St. Albans, VT 05478		
Applicant's Point of Contact	Joseph J. Sobecki		
Contact's Telephone Number	304- 599- 2595, ext 6429		
Contact's Fax Number	304- 285- 6407		
Original Submission Date(s)	December 31, 2009 October 8, 2010 (Dissolution Amendment)		
Submission Date(s) of Amendment(s) Under Review	August 20, 2013		
Reviewer	Suman Dandamudi, Ph.D.		
Study Number (s)	ORTH-0942	ORTH-0943	ORTH-09198
Study Type (s)	Fasting	Cumulative Irritation and Sensitization	Adhesion
Strength (s)	4.86 mg/0.53 mg/Patch	4.86 mg/0.53 mg/Patch	4.86 mg/0.53 mg/Patch
Clinical Site	Cetero Research		
Clinical Site Address	625 Demers Avenue, East Grand Forks, MN 56721 USA		
Analytical Site	Mylan Pharmaceuticals Inc.		
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Road, Morgantown, WV 26505		
OVERALL REVIEW RESULT	**INADEQUATE**		
OSI REPORT RESULT	**ADEQUATE**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 28	**DISSOUTION**	**4.86 mg/0.53 mg/Patch**	**INADEQUATE**
	FASTING STUDY	**0.15 mg/0.02 mg/day**	**ADEQUATE**

REVIEW OF AN AMENDMENT

1 EXECUTIVE SUMMARY

Mylan Technologies Inc. submitted its responses to the deficiency comments made by the Division of Bioequivalence I (DBI) in the letter dated June 13, 2013 **[DARRTS: CHUH, EUNJUNG E 06/13/2013 FAX 06/13/2013 COR-ANDAACTION-09(Complete Response) Original-1 (Not Applicable) Archive].** The submission references NDA 021180, Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch from Ortho-McNeil Pharmaceutical, Inc.

In the original application, the firm submitted the results of a fasting bioequivalence (BE) study with a pharmacokinetic (PK) endpoint, comparing the test product Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch to the corresponding reference product, Ortho-McNeil's Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch. The fasting BE study was tentatively found acceptable. However, the firm was asked to address the OSI findings at the analytical site (based on ANDA 200245) in order to determine whether or not the findings have an impact the outcome of the current ANDA.

In the current amendment, the firm submitted its responses for the objectionable OSI findings. The firm's responses are found acceptable and therefore the studies are now deemed **adequate (acceptable).**

In the original submission, the firm also submitted comparative dissolution testing data using both the FDA-recommended and in-house dissolution methods. Based on the dissolution data submitted, the firm's proposed method was considered most suitable for the test product. However, the dissolution testing using the firm's proposed method was found inadequate as the sampling time points employed are insufficient. The firm was asked to conduct additional dissolution testing using its method on fresh test lot and unexpired reference lot, using the time points of 0.5, 2, 6, 8, 14, 20 and 24 hours.

In the current amendment, the firm submitted the repeated dissolution testing data using their proposed method but with additional sampling time points. The dissolution testing using firm's proposed method is acceptable. However, the firm's proposed specifications for both norelgestromin and ethinyl estradiol are too liberal for its test product. Based on the data submitted, the firm will be asked to acknowledge the following FDA-recommended specifications which are more appropriate for the test product.

Norelgestromin: 0.5 hrs- NMT (b) (4)%, 2 hrs- (b) (4)%, 8 hrs- (b) (4)%, 20 hrs- NLT (b) (4)%

Ethinyl Estradiol: 0.5 hrs- NMT (b) (4)%, 2 hrs- (b) (4)%, 8 hrs- (b) (4)%, 20 hrs- NLT (b) (4)%

No Office of Scientific Investigations (OSI) inspection is pending for uif!bobmzujdbm!ps!dmjojdbm!tjuft[2-]![3]/!

The application is **Incomplete (Inadequate).**

NOTE TO REGULATORY PROJECT MANAGER (RPM): The Bio portion of this application is adequate. However, dissolution is still pending. Please contact the BIO PM prior to issuing the Complete Response (CR) letter.

NOTE TO BIOEQUIVALENCE PROJECT MANAGER (BIO-PM): Please see a SEPARATE DISSOLUTION DEFICIENCY LETTER (LETTER 2) attached to the SAME review.

[1] The clinical site was inspected for NDA 022503 DARRTS for NDA 022503 (routine) on 4/22/2010 and the outcome of the inspection was No Action Indicated (NAI) [**DARRTS for NDA 022503: RIVERA-LOPEZ, CAROL M 04/22/2010 N/A 04/22/2010 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Type 3- New Dosage Form) Archive]**

[2] The analytical site was inspected for ANDA 200245 (Routine) on 09/10/2010 and the outcome was Voluntary Action Indicated (VAI). **[DARRTS for ANDA 200245: DASGUPTA, ARINDAM 09/17/2010 N/A 09/17/2010 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Not Applicable) Archive]**

2 TABLE OF CONTENTS

3 BACKGROUND

1. Mylan Technologies Inc. has submitted ANDA 200910 for its product, Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch. The submission references NDA 021180, Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch from Ortho-McNeil Pharmaceutical, Inc.

2. In the original application, the firm submitted fasting bioequivalence (BE) study with a pharmacokinetic (PK) endpoint, comparing its test product Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch to the corresponding reference product, Ortho-McNeil's Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch. The BE study was found tentatively acceptable (pending OSI inspection) **[DARRTS: DANDAMUDI, SUMAN 06/11/2013 N/A 06/11/2013 REV-BIOEQ-21(Primary Review) Original-1 (Not Applicable) Archive]**. The results of fasting BE study are summarized in the tables below:

Norelgestromin and Ethinyl Estradiol Transdermal Film Dose 1 x 0.15 mg/0.02 mg/day × 7 days SUMMARY OF STATISTICAL ANALYSIS- Norelgestromin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. ORTH-0942							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	185.36	21	199.09	21	0.93	86.67	100.01
AUC∞ (hr *ng/ml)	189.82	21	204.21	21	0.93	86.61	99.76
Cmax (ng/ml)	1.32	21	1.35	21	0.98	90.08	105.87

Norelgestromin and Ethinyl Estradiol Transdermal Film Dose 1 x 0.15 mg/0.02 mg/day × 7 days SUMMARY OF STATISTICAL ANALYSIS-Ethinyl Estradiol Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. ORTH-0942							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	12526.39	21	14451.40	21	0.87	81.33	92.38
AUC∞ (hr *pg/ml)	12665.03	21	14612.44	21	0.87	81.33	92.37
Cmax (pg/ml)	95.16	21	105.52	21	0.90	82.48	98.60

3. The firm has conducted comparative dissolution testing using both the FDA-recommended and in-house dissolution methods. The firm's proposed method gave profiles with more gradual slopes, compared with the FDA method, for both the test and reference products, and therefore, demonstrated superiority. However, the firm's dissolution testing was found inadequate due to insufficient sampling time points used in characterizing the more gradual release profiles, The firm was asked

to conduct additional dissolution testing using its proposed method with the time points of 0.5, 2, 6, 8, 14, 20 and 24 hours]. In the current amendment, the firm submitted repeated dissolution testing data using in-house method.

4. In addition, in the deficiency letter, dated June 13, 2013[3], the firm was also asked to address the OSI findings at the analytical site (based on ANDA 200245) in order to determine whether or not the findings have an impact the outcome of the current ANDA 200910. In the current amendment, the firm submitted adequate responses to the OSI findings.

4 SUBMISSION SUMMARY

4.1 Drug Product Information, PK/PD Information, and Relevant DB History

See the review of the original submission, **DARRTS: DANDAMUDI, SUMAN 06/11/2013 N/A 06/11/2013 REV-BIOEQ-21(Primary Review) Original-1 (Not Applicable) Archive.**

- On July 1, 2013 changes were made in the reference-listed drug (RLD) labeling regarding the patient labeling and patient information card[4].

- There is no change in the BE recommendations for Norelgestromin and Ethinyl Estradiol Transdermal Patch since the review of the original submission. As per the Individual product Bioequivalence Recommendations (May 2009, Revised July 2009) posted at FDA website, a fasting and fed BE studies are recommended for this drug product.
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM162407.pdf.

[3] DARRTS for ANDA 200910: CHUH, EUNJUNG E 06/13/2013 FAX 06/13/2013 COR-ANDAACTION-09(Complete Response) Original-1 (Not Applicable) Archive
[4] Drugs@fda, last accessed August 29, 2013

4.2 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

4.3 Review of Current Amendment

Deficiency 1: *The comparative dissolution testing conducted using your proposed method is considered inadequate. Your proposed method gave release profiles with more gradual slopes, compared with the FDA method, for both the test and reference products, and therefore, demonstrated superiority. However, the dissolution testing based on your method did not include sufficient sampling time points to characterize adequately the more gradual release profiles. Please conduct additional comparative dissolution testing using your method on a fresh test lot and unexpired reference lot, using the time points of 0.5, 2, 6, 8, 14, 20 and 24 hours. The fresh test lot should be manufactured using the same manufacturing conditions, specifications and formulation as the bio study test lot, and the Chemistry, Manufacturing and Controls records for the fresh test lot should be submitted to the Division of Chemistry for evaluation. The Certificate of Analysis for this fresh test lot should also be submitted to DBI for confirmation.*

Firm's Response: As requested, Mylan performed comparative dissolution testing on test and reference product with the additional time points recommended by the Agency. Drug release profiles for the test and reference lot are provided in Section 3.2.P.5.4. A revised Bioequivalence Summary table 5 –Summary of In Vitro Dissolution Studies is provided in Section 2.7. A fresh lot of test product was manufactured (b) (4) [redacted] are provided in Section 3.2.R. Certificates of Analysis from both Mylan (b) (4) for Norelgestromin Drug Substance (Lot 214047N) and from both Mylan (b) (4) for Norelgestromin Drug Substance (Lot 27A211F), and Certificates of Analysis from both Mylan (b) (4) for Ethinyl

Estradiol drug substance (Lot L00033722) used in the production of this test product are also provided in Section 3.2.S.4.4. (b) (4) used in the comparative dissolution testing, are provided in Section 3.2.P.5.4. A Certificate of Analysis for the RLD lot (Lot 2JM7719P2) used in the comparative dissolution testing is also provided in Section 3.2.P.5.4

Reviewer's Comments:

- In the original submission, the firm submitted the comparative dissolution data for Norelgestromin and Ethinyl Estradiol Transdermal Patch, using both the FDA recommended and in-house dissolution methods.

  FDA-Recommended Method:
  Medium: 0.1% Hydroxypropyl-beta-cyclodextrin in water
  Apparatus: USP – V (Paddle over disk)
  Speed/RPMs: 50 rpm
  Volume: 900 mL

  Firm's Proposed Method:
  Medium: 0.25% Tween 20 in water
  Apparatus: USP – V (Paddle over disk)
  Speed/RPMs: 50 rpm
  Volume: 900 mL
  Sampling Times: (b) (4) hours

- Based on the dissolution data submitted, the firm's proposed method was considered most suitable for the test product. However, the dissolution testing using the firm's proposed method was found inadequate as the sampling time points employed are insufficient[5].

- Therefore, the firm was asked to conduct additional dissolution testing using in-house method on fresh test lot and unexpired reference lot, using the time points of 0.5, 2, 6, 8, 14, 20 and 24 hours.

- In the current amendment, the firm submitted the repeated dissolution testing data using their proposed method but with additional sampling time points. The data submitted with additional sampling time points captured the gradual and complete release profile for both the components. Therefore, the dissolution testing using firm's proposed method is acceptable.

- However, the firm's proposed specifications for both norelgestromin and ethinyl estradiol are too liberal for its test product. Based on the data submitted, the firm

[5] DARRTS for ANDA 200910: DANDAMUDI, SUMAN 06/11/2013 N/A 06/11/2013 REV-BIOEQ-21(Primary Review) Original-1 (Not Applicable) Archive

will be asked to acknowledge the following FDA-recommended specifications which are more appropriate for the test product.

Norelgestromin: 0.5 hrs- NMT (b) (4)%, 2 hrs- (b) (4)%, 8 hrs- (b) (4)%, 20 hrs- NLT (b) (4)%

Ethinyl Estradiol: 0.5 hrs- NMT (b) (4)%, 2 hrs- (b) (4)%, 8 hrs- (b) (4)%, 20 hrs- NLT (b) (4)%

- The firm manufactured a new lot of the test product, since the test lot (R6A0014) used in the original dissolution testing was expired. The firm stated that the new test lot (6D0083) is manufactured using the same composition and under identical manufacturing conditions as that of the original test batch (R6A0014).

- In addition, the reference lot (8HM6015P1) used in originally submitted dissolution data has expired. So the firm used a new Reference lot (2JM7719P2) for the repeated dissolution testing.

- The firm also submitted certificate of analysis (COA) for both test and reference lots.

- **The dissolution testing is incomplete.**

Dissolution Data of Test Product using Firm's Proposed Method:

Dissolution Conditions	**Apparatus:**	USP – V(Paddle over disk)
	Sinker:	No
	Speed of Rotation:	50 rpm
	Medium:	0.25% Tween 20 in water
	Volume:	900 mL
	Temperature:	32°C ± 0.5 °C
Firm's Proposed Specifications	Ethinyl Estradiol: Norelgestromin:	(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 & Form**	**No. of Dosage Units**		**Collection Times (hrs)**							**Study Report Location**
						0.5	**2**	**6**	**8**	**14**	**20**	**24**	
N/A	June 2013	Norelgestromin/Ethinyl Estradiol Transdermal System 14 cm^2 Batch # 6D0083 Mfg date: Sep 2012	NGMN 4.86 mg	12	Mean	11	25	47	55	83	95	97	3.2.P.5.4 Batch Analysis
					Range	(b) (4)							
					%CV	6.9	2.7	1.7	2.3	1.9	1.3	0.8	
			EE 0.53 mg		Mean	12	28	52	61	86	96	98	
					Range	(b) (4)							
					%CV	0.0	1.8	1.2	1.3	1.8	0.9	0.7	
	June 2013	Ortho Evra® Transdermal System 20 cm^2 Batch # 2JM7719P2 Exp. Date: Aug 2014	NGMN 6.00 mg	12	Mean	11	29	53	65	87	92	95	
					Range	(b) (4)							
					%CV	4.7	2.5	2.8	2.5	1.7	1.5	1.6	
			EE 0.75 mg		Mean	13	32	56	68	89	94	96	
					Range	(b) (4)							
					%CV	4.0	3.4	2.2	2.4	1.6	1.7	1.8	

Deficiency Comment 2: *Following the inspection of the analytical site, Mylan Pharmaceuticals Inc. Bioanalytical Department, 3711 Collins Ferry Rd, Morgantown, WV, between August 18-26, 2010, by the Office of Scientific Investigations (OSI) for bioequivalence (BE) studies from another application, Form FDA- 483 was issued for the site.*

For considering the impact of similar study conduct and site practices by the same analytical facility on the fasting bioequivalence (BE) study of the current ANDA, the DBI reviewed the above OSI inspection report and found that the following objectionable findings by the OSI at the analytical site could potentially compromise the integrity of the study of current ANDA as well:

- *Stability of processed samples was determined with only mid level QCs during pre-study validation for the audited studies. Processed stability was not evaluated with low and high QC concentrations.*

- *Failure to document all aspects of the study conduct.*

- *No documentation was maintained for identity of the weighing scales used for quarterly qualification for pipettes during the audited studies.*

Please address the above specific findings by the OSI with respect to their impact on the fasting BE study of the current ANDA, providing any necessary supporting documents in your response.

Firm's Response:

Processed Sample Stability: Processed sample stability (PPS) at the low and high quality control (QC) levels was demonstrated for the analytes measured in the ORTH-0942 study in Ethinyl Estradiol (EEST) Validation Addendum 8 (124.5 hours) and Norelgestromin (NORE) Validation Addendum 2 (76.5 hours). These reports are provided in Section 5.3.1.4.

The processed sample stability intervals established at the low and high QC levels were sufficient to cover the maximum processed sample storage intervals for the ORTH-0942 study samples (36 hours for ethinyl estradiol and 49 hours for norelgestromin). Thus there was no impact of this finding on the current ANDA.

Balance Documentation: As detailed in our 08-Sep-2010 483 response, to ensure the ID of the balance was captured, Laboratory Procedure (LP) LP-013 ("Maintenance, Qualification and Use of Handheld Pipettes") was revised to include a prompt on the data worksheet for the analyst to record the balance ID at the time that pipette qualification is performed. The revised LP was made effective on 03-Sep-2010. The bioanalytical phase the ORTH-0942 study ran from 11-Aug-2009 through 19-Aug-2009 (ethinyl estradiol) and 17-Sep-2009 through 24-Sep-2009 (norelgestromin), and thus was conducted under the

previous version of LP-013. To assess impact on this study, a similar assessment as that detailed in our 08-Sep-2010 483 response was performed.

As summarized in Table 2-1, five (5) pipettes were used in the ORTH-0942 study. The then current (at the time of study use) qualification dates for these pipettes are also provided in Table 2-1. Copies of the Qualification Worksheets are provided in Section 5.4.

With regard to the identity of the balances used for the pipette qualifications, as noted in the 2010 483 response, analysts in the laboratory typically use a specific Mettler-Toledo SAG285 analytical balance (PLE 8622), located in the laboratory's balance room, for pipette qualification. This balance is interfaced to a PC that runs a validated spreadsheet application that processes the pipette qualification data. This system was viewed by one of the DSI inspectors during the 2010 inspection. We recognize, however, that this does not provide conclusive evidence that balance 8622 was used for the qualification of pipettes used in this project. However as discussed below, we have established that all Bioanalytical Laboratory balances were in a qualified state and were therefore valid to use during this time period.

All Bioanalytical Laboratory balances are tracked, maintained, and qualified from receipt until retirement. There were 8 balances in operation when the ORTH-0942 study was conducted: 4 analytical balances, 2 top-loading balances, and 2 micro balances.

The top-loading balances (Mylan IDs 8612 and 8633) read to a maximum of 3 decimal places. The weights recorded during the pipette qualifications contain 5 decimal place readings, precluding the possibility of using a precision balance. The requisite precision for the pipette qualification could have been provided only by the analytical or micro balances. To that end, all then-current quarterly balance qualification records for these 6 balances (Analytical Balances: Mylan IDs 8492, 8507, 02-2009-A1, 8622 and Micro Balances: Mylan IDs 8600, 8611) encompassing the time period from May through September 2009 (covering the qualification of all hand-held pipettes used in the ORTH-0942 study) were reviewed. These records, which are provided in Section 5.4, show that each balance was in a qualified state.

Based on the above, there was no impact of this finding on the current ANDA

Reviewer's Comments on Firm's Response #2:

Processed Stability:

- In the current amendment, the firm submitted addendums to validation reports of norelgestromin (Addendum 2) and ethinyl estradiol (Addendum 8) which contains processed stability data. In these validation reports, the firm demonstrated the processed stability for both the analytes at the low and high QC levels. However, this supplemental validation was performed after the analyses of the study samples.

- The pre-study validation report submitted in the original submission contains processed sample stability data which was demonstrated only with mid level QCs.

- Even though the firm demonstrated processed stability with only mid QC, acceptable calibration standards (CCs) and Quality control samples (QCs) which were processed along with the study samples, assures the validity of the study data. Therefore, the reviewer is of opinion that **the OSI finding does not have any impact on the outcome of the current fasting BE study.**

Balance Documentation:

- The firm stated that after the OSI inspection, Laboratory Procedure LP013 "Maintenance, qualification and Use of Handheld Pipettes" was revised to include a prompt on the data worksheet for the analyst to record balance ID at the time that pipette qualification is performed.

- However, this revised SOP was not implemented during the study analyses, since the SOP was revised after the completion of the BE study of the current ANDA.

- The firm stated that although the balance ID was not recorded, only one balance interfaced to a PC running a validated spreadsheet application for pipette qualification data was typically used for pipette calibration.

- In addition the firm also submitted balance qualification records for all the balances that were used in the study analyses of the current ANDA. The records indicate that each balance passed the quarterly calibration.

- Therefore, the reviewer is of opinion that **the OSI finding does not have any impact on the outcome of the current fasting BE study**

Deficiency Comment #3**:** *During the fasting BE study (ORH-0942), two (2) study samples for norelgestromin were re-assayed for the reason of "Abnormal Internal Standard Response" as per Bioanalytical report (ORTH-0942_NORE), Table 5- Repeat Analysis Results for NORE in Human Plasma. However, in the table of Reanalysis of Study Samples, you have stated the reason for the re-assay as "Documented Sample Processing Error". Please be advised that for the future submissions, you should provide consistent information concerning repeat analyses throughout your submission.*

Firm's Response: In response to the Agency's comment, we have reviewed the ORTH-0942 bioanalytical study reports and Bioequivalence Summary Table 9 ("Reanalysis of Study Samples") as submitted with the ANDA. The two study samples re-assayed for norelgestromin were correctly identified in Bioequivalence Summary Table 9 as having been re-assayed for "Abnormal Internal Standard Response". Samples re-assayed for ethinyl estradiol were also summarized in Bioequivalence Summary Table 9 (lower panel

of the table). As shown in this table, there were 2 study samples re-assayed for ethinyl estradiol due to "Documented Sample Processing Error". For this response, all the re-assay reasons listed in Bioequivalence Summary Table 9 for both analytes were verified against the respective bioanalytical study reports and found to be correct.

Reviewer's Comments on Firm's Response #3: The firm confirmed that the samples for norelgestromin that were re-assayed were indeed for the reason of "Abnormal Internal Standard Response". **The firm's response to the 3rd deficiency is acceptable.**

4.4 Deficiency Comment

The dissolution testing with firm's own proposed method is acceptable. However, the firm should acknowledge the FDA-recommended specification.

4.5 Recommendations

1. The Division of Bioequivalence I accepts the fasting BE study (ORTH-0942) conducted by the Mylan technologies Inc. on its Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch (Lot #R6A0014) comparing it to Ortho-McNeil Pharmaceuticals' Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch (Lot # 7LM5212).

2. The firm's *in vitro* dissolution testing is incomplete. The firm should acknowledge the following dissolution method and specification:

   The dissolution testing should be conducted in 900 mL of 0.25% Tween 20 at (b)(4)°C±0.5°C, using USP apparatus V (paddle over disk) at 50 rpm. The test product should meet the following specifications:

   Norelgestromin: 0.5 hrs- NMT (b)(4)%, 2 hrs- (b)(4)%, 8 hrs- (b)(4)%, 20 hrs- NLT (b)(4)%
   Ethinyl Estradiol: 0.5 hrs- NMT (b)(4)%, 2 hrs- (b)(4)%, 8 hrs- (b)(4)%, 20 hrs- NLT (b)(4)%

3. The Division of Bioequivalence tentatively deems the test product Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch manufactured by Mylan technologies Inc., to be bioequivalent to the reference product, Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch manufactured by Ortho-McNeil Pharmaceuticals.

4.6 Comments for Other OGD Disciplines

Discipline	Comment
None	

LETTER 1 of 2: BIOEQUIVALENCE COMMENTS TO BE PROCESSED BY REGULATORY PROJECT MANAGER (RPM)
NOTE to RPM: The Bio portion of this application is adequate. However, dissolution is still pending. Please contact the BIO PM prior to issuing the Complete Response (CR) letter.

NOTE TO BIOEQUIVALENCE PROJECT MANAGER (BIO-PM): Please see LETTER 2 FOR DISSOLUTION DEFICIENCIES (FOLLOWING THIS LETTER) TO BE PROCESSED BY BIO-PM

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	200910
APPLICANT:	Mylan Technologies, Inc.
DRUG PRODUCT:	Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch

The Division of Bioequivalence I (DBI) has completed the review of your submission acknowledged on the cover page and has no further questions at this time.

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

LETTER 2 of 2: DISSOLUTION DEFICIENCY LETTER TO BE SENT TO THE APPLICANT BY BIOEQUIVALENCE PROJECT MANAGER (BIO-PM)

NOTE TO REGULATORY SUPPORT PROJECT MANAGER (RPM): Please see LETTER 1 FOR BIOEQUIVALENCE COMMENTS TO BE PROCESSED BY RPM

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200910

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch

The Division of Bioequivalence I (DBI) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the fasting bioequivalence (BE) study will be conducted later. The following deficiency has been identified:

The dissolution testing using your proposed method in 0.25% Tween 20 in water is acceptable. However, your proposed specifications are not acceptable. Based on the data submitted, the DBI has recommended more appropriate specifications for the test product. Please acknowledge your acceptance of the following method and specifications:

The dissolution testing should be conducted in 900 mL of 0.25% Tween 20 at (b) (4)ºC±0.5ºC, using USP apparatus V (paddle over disk) at 50 rpm. The test product should meet the following specifications:

Norelgestromin: 0.5 hrs- NMT (b) (4)%, 2 hrs- (b) (4)%, 8 hrs- (b) (4)%, 20 hrs- NLT (b) (4)%
Ethinyl Estradiol: 0.5 hrs- NMT (b) (4)%, 2 hrs- (b) (4)%, 8 hrs- (b) (4)%, 20 hrs- NLT (b) (4)%

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

5 OUTCOME PAGE

ANDA: 200910

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
20613	8/20/2013	Other (REGULAR)	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/

HARITHA MANDULA on behalf of SUMAN DANDAMUDI
09/04/2013

APRIL C BRADDY
09/05/2013

HOAINHON N CARAMENICO
09/06/2013

HOAINHON N CARAMENICO on behalf of DALE P CONNER
09/06/2013

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	200910		
Drug Product Name	Norelgestromin and Ethinyl Estradiol Transdermal Patch		
Strength(s)	4.86 mg/0.53 mg/Patch		
Applicant Name	Mylan Technologies Inc.		
Applicant Address	110 Lake St. St. Albans, VT 05478		
US Agent Name and the mailing address	S. Wayne Talton		
US agent's Telephone Number	304- 599- 2595		
US Agent's Fax Number	304- 285- 6407		
Original Submission Date(s)	December 31, 2009		
Submission Date(s) of Amendment(s) Under Review	October 8, 2010 (Dissolution Amendment)		
First Generic (Yes or No)	No		
Reviewer	Suman Dandamudi, Ph.D.		
Study Number (s)	ORTH-0942	ORTH-0943	ORTH-09198
Study Type (s)	Fasting	Cumulative Irritation and Sensitization	Adhesion
Strength (s)	4.86 mg/0.53 mg/Patch	4.86 mg/0.53 mg/Patch	4.86 mg/0.53 mg/Patch
Clinical Site (PK BE Study)	Cetero Research		
Clinical Site Address (PK BE Study)	625 Demers Avenue, East Grand Forks, MN 56721 USA		
Analytical Site	Mylan Pharmaceuticals Inc.		
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Road, Morgantown, WV 26505		
OSI REPORT RESULT	**INADEQUATE**		
OVERALL REVIEW RESULT	**INADEQUATE**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 3	**DISSOUTION**	**4.86 mg/0.53 mg/Patch**	**INADEQUATE**
1	**FASTING STUDY**	**0.15 mg/0.02 mg/day**	**ADEQUATE***

** Only pending firm's response to OSI findings*

1 EXECUTIVE SUMMARY

This application contains the results of three studies, (1) a fasting bioequivalence (BE) study with a pharmacokinetic (PK) endpoint, comparing the test product Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch to the corresponding reference product, Ortho-McNeil's Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch; (2) Adhesion study (Orth-Cln-09198); and (3) Sensitization/Irritation study (Orth-Cln-0943). The Division of Bioequivalence is responsible for the review of the BE study, and the Division of Clinical Review is responsible for review of the Adhesion and Sensitization/Irritation Studies[1]. Therefore, this document is a review of the fasting BE study only.

The fasting bioequivalence (BE) study is designed as a single-dose, two-way crossover in healthy female subjects. The firm's fasting BE study is tentatively acceptable. The results are summarized in the tables below:

Norelgestromin and Ethinyl Estradiol Transdermal Film
Dose 1 x 0.15 mg/0.02 mg/day × 7 days
SUMMARY OF STATISTICAL ANALYSIS- Norelgestromin
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Fasting Bioequivalence Study, Study No. ORTH-0942

Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	185.36	21	199.09	21	0.93	86.67	100.01
AUC∞ (hr *ng/ml)	189.82	21	204.21	21	0.93	86.61	99.76
Cmax (ng/ml)	1.32	21	1.35	21	0.98	90.08	105.87

Norelgestromin and Ethinyl Estradiol Transdermal Film
Dose 1 x 0.15 mg/0.02 mg/day × 7 days
SUMMARY OF STATISTICAL ANALYSIS-Ethinyl Estradiol
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Fasting Bioequivalence Study, Study No. ORTH-0942

Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *pg/ml)	12526.39	21	14451.40	21	0.87	81.33	92.38
AUC∞ (hr *pg/ml)	12665.03	21	14612.44	21	0.87	81.33	92.37
Cmax (pg/ml)	95.16	21	105.52	21	0.90	82.48	98.60

The firm has conducted comparative dissolution testing using both the FDA-recommended and in-house dissolution methods. The firm's proposed method gave profiles with more gradual slopes, compared with the FDA method, for both the test and reference products, and therefore, demonstrated superiority. However, the firm's dissolution testing is inadequate due to insufficient sampling time points used in characterizing the more gradual release profiles, The firm is asked to conduct additional

[1] DARRTS for ANDA 200910: LEE, NICOLE 05/14/2013 N/A 05/14/2013 REV-CLINICAL-21(Primary Review) Original-1 (Not Applicable) Archive

dissolution testing using its method on fresh test lot and unexpired reference lot, using the time points of 0.5, 2, 6, 8, 14, 20 and 24 hours.

No Office of Scientific Investigations (OSI) inspection is pending for the clinical[2] and analytical sites.[3] However, the firm will be asked to address the OSI findings at the analytical site (based on ANDA 200245) in order to determine whether or not the findings will have an impact the outcome of the current ANDA 200910.

The application is incomplete (**inadequate)**.

[2] The clinical site was inspected for NDA 022503 DARRTS for NDA 022503 (routine) on 4/22/2010 and the outcome of the inspection was No Action Indicated (NAI) [**DARRTS for NDA 022503: RIVERA-LOPEZ, CAROL M 04/22/2010 N/A 04/22/2010 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Type 3- New Dosage Form) Archive]**

[3] The analytical site was inspected for ANDA 200245 (Routine) on 09/10/2010 and the outcome was Voluntary Action Indicated (VAI). **[DARRTS for ANDA 200245: DASGUPTA, ARINDAM 09/17/2010 N/A 09/17/2010 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Not Applicable) Archive]**

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[4, 5]

Test Product	Norelgestromin and Ethinyl Estradiol Transdermal Film Extended Release, 4.86 mg/0.53 mg (0.15 mg/0.02 mg/day)
Reference Product	Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal Film Extended Release, 6 mg/0.75 mg (0.15 mg/0.02 mg/day)
RLD Manufacturer	Ortho-McNeil Pharmaceutical, Inc.
NDA No.	021180
RLD Approval Date	November 20, 2001
Indication	Ortho Evra® is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception

3.2 PK/PD Information[5,6]

Bioavailability	Following a single application of the drug product, both Norelgestromin (NGMN) and Ethinyl Estradiol (EE) reach a plateau by approximately 48 hours. Pooled data from the 3 clinical studies have demonstrated that steady state is reached within 2 weeks of application. Absorption of NGMN and EE following application of ORTHO EVRA® to the buttock, upper outer arm, abdomen and upper torso (excluding breast) was examined. While absorption from the abdomen was slightly lower than from other sites, absorption from these anatomic sites was considered to be therapeutically equivalent. The absorption of NGMN and EE following application of ORTHO EVRA® was studied under conditions encountered in a health club (sauna, whirlpool and treadmill) and in a cold water bath. The results indicated that for NGMN there were no significant treatment effects on Css or AUC when compared to normal wear. For EE, increased exposures were observed due to sauna, whirlpool and treadmill. There was no significant effect of cold water on these parameters. Results from a study of consecutive ORTHO EVRA® wear for 7 days and 10 days indicated that serum concentrations of NGMN and EE dropped slightly during the first 6 hours after the patch replacement, and recovered within 12 hours. By Day 10 of patch administration, both NGMN and EE concentrations had decreased by approximately 25% when compared to Day 7 concentrations.

[4] Online-Orange Book (2013). http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021180&TABLE1=OB_Rx (Last accessed: 4/22/2013)
[5] Labeling for the RLD Product, http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f8e8a69e-a018-469a-af56-e20f61fe4e06 (Last accessed: 4/22/2013)
[6] http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=2572&sec=monphar&t=0 (Last accessed: 4/22/2013)

Food Effect	N/A
Tmax	48 hours
Metabolism	Since ORTHO EVRA® is applied transdermally, first-pass metabolism (via the gastrointestinal tract and/or liver) of NGMN and EE that would be expected with oral administration is avoided. Hepatic metabolism of NGMN occurs and metabolites include norgestrel (active) and various hydroxylated and conjugated metabolites. Ethinyl estradiol is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.
Excretion	Ethinyl estradiol is excreted in the urine primarily as glucuronide conjugates. The metabolites of NGMN and EE are eliminated by renal and fecal pathways.
Half-life	Half-lives of NGMN and EE are approximately 28 hours and 17 hours respectively.
Dosage and Administration	This system uses a 28-day (four-week) cycle. A new patch is applied each week for three weeks (21 total days). Week Four is patch-free. Every new patch should be applied on the same day of the week. This day is known as the "Patch Change Day." For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time. The ORTHO EVRA® patch should not be cut, damaged or altered in any way. If the ORTHO EVRA® patch is cut, damaged or altered in size, contraceptive efficacy may be impaired. On the day after Week Four ends a new four-week cycle is started by applying a new patch. Under no circumstances should there be more than a seven-day patch-free interval between dosing cycles.
Maximum Daily Dose	1 patch/week
Drug Specific Issues (if any)	Black Box Warning: **Cigarette Smoking and Serious Cardiovascular Risks:** Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, hormonal contraceptives, including ORTHO EVRA®, should not be used by women who are over 35 years of age and smoke. **Risk of Venous Thromboembolism:** The risk of venous thromboembolism (VTE) among women aged 15–44 who used the ORTHO EVRA® patch compared to women who used several different oral contraceptives was assessed in five U.S. epidemiologic studies using electronic healthcare claims data. The relative risk estimates ranged from 1.2 to 2.2; one of the studies found a statistically significant increased relative risk of VTE for current users of ORTHO EVRA®. **Pharmacokinetic Profile of Ethinyl Estradiol:** The pharmacokinetic (PK) profile for the ORTHO EVRA® patch is different from the PK profile for oral contraceptives in that it has higher steady state concentrations and lower peak concentrations. Area under the time-

	concentration curve (AUC) and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using ORTHO EVRA® compared with women using an oral contraceptive containing 35 mcg of EE. In contrast, peak concentrations for EE are approximately 25% lower in women using ORTHO EVRA®. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using ORTHO EVRA® compared with women using oral contraceptives containing 30–35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including venous thromboembolism.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2 Studies

1.	**Type of study:**	Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints and Adhesion
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	0.02 mg/hr; 0.15 mg/24 hr
	Subjects:	Healthy nonpregnant females, general population, who are candidates for hormone contraception
	Additional Comments:	

2.	**Type of study:**	Skin Irritation and Sensitization
	Design:	Randomized, evaluator-blinded, in vivo with-in subject repeat test
	Strength:	0.02 mg/hr; 0.15 mg/24 hr (Dose: one-half of a 0.02 mg/hr; 0.15 mg/24 hr patch)
	Subjects:	Healthy nonpregnant females, general population, who are candidates for hormone contraception
	Additional Comments:	

Analytes to measure (in plasma/serum/blood):	Ethinyl Estradiol and Norelgestromin in plasma (PK study only)
Bioequivalence based on:	(90% CI) Ethinyl Estradiol and Norelgestromin (PK study only)
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	Based on Guidance for Industry: Individual product Bioequivalence Recommendations; Recommended May 2009, Revised Jul 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM162407.pdf .

Summary of OGD or DBE History	**ANDAs:** Currently there are no approved generic products of Norelgestromin and Ethinyl Estradiol Transdermal Film Extended Release listed in the Orange Book[4]. (b) (4) (b) (4) . **Control Documents:** There are many control documents on bioequivalence guidance for this particular product[8]. **Protocol:** (b) (4)

7 (b) (4)

OGD Control Documents Database http://cdsogd1/controls/DOCGRID.ASP. Last accessed 4/22/2013.

(b) (4)

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	--	--
In vitro dissolution	Yes	3
Waiver requests	Yes	2
BCS Waivers	--	--
Clinical Endpoints	--	--
Failed Studies	--	--
Amendments	Yes	1

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Analyte 1 Location in Report (Module, Section, Page)
Bioanalytical method validation report location	Ethinyl Estradiol Bioanalytical Method Validation Report, Sections 5.3.1.4. See Ethinyl Estradiol Validation Addendum 5, Table 2
Study Report Number	08-021-05
Analyte	Ethinyl Estradiol
Internal standard (IS)	(b) (4)
Method description	Solid phase and liquid/liquid extraction; LC/MS/MS - ESI
Limit of quantitation	4.0 pg/mL
Anticoagulant Used	K_2EDTA
LLOQ Intraday precision (%)	6.57%- 9.88%[f]
LLOQ Intraday accuracy (%)	97.07%- 108.75%[f]
LLOQ Interday precision (%)	8.79%[f]
LLOQ Interday accuracy (%)	104.23%[f]
% recovery (and %CV) at each concentration tested	LQC (12 pg/mL): 80.38%, %CV- 4.38[e] MQC (50 pg/mL): 90.58%, %CV- 3.06 HQC (300 pg/mL): 85.34%, %CV- 1.23
Average recovery of IS (%)	93.66%[e], %CV- 4.15
Standard curve concentrations (units/mL)	4, 8, 12, 25, 50, 100, 200, 300, 400 and 500 pg/mL
QC concentrations (units/mL)	12 pg/mL, 50 pg/mL, 125 pg/mL and 300 pg/mL
QC Intraday precision range (%)	0.54% to 5.38%[f]
QC Intraday accuracy range (%)	95.92% to 107.67%[f]
QC Interday precision range (%)	1.85% to 5.87%[f]
QC Interday accuracy range (%)	98.88% to 102.72%[f]
Bench-top stability (hrs)	27.5 hours at room temperature[a]
Stock stability (days)	145 days at room temperature[c]
Processed stability (hrs)	75.5 hrs @ 4°C[a]
Freeze-thaw stability (cycles)	4 cycles[a]
Long-term storage stability (days)	4 days @ -15°C and 162 days at - 70 °C[d]
Dilution integrity (concentration, percent CV) dilution factor, accuracy	Concentration (2000 pg/mL) diluted 5-fold[a]
Selectivity	No interference observed in blank plasma samples
For combination products: Did the matrix include all analytes?	Yes

[a]Generated in EEST VALI
[c]Generated in EEST VALI_ADD 2
[d]Generated in EEST VALI_ADD 3
[e]Generated in EEST VALI_ADD 4
[f]Generated in EEST VALI_ADD 5

SOPs submitted	Yes
Was the % recovery consistent across QC concentrations?	Yes (the difference in the recovery of analyte between the QC samples is less than 15%)
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?	No study samples were diluted
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	No study samples were diluted
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

Bioanalytical Method Validation History

Validation/Addendum (Project#)	Purpose
Original (08-021-00)	Original
Addendum 1 (08-021-00)	• To extend the solution stability of Ethinyl Estradiol and the internal standard
Addendum 2 (08-021-01)	• To establish the long-term frozen stability of Ethinyl Estradiol in conical flask bottom tubes in human plasma with K2EDTA as the anticoagulant • To demonstrate selectivity in the presence of concomitantly administered drugs • To conduct a matrix assessment in plasma from male donors • To extend the solution stability of Ethinyl Estradiol and the internal standard
Addendum 3 (08-021-02)	• To extend the long-term frozen stability of Ethinyl Estradiol in 8mL tubes in human plasma with K2EDTA as the anticoagulant • To extend the long-term frozen stability of Ethinyl Estradiol in conical false bottom (CFB) tubes in human plasma with K2EDTA as the anticoagulant
Addendum 4 (08-021-04)	• To validate a change to the method that included 1) the addition of a liquid/liquid extraction portion to the sample preparation 2) an alteration of the QS solvent and 3) changes to the instrument conditions such as a modified gradient, removal of the switch valve, and a flow rate change.
Addendum 5 (08-021-05)	• To validate a change to the method that included 1) a modified gradient and extended run time 2) a lowered column temperature (45°C) and 3) the insertion of a vortex step following internal standard addition to the sample

Information Requested	Analyte 1 Location in Report (Module, Section, Page)
Bioanalytical method validation report location	Norelgestromin Bioanalytical Method Validation Report, Sections 5.3.1.4. see Norelgestromin Validation Table 1
Study Report Number	09-011
Analyte	Norelgestromin
Internal standard (IS)	(b) (4)
Method description	Liquid/Liquid extraction; LC/MS/MS - ESI
Limit of quantitation	30 pg/mL
Anticoagulant Used	K_2EDTA
LLOQ Intraday precision (%)	4.42%- 6.13%
LLOQ Intraday accuracy (%)	95.37%- 97.77%
LLOQ Interday precision (%)	5.21%
LLOQ Interday accuracy (%)	96.87%
% recovery (and %CV) at each concentration tested	LQC (90 pg/mL): 66.77%, %CV- 6.46 MQC (300 pg/mL): 71.33%, %CV- 3.36 HQC (2250 pg/mL): 73.63%, %CV- 5.52
Average recovery of IS (%)	79.41%, %CV- 5.46
Standard curve concentrations (units/mL)	30, 60, 90, 150, 300, 600, 1200, 1800, 2400 and 3000 pg/mL
QC concentrations (units/mL)	LQC- 90 pg/mL, MQC-300 pg/mL, MQC-1500 pg/mL and HQC-2250 pg/mL
QC Intraday precision range (%)	1.32% to 4.96%
QC Intraday accuracy range (%)	95.2% to 100.8%
QC Interday precision range (%)	1.27% to 3.95%
QC Interday accuracy range (%)	96.87% to 99.81%
Bench-top stability (hrs)	23 hours at room temperature
Stock stability (days)	15 days @ 4ºC
Processed stability (hrs)	99.5 hrs @ ambient temperature
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	175 days @ -15ºC and -70ºC[a]
Dilution integrity (concentration, percent CV) dilution factor, accuracy	Concentration (12000 pg/mL) diluted 5-fold
Selectivity	No interference observed in blank plasma samples
For combination products: Did the matrix include all analytes?	Yes

a Addendum 1 Validation

SOPs submitted	Yes
Was the % recovery consistent across QC concentrations?	Yes
Is the same anticoagulant used in the pre-method validation study used in	Yes

the sample assay?	
If not, was cross validation study conducted?	N/A
Was the dilution factor adequate for the current study sample analysis?	No study samples were diluted
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	No study samples were diluted
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:

- The firm used di-potassium ethylenediaminetetraacetic acid (K_2EDTA) as anticoagulant in their fasting BE study, and in conducting its pre-study and with-in study validation. The calibration standards and quality control samples were prepared with human plasma containing K_2EDTA.

- In the amendment dated 10/8/2010 the firm submitted the long term storage stability data of norelgestromin. The long term storage data of norelgestromin for 175 days at -70ºC exceed the storage period for the samples of fasting (96 days) BE study.

- The firm submitted the original and also the addendum (1-6) validation reports for ethinyl estradiol. The purpose for the addendums includes extending the long term storage stability, change in the extraction procedure, change in the analytical method etc. The analytical procedure in the actual study sample analyses is different from the original validation (08-021-00). Therefore, the firm performed partial validation (accuracy and precision of QC samples) to validate the changes in the analytical procedure and submitted the validation report as addendum -5 (08-021-05). The study samples were analyzed using the validated assay 08-021-05.

- The long term storage data of ethinyl estradiol for 162 days at -70ºC exceed the storage period for the samples of fasting (60 days) BE study.

- The pre-study validation data of norelgestromin and ethinyl estradiol are acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range)	Mean Parameters (+/-SD)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/ mL)	AUCi (ng*hr/ mL)	tHalf (hr)	Kel (1/hr)	
					Norelgestromin						
Study No: ORTH -0942	Bioequivalence Study of Norelgestromin and Ethinyl Estradiol Transdermal System (NEETS) Patch (0.15 mg/0.02 mg/day; Mylan) and Ortho Evra® Patch (0.15 mg/0.02 mg/day; Ortho) in Normal Healthy Female Volunteers	Open-Label, Single-Dose, Randomized, Two-Period, Two-Treatment Crossover, bioequivalence study	**Test (T):** Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day × 7 days [Batch No: R6A0014] Mfg Date: Dec 2010	21 Healthy Female subjects Age: 24 (19-35)	1.337 (±0.253)	72 (48–120)	187.2 (±39.12)	191.9 (±0.253)	26.72 (±5.78)	0.0272 (±0.0063)	Section 5.3.1.2
			Reference (R): Ortho Evra® 0.15 mg/0.02 mg/day × 7 days Film (norelgestromin and ethinyl estradiol) [Lot No.: 7LM5212] Expiry Date: March 2013		1.388 (±0.292)	72 (48 – 120)	203.7 (±43.77)	209.0 (±45.63)	26.77 (±6.29)	0.0274 (±0.0071)	

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range)	Mean Parameters (+/-SD)						Study Report Location
					Cmax (pg/mL)	Tmax (hr)	AUCt (pg*hr/ mL)	AUCi (pg*hr/ mL)	tHalf (hr)	Kel (1/hr)	
					Ethinyl Estradiol						
Study No: ORTH -0942	Bioequivalence Study of Norelgestromin and Ethinyl Estradiol Transdermal System (NEETS) Patch (0.15 mg/0.02 mg/day; Mylan) and Ortho Evra® Patch (0.15 mg/0.02 mg/day; Ortho) in Normal Healthy Female Volunteers	Open-Label, Single-Dose, Randomized, Two-Period, Two-Treatment Crossover, bioequivalence study	**Test (T):** Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day × 7 days [Batch No: R6A0014] Mfg Date: Dec 2010	21 Healthy Female subjects Age: 24 (19-35)	99.59 (±24.11)	120 (48–170)	12853.9 (±2669.8)	12996.8 (±2701.3)	17.29 (±3.45)	0.0417 (±0.0085)	Section 5.3.1.2
			Reference (R): Ortho Evra® 0.15 mg/0.02 mg/day × 7 days Film (norelgestromin and ethinyl estradiol) [Lot No.: 7LM5212] Expiry Date: March 2013		111.0 (±27.42)	96 (48 – 168)	14948.1 (±3244.2)	15108.5 (±3252.8)	17.02 (±2.58)	0.0417 (±0.0065)	

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Norelgestromin and Ethinyl Estradiol Transdermal Film Dose 1 x 0.15 mg/0.02 mg/day × 7 days SUMMARY OF STATISTICAL ANALYSIS- Norelgestromin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. ORTH-0942							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	185.36	21	199.09	21	0.93	86.67	100.01
AUC∞ (hr *ng/ml)	189.82	21	204.21	21	0.93	86.61	99.76
Cmax (ng/ml)	1.32	21	1.35	21	0.98	90.08	105.87

Norelgestromin and Ethinyl Estradiol Transdermal Film Dose 1 x 0.15 mg/0.02 mg/day × 7 days SUMMARY OF STATISTICAL ANALYSIS-Ethinyl Estradiol Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. ORTH-0942							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	12526.39	21	14451.40	21	0.87	81.33	92.38
AUC∞ (hr *pg/ml)	12665.03	21	14612.44	21	0.87	81.33	92.37
Cmax (pg/ml)	95.16	21	105.52	21	0.90	82.48	98.60

Are the PK parameters within the acceptance limits for the 90% CI and meeting BE? Yes

Table 3. Reanalysis of Study Samples

Norelgestromin

Fasted Study, Study No. ORTH-0942 Additional information in Analytical Report Section 3.5 ORTH0942_NORE								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0.0	0.0	0.00	0.00	0.0	0.0	0.00	0.00
Documented Sample Processing Error	0.0	2.0	0.00	0.28	0.0	2.0	0.00	0.28
Total	**0.0**	**2.0**	**0.00**	**0.28**	**0.0**	**2.0**	**0.00**	**0.28**

Ethinyl Estradiol

Fasted Study, Study No. ORTH-0942 Additional information in Analytical Report Section 3.5 ORTH0942_EEST								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used in reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0.0	0.0	0.00	0.00	0.0	0.0	0.00	0.00
Documented Sample Processing Error	0.0	2.0	0.00	0.28	0.0	2.0	0.00	0.28
Sample Outside Limits of Curve Range (BLQ)	4.0	2.0	0.56	0.28	4.0	2.0	0.56	0.28
Total	**4.0**	**4.0**	**0.56**	**0.56**	**4.0**	**4.0**	**0.56**	**0.56**

Table 4. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
MA.BABE.AL.SOP.024 (Version No. 3, Edition No.2)	24 AUG 2009	Repeat analysis of samples

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	
Are the data in the summary table consistent with the data in the full analytical report?	Yes
If not, provide comment below	
Did reviewer reanalyze study results?	No
Was the study outcome changed based on reviewer reanalysis?	N/A

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

Comments from the Reviewer:

Norelgestromin

- There were no samples repeated for PK reasons. The study samples were reassayed based on the following SOP D-400-09: Reassay or Reinjection of Clinical Samples. A total of 2 samples (S08P1, 12 hrs and S18P1, 144 hrs) were re-assayed due to an analytical reason. In the above re-analysis summary table, the firm stated the reason for the re-assay of these 2 samples as "Documented Sample Processing Error". However, based on the Bioanalytical report[12], the above samples were re-assayed for the reason of "Abnormal Internal Standard Response". The reviewer verified the raw data and confirmed that the above two samples indeed have abnormal internal standard response. Therefore, the reviewer agrees with the firm in reassaying these samples.

- Run 12 (Subjects 21 and 24) was rejected due to instrument malfunction. However the firm did not list them in the above re-analysis table. The reviewer agrees with the firm's rejection of run 12. The firm rejected the above run based on the following SOP D-401-10: Evaluation and Acceptance Criteria for Analytical Runs. The reviewer verified the raw data and confirmed that the above run indeed contains incorrect plate configuration (instrument malfunction). These samples were subsequently analyzed in the following run and they were acceptable.

Ethinyl Estradiol

- There were no samples repeated for PK reasons. The firm reassayed the study samples because of analytical reasons. The firm reassayed the study samples based on the following SOP D-400-09: Reassay or Reinjection of Clinical Samples. A total of 8 samples were reassayed due to the analytical reasons. Two samples were re-analyzed (S05P2, 180 hrs and S10P1, 192 hrs) for the reason of "Documented Sample Processing Error". The reviewer verified the raw data and confirmed that the firm indeed re-assayed the samples for the above stated reason. The remaining six samples were re-analyzed for reason of "Sample Outside Limits of Curve Range (BLQ)' and the reassayed value for 4 out of 6 samples is still BLQ. For all these samples, the reassayed values were used in the final pharmacokinetic and statistical analyses. The reviewer agrees with the firm in reassaying these samples.

[12] Module 5.3.14. ORTH-0942_NORE- Table 5- Repeat Analysis Results for NORE in Human Plasma

3.7 Summary of Adhesion and Irritation Assessment of Norelgestromin and Ethinyl Estradiol Patch in the PK Study

In addition to conducting a separate skin irritation and sensitization study (ORTH-Cln-0943) and adhesion study (ORTH-cln-09198), the firm also conducted adhesion and irritation assessments during the pivotal BE study (ORTH-0942). The OGD's Division of Clinical Review (DCR) conducted the review of the skin irritation/sensitization and adhesion studies and found that the firm's adhesion study is inadequate[1].

The information for the skin irritation and adhesion from the pivotal BE study (ORTH-0942) as provided by the firm is included here for information purpose only.

Summary of Adhesion Assessment: Adhesion assessments to ensure skin contact of patch and overlay occurred at 24, 48, 72, 96, 120, 144 and 168 hours (±10 minutes) following patch application.

Rating Scale for Assessing Patch Adhesion:

Score	Definition
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 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)

In the PK report, the firm stated that all the patches adhered to the skin through out the duration of the study. In addition, the firm also stated that there was no difference in acute dermal adhesion between the two treatments. The firm also submitted the adhesion scores at the above mentioned time points for each patch applied in all the subjects.

Score by Hour for Test Treatment

Frequency	24 hr	48 hr	72 hr	96 hr	120 hr	144 hr	168 hr
0	21	21	21	21	21	17	19
1	0	0	0	0	0	4	2
N	**21**	**21**	**21**	**21**	**21**	**21**	**21**
Mean	0	0	0	0	0	0.19	0.10
STD	-	-	-	-	-	0.402	0.301
Max	0	0	0	0	0	1	1
Median	0	0	0	0	0	0	0
Min	0	0	0	0	0	0	0

Score by Hour for Reference Treatment

Frequency	24 hr	48 hr	72 hr	96 hr	120 hr	144 hr	168 hr
0	21	20	21	21	18	17	16
1	0	1	0	0	3	4	5
Total	**21**	**21**	**21**	**21**	**21**	**21**	**21**

Mean	0	0.05	0	0	0.14	0.19	0.24
STD	-	0.218	-	-	0.359	0.402	0.436
Max	0	1	0	0	1	1	1
Median	0	0	0	0	0	0	0
Min	0	0	0	0	0	0	0

Based on the above results, the patch adhesion was ≥75% for both treatments at all the time points.

Summary of Irritation Assessment: Upon patch removal, the skin area was to be evaluated for irritation for each period. Skin irritation assessments were performed at 0.5 and 1 hour (± 5 min) after the patch removal.

Skin Irritation Evaluation Scoring System
Dermal Response:

Scale	Irritation
0	No visible irritation
1	Minimal erythema, barely perceptible
2	Moderate erythema, without edema or papules
3	Moderate erythema with definite but minimal edema and/or popular response
4	Moderate to severe erythema with moderate to severe edema and/or popular response
5	Vesicular eruption
6	Strong reaction spreading beyond test site

Other Effects

Scale	Appearance
0	No other observed effects
1	Slight glazed appearance
2	Marked glazing
3	Glazing with peeling and cracking
4	Glazing with fissures
5	Film of dried serious exudate covering al or part of the patch site
6	Small petechial erosions and/or scabs

After 30 minutes, the mean (± SD) irritation score was 0.91 ± 0.70 and 0.91 ± 0.54 for test and reference products respectively. After 1 hour, the mean (± SD) irritation score was 0.62 ± 0.59 and 0.62 ± 0.50 for test and reference products respectively. Therefore based on the above scores, minimal barely perceptible erythema was seen on average with both treatments one half hour after patch removal, which had lessened on average 1 hour after patch removal. The firm also provided statistical analysis data to confirm that there is no difference between acute irritation between the two treatments.

Frequency table on Patch Irritation Score at 0.5 Hour After Patch Removal

Frequency	0	1	2	3
A	5	14	1	1
B	4	15	2	0
Total	9	29	3	1

Frequency table on Patch Irritation Score at 1 Hour After Patch Removal

Frequency	0	1	2
A	9	11	1
B	8	13	0
Total	17	24	1

3.7 Summary of Residual Patch Analysis in the PK Study

The firm determined the amount of adhesive residue from each patch left on the skin in the residual patch assay. The transdermal systems worn during the study were saved and were analyzed for their residual norelgestromin and ethinyl estradiol levels. These values, along with the residual norelgestromin and ethinyl estradiol levels on the alcohol wipes used to clean the skin area after transdermal system removal, were subtracted from control patch levels to arrive at an apparent dose. In the PK report, the firm stated that consistent with pharmacokinetic results, similar amounts of norelgestromin and ethinyl estradiol were depleted from the worn patches for both test and reference products.

Overall Summary of Depletion (in mg) from Test and Reference Products

Mylan

	Period 1		Period 2		Total	
	EE	NGMN	EE	NGMN	EE	NGMN
Average	0.381	1.972	0.362	1.803	0.371	1.880
Standard Deviation	0.063	0.291	0.110	0.491	0.090	0.412
RSD, %	16.5	14.8	30.4	27.2	24.3	21.9
Median	0.371	1.918	0.394	1.823	0.394	1.918
Range		(b) (4)		(b) (4)		(b) (4)
Number of subjects	10	10	12	12	22	22

Innovator

	Period 1		Period 2		Total	
	EE	NGMN	EE	NGMN	EE	NGMN
Average	0.469	2.143	0.452	2.104	0.461	2.125
Standard Deviation	0.148	0.489	0.096	0.290	0.124	0.402
RSD, %	31.6	22.8	21.2	13.8	26.9	18.9
Median	0.472	2.305	0.430	1.968	0.437	2.086
Range		(b) (4)		(b) (4)		(b) (4)
Number of subjects	12	12	10	10	22	22

The above results indicate that the amount of residual drug in the test product do not exceed that of the reference product.

3.7 Formulation

Location in appendix	Section 4.2
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**INCOMPLETE**
If not acceptable, why?	Refer to Section 4.2 for details

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS: CHERSTNIAKOVA, SVETLANA A 07/30/2010 N/A 07/30/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Not Applicable) Archive and Current Review
Submitted Method (USP, FDA, or Firm)	FDA and In-House
Recommended Method (details below)	FDA
Medium	0.1% Hydroxypropyl-beta-cyclodextrin at 32°C
Volume (mL)	900 mL
USP Apparatus type	USP II (Paddle)
Rotation (rpm)	50 rpm
Specifications	**Norelgestromin:** (b) (4) [redacted] **Ethinyl Estradiol:** (b) (4) [redacted]
Do the data meet the recommended specifications at S1, L1, A1, or B1 acceptance criteria?	Yes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	N/A
If no, reason why F2 not calculated	
Is method acceptable?	**INCOMPLETE**
If not then why?	Refer to Section 4.3 for details

3.9 Waiver Request(s) For Immediate Release Dosage Forms

Strengths for which waivers are requested, if applicable	N/A
Waiver regulation cited?	N/A
Strengths considered for 21 CFR 320.24 (b)(6)	N/A
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	N/A
If not then why?	

3.10 Deficiency Comments

1. The firm has conducted comparative dissolution testing using both the FDA-recommended and in-house dissolution methods. The firm's proposed method gave profiles with more gradual slopes, compared with the FDA method, for both the test and reference products, and therefore, demonstrated superiority. However, the firm's dissolution testing is inadequate due to insufficient sampling time points used in characterizing the more gradual release profiles, The firm is asked to conduct additional dissolution testing using its method on fresh test lot and unexpired reference lot, using the time points of 0.5, 2, 6, 8, 14, 20 and 24 hours.

2. A Form FDA- 483 was issued following the inspection of the analytical site, Mylan Pharmaceuticals Inc. Bioanalytical Department, 3711 Collins Ferry Rd, Morgantown, WV, between August 18-26, 2010, by the Office of Scientific Investigations (OSI) for bioequivalence (BE) studies from another application.

   Based on the above inspection report, the following objectionable findings by the OSI at the analytical site may potentially compromise the integrity of the study of current ANDA as well:

   - Stability of processed samples was determined with only mid level QCs during pre-study validation for the audited studies. Processed stability was not evaluated with low and high QC concentrations.

   - Failure to document all aspects of the study conduct.

     No documentation was maintained for identity of the weighing scales used for quarterly qualification for pipettes during the audited studies.

   The firm should address the above specific findings by the OSI with respect to its impact on the fasting and fed BE studies of the current ANDA, providing any necessary supporting documents in its response.

3. During the BE study, 2 study samples for norelgestromin were re-assayed for the reason of "Abnormal Internal Standard Response". However, in the re-analysis DB summary table, the firm stated the reason for the re-assay as "Documented Sample Processing Error". For the future submissions, firm should properly label the reasons for repeat analysis.

3.11 Recommendations

1. The Division of Bioequivalence I *tentatively* accepts the fasting BE study (ORTH-0942) conducted by the Mylan technologies Inc. on its Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch (Lot #R6A0014) comparing it to Ortho-McNeil Pharmaceuticals' Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch (Lot # 7LM5212).

2. The firm's *in vitro* dissolution testing is incomplete due to deficiencies mentioned above.

The firm should be informed of the above deficiency comments and recommendations.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
None	

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	ORTH-0942			
Study Title	Bioequivalence Study of Norelgestromin and Ethinyl Estradiol Transdermal System (NEETS) Patch (0.15 mg/0.02 mg/day; Mylan) and Ortho Evra® Patch (0.15 mg/0.02 mg/day; Ortho) in Normal Healthy Female Volunteers			
Study Type	☒ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other (Specify)
Submission Location: **Study Report**	location, ex: 5.3.1.2			
Validation Report	location, ex: 5.3.1.2			
Bioanalytical Report	location, ex: 5.3.1.4			
Clinical Site (Name, Address)	Cetero Research 625 Demers Avenue East Grand Forks, MN 56721, USA			
Principal Investigator	Alan K. Copa, Pharm.D.			
Dosing Dates	Period I: 20-June-2009 Period II:18-July-2009			
Analytical Site (Name & Address)	Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Rd Morgantown, WV 26505			
Analysis Dates	Norelgestromin: 18-Sep-2009 to 24-Sep-2009 Ethinyl Estradiol: 11-Aug-2009 to 19-Aug-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)	Norelgestromin: Aliquot 1: 96 Days @ -70°C Ethinyl Estradiol: Aliquot 1: 60 Days @ -70°C Date of 1st Sample Collected: 20-June-2009 Date of Last Sample Extracted: 24-Sep-2009 for Norelgestromin Date of Last Sample Extracted: 19-Aug-2009 for Ethinyl Estradiol			

Table 6. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Norelgestromin and Ethinyl Estradiol Transdermal System	Ortho Evra® (norelgestromin and ethinyl estradiol) Film
Manufacturer	Mylan	Jansseen Ortho, LLC
Batch/Lot No.	R6A0014	7LM5212
Manufacture Date	May 19 2009	
Expiration Date		10/2009
Strength	0.15 mg/0.02 mg/day	0.15 mg/0.02 mg/day
Dosage Form	Transdermal Patch	Transdermal Patch
Bio-Batch Size	(b) (4)	
Production Batch Size		
Potency (Assay)	Norelgestromin – 100.6% Ethinyl Estradiol – 99.8%	Norelgestromin – 97.7% Ethinyl Estradiol – 98.1%
Content Uniformity (expressed as mean, %CV or per USP)*	Norelgestromin – 99.0%, %CV-0.7% Ethinyl Estradiol – 98.2% %CV-0.2%	Norelgestromin – 97.7% %CV- 0.9% Ethinyl Estradiol – 98.1% %CV -1.7%
Dose Administered	1 x 0.15 mg/0.02 mg/day x 7 days	1 x 0.15 mg/0.02 mg/day x 7 days
Route of Administration	Transdermal	Transdermal

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	Yes
Is the bio-batch size at least the recommended minimum of 100K for oral solid dosage form?	N/A

Table 7. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	**Enrolled:** 26 **Dosed:** 26 **Completed:** 22 **Samples Analyzed:** 21 **Data Analyzed:** 21
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	28 days
Randomization Scheme (Sequence of T and R)	**TR:** 2, 3, 5, 6, 9, 11, 15, 16, 17, 20, 22, 24, 26, and 27 **RT:** 1, 4, 7, 8, 10, 12, 13, 14, 18, 19, 21, 23, 25, and 28
Blood Sampling Times	Predose, 6, 12, 24, 48, 72, 96, 120, 144, 168, 170, 174, 180, 192, 204, 216 and 240 hours after patch application [Patches were applied for 7 days (168 hours)]
Blood Volume Collected/Sample	10 mL
Anticoagulant Used	K_2EDTA
Blood Sample Processing & Storage (include storage temperature)	Blood samples were collected by direct venipuncture in to pre-labeled tubes containing K_2EDTA as the anticoagulant. After blood collection, tubes were centrifuged at 3000 rpm for 10 minutes at 4° C. Plasma samples were aliquoted in duplicate and then stored at -70° C ± 15°C pending analysis.
IRB Approval	Institutional Review Board was approved on June 3, 2009
Informed Consent	Yes (IEC approved on June 3, 2009)
Length of Fasting	All the subjects fasted for at least 10 hours prior to the administration of the study drug in each period until 1 hour post dose.
Length of Confinement	At least 14 hours preceding each study and 24 hours following each dose
Safety Monitoring	Adverse events were collected and reports were tabulated. The vital signs were measured throughout the study.

Was the study design used for the fasting BE study acceptable?	YES

4.1.1.2 Clinical Results

Table 8A. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. ORTH-0942			
		Treatment Groups	
		Test Product N = 21	Reference Product N = 21
Age (years)	Mean ± SD	24.0 ± 4.7	24.0 ± 4.7
	Range	19-35	19-35
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 – 39	21 (100%)	21 (100%)
	40 – 64	0 (0.0%)	0 (0.0%)
	65 – 75	0 (0.0%)	0 (0.0%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Female	21 (100%)	21 (100%)
	Male	0 (0.0%)	0 (0.0%)
Race	American Indian	0 (0.0%)	0 (0.0%)
	Asian	2 (9.5%)	2 (9.5%)
	Black	2 (9.5%)	2 (9.5%)
	Native Hawaiian	0 (0.0%)	0 (0.0%)
	White	17 (81.0%)	17 (81.0%)
BMI (Kg/m2)	Mean + SD	24.6 ± 2.8	24.6 ± 2.8
	Range	19.7 – 30.3	19.7 – 30.3
Other Factors		Nil	Nil

Table 8B. Demographics Profile of Individual Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. ORTH-0942				
Subject No	**Age**	**Gender**	**Race**	**BMI**
1	23	Female	Asian	22.0
2	27	Female	White	23.8
3	23	Female	White	22.8
4	19	Female	White	22.3
5	21	Female	White	25.2
6	22	Female	White	23.7
7	21	Female	White	21.5
8	35	Female	White	29.8
9	20	Female	American Indian	29.9
10	30	Female	White	23.5
11	27	Female	White	27.9
12	20	Female	White	19.7
13	26	Female	Black	25.7
14	23	Female	Black	24.9
15	29	Female	Asian	25.2
16	20	Female	White	26.3
17	20	Female	White	24.8
18	34	Female	White	25.7
19	24	Female	White	21.5
20	23	Female	White	21.7
21	20	Female	White	27.6
22	22	Female	White	29.9
23	18	Female	White	25.0
24	19	Female	White	30.3
25	25	Female	White	27.9
26	19	Female	White	31.9

Table 9. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
09	Subject withdrew consent prior to period II due to adverse event (toothache)	I	N/A
11	Subject was discontinued by sponsor due to positive pregnancy post period II dosing	II	N/A
22	Subject was dropped from study during period II, study hour 144.00 blood sample collection due to positive pregnancy	II	N/A
23	Subject was dropped from study during Period II, prior to study hour 96.00 blood sample collection due to protocol violation; non-compliance (induced excessive sweating)	II	N/A
26	Subject withdrew consent prior to period II due to schedule conflict	I	N/A

Table 10. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. ORTHO-0942	
	Test	Reference
Gastrointestinal Disorders		
Nausea	3 (11.54%)	5 (20.83%)
Abdominal Pain Upper	-	1 (4.17%)
Toothache	1 (3.85%)	-
Vomiting	6 (23.08%)	3 (12.51%)
General Disorders and Administration Site Conditions		
Application Site Irritation	20 (76.92%)	20 (76.92%)
Application Site Pruritus	6 (23.08%)	2 (8.33%)
Infections and Infestations		
Nasopharyngitis	1 (3.85%)	-
Musculo Skeletal and Connective Tissue Disorders		
Myalgia	1 (3.85%)	-
Muscle Spasms	-	1 (4.17%)
Nervous System Disorders		
Application Site Irritation	1 (3.85%)	1 (4.17%)
Dizziness	1 (3.85%)	4 (16.68%)
Headache	6 (23.08%)	4 (20.83%)
Psychiatric Disorders		
Mood Swings	1 (3.85%)	1 (4.17%)
Reproductive System and Breast Disorders		
Breast Tenderness	1 (3.85%)	2 (8.33%)
Menstruation Irregular	2 (7.69%)	1 (4.17%)
Dysmenorrhoea	-	1 (4.17%)
Menstrual Disorder	-	1 (4.17%)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1 (3.85%)	1 (4.17%)
Nasal Congestion	2 (7.69%)	-
Oropharyngeal Pain	2 (7.69%)	
Skin and Subcutaneous Tissue Disorders		
Pruritus	1 (3.85%)	1 (4.17%)
Acne	-	1 (4.17%)
Skin Burning Sensation	-	2 (8.33%)
Total subjects reporting at least one adverse event	**23 (88.46%)**	**22 (91.67%)**

Subjects Experiencing Emesis (Include in eCTD)

Subject Number*	Test/Reference	Period	Time Post-Dose	Duration Between Dosing and Emesis (hrs)
N/A				

Do any of the adverse events require statistical analysis consideration (e.g. emesis)?
Since the drug product is a transdermal patch (non-oral route of administration), vomiting will not influence drug absorption.

If yes, does the time exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products) according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*?
N/A

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.
All of the reported adverse events were mild to moderate in intensity. Based on this study, there is no strong evidence suggesting that the test drug product caused substantially more serious adverse events compared to the reference drug product.

Are there any safety concerns based on the adverse event profile?
No.

Table 11. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Concomitant medications	09, 15	08, 18
Subject 06, 08, and 10 Period I, Day 1, Hour 0, dosed left side of back instead of right side due to staff oversight	06	08, 10
Subject 06, 08, and 10 Period I, Day 1, Hour 0, dosed right side of back instead of left side due to Period I staff oversight when the opposite side was dosed	08, 10	06
Period I: Draw 4, 24.00 Hour, No Sample due to difficult phlebotomy	N/A	13
Unapproved tape applied over overlay. Non-Compliance (non-approved medical tape for adhesion)	N/A	07
Period I: Day 7, 144.00 hour adhesion evaluation done 148 hour and 49 minutes post application due to schedule conflict	N/A	14
Period I: Unapproved tape applied over overlay. Non-Compliance (non-approved medical tape for adhesion)	N/A	23
Period I: Sun exposure during patch wear period (30 min). Non-Compliance (excessive sun exposure)	N/A	07

Period I: Left during, 12 hour confinement due to schedule conflict	N/A	12
Period I: Draw 17, 240.00 hour, no sample due to schedule conflict	N/A	23
Period II: Patch became unattached from skin due to excessive sweating being induced. Non-Compliance (induced excessive sweating)	23	N/A
Period II: Draw 26, 144.00 hour, sample not placed in centrifuge within 30 minutes of collection (36 minutes) due to staff oversight	25	N/A
Period II: Draw 23, 72.00 hour, sample not placed in centrifuge within 30 minutes of collection (33 minutes) due to staff oversight	01	N/A
Period II: Draw 23, 72.00 hour, sample not placed in centrifuge within 30 minutes of collection (34 minutes) due to staff oversight	04	02, 03
Period II: Draw 23, 72.00 hour, sample not placed in centrifuge within 30 minutes of collection (32 minutes) due to staff oversight	N/A	05, 06
Period II: Draw 28, 170.00 hour, sample not placed in centrifuge within 30 minutes of collection (31 minutes) due to staff oversight	01	02
Period II: Day 30, 24.00 hour repeat vitals not collected within 15 minutes of initial vitals collection (31 minutes) due to interfering Adverse Event	21	N/A

Did dropouts/adverse events/protocol deviations affect the study outcome?

- Four subjects were administered concomitant medications during the study.

Subject	Period	Medication	Route	Start Date	Stop Date	Reason
9	I	Advil	Oral	7/13/09	7/15/09	Toothache
8	I	Acetaminophen	Oral	7/17/09	7/17/09	Headache
15	I	Acetaminophen	Oral	6/28/09	6/28/09	Headache
18	I	Acetaminophen	Oral	6/20/09	6/20/09	Headache

During the pre-study validation, the firm assessed potential interference with 20 over-the-counter (OTC) drugs. Acetaminophen and ibuprofen were among the 20 compounds. None of the OTCs showed any significant interference with norelgestromin and ethinyl estradiol.

- Subjects 7 and 23 had protocol deviation of "Unapproved tape applied over overlay". Subject 23 was eventually dropped from the study due to protocol violation; non-compliance (induced excessive sweating). As per the case report form, subject 7 during Period I (reference treatment) applied an unapproved tape over the patch. As per study protocol, criteria for removal from the study include

'Volunteers will be discontinued based on non-compliance'. However, the firm did not drop subject 7 from the BE study.

The reviewer excluded subject 7 (both Period I & II) data from the final statistical analysis. The 90% confidence intervals for LAUC0-t, LAUC∞ and LCmax, are still within the acceptable limits of 80-125% (see table below). Therefore, the above protocol deviation did not affect the study outcome.

Norelgestromin and Ethinyl Estradiol Transdermal Film Dose 1 x 0.15 mg/0.02 mg/day × 7 days SUMMARY OF STATISTICAL ANALYSIS- Norelgestromin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. ORTH-0942							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	185.03	20	198.85	20	0.93	86.31	100.31
AUC∞ (hr *ng/ml)	189.60	20	204.08	20	0.93	86.26	100.06
Cmax (ng/ml)	1.31	20	1.35	20	0.97	89.20	105.40

Norelgestromin and Ethinyl Estradiol Transdermal Film Dose 1 x 0.15 mg/0.02 mg/day × 7 days SUMMARY OF STATISTICAL ANALYSIS-Ethinyl Estradiol Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. ORTH-0942							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	12642.98	20	14514.34	20	0.87	81.54	93.06
AUC∞ (hr *pg/ml)	12782.99	20	14677.16	20	0.87	81.53	93.04
Cmax (pg/ml)	94.75	20	105.33	20	0.90	81.92	98.79

- Twenty six subjects experienced a total of 107 adverse events over the course of the study. Application site irritation was the most frequently reported adverse event experienced by subjects following the administration of both test and reference products. The firm's handling of adverse events is adequate.

- Subject 11 and 22 were discontinued from the study due to positive pregnancy test. As per the case report forms, both the subjects had a negative serum beta human chorionic gonadotropin prior to the start of the study and also at the end of period I. However, positive pregnancy screen was observed for subject 11 at study exit and for subject 22 at 144 time point during Period II. Therefore, the firm removed the above subjects from the study. The removal of subjects from the study, was in accordance with the firm's study protocol (as per the study protocol, criteria for removal from the study include 'Volunteers will be discontinued based on any clinical sign or symptom deemed relevant by the clinician').

- Subject 23 was discontinued from the study for the protocol violation (non-compliance) of 'induced excessive sweating'. As per the study protocol, "excessive sweating, long showers, baths, soaking in water or swimming should be avoided during the wear period". Based on the case report form, the above subjects performed physical activity that induced sweating. The removal of subject from the study, was in accordance with the firm's study protocol (as per the study protocol, criteria for removal from the study include 'Volunteers will be discontinued based on non-compliance')

- There were some blood sampling deviations during the fasting bioequivalence study. However, these sampling time deviations occurred in less than 10% of the nominal time points, thus are considered to be insignificant by the reviewer. It should be noted that the firm used actual sampling times for its PK calculation, while the reviewer used the nominal times for PK calculation. And from the data analyses, the sampling time deviations do not compromise the outcome of the BE study.

4.1.1.3 Bioanalytical Results

Table 12. Sample Analysis Calibration and Quality Control – During the Fasting Bioequivalence Study

Norelgestromin										
Parameter	**Standard Curve Samples**									
Concentration (pg /mL)	30	60	90	150	300	600	1200	1800	2400	3000
Inter day Precision (%CV)	1.99	3.71	2.45	1.87	1.40	1.54	1.42	1.43	1.60	1.36
Inter day Accuracy (%Actual)	100.7	100.22	99.36	98.33	97.07	99.18	100.92	101.22	101.83	101.23
Linearity	0.9980 to 0.9995									
Linearity Range (pg/mL)	30 to 3000 pg/mL									
Sensitivity/ LOQ (pg/mL)	30 pg/mL									

Parameter	Quality Control Samples			
Concentration (pg /mL)	90.00	300.0	1500	2250
Inter day Precision (%CV)	4.37	2.99	2.70	2.00
Inter day Accuracy (%Actual)	100.87	102.27	100.00	99.07
Number of Acceptable Runs	14 acceptable runs (13 + 1 run which contain repeated samples)			
Number of Rejected Runs (Run ID, volume/page location)	1 Rejected run, Run ID # 12 (SUB-21 and 24), Module 5.3.1.4. ORTH-0942_NORE Bioanalytical Report, Table 1 The above run was rejected due to instrument malfunction (incorrect plate configuration setting in autosampler) The above samples were re-analyzed in the subsequent acceptable run (run 14)			
If sample and QC diluted during study, specify all dilution factors	No study samples were diluted			
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

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially (1-6)
Were the chromatograms submitted by the firm acceptable?	Yes

Ethinyl Estradiol										
Parameter	**Standard Curve Samples**									
Concentration (pg /mL)	4.000	8.000	12.00	25.00	50.00	100.0	200.0	300.0	400.0	500.0
Inter day Precision (%CV)	1.68	3.86	3.43	2.12	1.68	1.37	1.25	1.14	1.02	1.36
Inter day Accuracy (%Actual)	101.28	98.77	98.92	98.84	98.74	100.4	101.15	100.27	101.05	100.66
Linearity	0.9979 to 0.9999									
Linearity Range (pg/mL)	4.0 to 500 pg/mL									
Sensitivity/ LOQ (pg/mL)	4.0 pg/mL									

Parameter	**Quality Control Samples**			
Concentration (pg /mL)	12.00	50.00	125.0	300.0
Inter day Precision (%CV)	5.05	2.83	2.06	2.12
Inter day Accuracy (%Actual)	100.00	100.92	101.76	101.27
Number of Acceptable Runs	23 acceptable runs (22 + 1 run which contain repeated samples)			
Number of Rejected Runs (Run ID, volume/page location)	There were no run rejections			
If sample and QC diluted during study, specify all dilution factors	No study samples were diluted			
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

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially (1-5)

Were the chromatograms submitted by the firm acceptable?	Yes

Table 13. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
D-400-09	03/11/09	Reassay or Reinjection of Clinical Samples
D-416-06	03/11/09	Reassay of Whole Subjects

Table 14. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	There is no PK repeat
Does the reviewer agree with the outcome of the repeat assays?	N/A
If no, reason for disagreement	

Were Calibration and Quality Control for the Sample Analysis acceptable?

Norelgestromin

- The calibration standards (CC's) and quality control (QC's) samples were prepared with human plasma containing K_2EDTA. The firm did not specify the preparation date of CC's and QC's, however as per the SOP they were prepared and used on the same day. During the study sample analyses, the accuracy and precision of norelgestromin and ethinyl estradiol determined at each QC level is within 15% of the nominal in human plasma containing K_2EDTA. This suggests that the CC's and QC's used were stable throughout the entire period of study sample analyses.

- A total of 48 and 36 samples (out of 713 samples) were analyzed as incurred repeats for norelgestromin and ethinyl estradiol respectively. Incurred Samples Reanalysis (ISR) was demonstrated with 100% of these samples being within ± 20% variability of their respective original reported values.

Summary/Conclusions, Study Assays:

Acceptable

4.1.1.4 Pharmacokinetic Results

Table 15. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 19 and Figure 1

Norelgestromin

Fasting Bioequivalence Study, Study No. ORTH-0942									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr*ng/ml)	187.232	20.89	113.50	298.08	203.164	21.73	143.58	302.63	0.92
AUC∞ (hr *ng/ml)	191.985	21.83	114.44	314.01	208.519	22.20	147.06	312.59	0.92
Cmax (ng/ml)	1.337	18.90	0.93	2.03	1.388	21.04	0.94	1.96	0.96
Tmax* (hr)	72.000	.	48.00	120.00	72.000	.	48.00	120.00	1.00
Kel (hr^{-1})	0.028	24.66	0.02	0.04	0.027	24.04	0.01	0.05	1.01
T1/2 (hr)	26.576	23.28	15.64	41.34	26.792	25.31	15.12	47.97	0.99

* Tmax values are presented as median, range

Ethinyl Estradiol

Fasting Bioequivalence Study, Study No. ORTH-0942									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr*pg/ml)	12853.76	20.77	8231.16	17606.63	14920.85	21.99	7937.68	20295.35	0.86
AUC∞ (hr *pg/ml)	12992.95	20.77	8390.56	17723.79	15078.70	21.81	8055.09	20482.59	0.86
Cmax (pg/ml)	99.585	24.21	55.28	153.50	110.959	24.71	54.73	157.70	0.90
Tmax* (hr)	120.000	.	48.00	170.00	96.000	.	48.00	168.00	1.25
Kel (hr^{-1})	0.043	19.76	0.03	0.06	0.043	19.13	0.03	0.06	0.99
T1/2 (hr)	16.881	19.35	11.15	22.93	16.703	17.52	11.03	21.44	1.01

Table 16. Geometric Means and 90% Confidence Intervals - Firm Calculated

Norelgestromin and Ethinyl Estradiol Transdermal Film Dose 1 x 0.15 mg/0.02 mg/day × 7 days SUMMARY OF STATISTICAL ANALYSIS-Norelgestromin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study, Study No. ORTH-0942						
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	185.4	21	199.7	21	0.93	86.5%-99.7%
AUC∞ (hr *ng/ml)	189.9	21	204.8	21	0.93	86.5%-99.4%
Cmax (ng/ml)	1.316	21	1.347	21	0.98	90.1%-105.9%

Norelgestromin and Ethinyl Estradiol Transdermal Film Dose 1 x 0.15 mg/0.02 mg/day × 7 days SUMMARY OF STATISTICAL ANALYSIS-Ethinyl Estradiol Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study, Study No. ORTH-0942						
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**
AUC0-t (hr *pg/ml)	12529.4	21	14486.1	21	0.86	81.2%-92.2%
AUC∞ (hr *pg/ml)	12671.3	21	14650.0	21	0.86	81.2%-92.2%
Cmax (pg/ml)	95.16	21	105.5	21	0.90	82.5%-98.6%

Table 17. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Norelgestromin and Ethinyl Estradiol Transdermal Film Dose 1 x 0.15 mg/0.02 mg/day × 7 days SUMMARY OF STATISTICAL ANALYSIS- Norelgestromin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. ORTH-0942							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	185.36	21	199.09	21	0.93	86.67	100.01
AUC∞ (hr *ng/ml)	189.82	21	204.21	21	0.93	86.61	99.76
Cmax (ng/ml)	1.32	21	1.35	21	0.98	90.08	105.87

Norelgestromin and Ethinyl Estradiol Transdermal Film Dose 1 x 0.15 mg/0.02 mg/day × 7 days SUMMARY OF STATISTICAL ANALYSIS-Ethinyl Estradiol Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. ORTH-0942							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	12526.39	21	14451.40	21	0.87	81.33	92.38
AUC∞ (hr *pg/ml)	12665.03	21	14612.44	21	0.87	81.33	92.37
Cmax (pg/ml)	95.16	21	105.52	21	0.90	82.48	98.60

Table 18. Additional Study Information, Fasting Study No. ORTH-0942

Norelgestromin

DBE SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALCKE	
Reason(s) for Selecting Above SAS Program Macro	For the verification of Kel and AUC	
Root mean square error, AUC0-t	0.1327	
Root mean square error, AUC∞	0.1310	
Root mean square error, Cmax	0.1498	
	Test	**Reference**
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞	21	21
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC∞	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Cmax at the first time point	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞[13]				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	21	0.98	0.95	0.99
Reference	21	0.98	0.93	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule?	N/A			

Ethinyl Estradiol

DBE SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALCKE	
Reason(s) for Selecting Above SAS Program Macro	For the verification of Kel and AUC	
Root mean square error, AUC0-t	0.1181	
Root mean square error, AUC∞	0.1180	
Root mean square error, Cmax	0.1656	
	Test	**Reference**
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞	21	21

[13] See individual test to reference ratios of PK Parameters in SAS Output.

If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC∞	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Cmax at the first time point	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	21	0.99	0.98	0.99
Reference	21	0.99	0.98	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule?	N/A			

Comments on SAS Program selected, Subject variability, any Tmax differences (if applicable), Pharmacokinetic and Statistical Analysis:

- The reviewer utilized the CALCKE SAS program and selected the time points for each subject individually in order to calculate the Kel for all the subjects of the fasting BE study.

- The median Tmax (120 hrs) of the test product in the fasting study is slightly different from the reference product (96 hrs) with the T/R ratio of 1.25. Even though the absolute time difference is 24 hours, the range (48- 170 hrs) of the Tmax is same for both test and reference products. During the fasting study, for the analysis of norelgestromin and ethinyl estradiol, samples were collected at the time points of pre-dose, 6, 12, 24, 48, 72, 96, 120, 144…240 hrs. Based on this sampling schedule, no sample was collected between the test (120 hrs) and reference (96 hrs) Tmax values. Since the measurement of Tmax depends on the sampling time points, the above Tmax difference can be attributed to the firm's sample collection. Also, for both test and reference PK profiles of EE, the mean curves were relatively flat between 48 to 170 hours. Thus, the difference in Tmax determined within this time period appeared to be due to the data variability rather than formulation difference. Based on the NDA review, variability in the Tmax for ethinyl estradiol was observed under different conditions and also different application sites[14]. Therefore, the apparent difference observed in the median Tmax between the test and reference treatments is not considered significant.

[14] DARRTS for NDA 021180 CHATTERJEE, DHRUBA J 11/19/2001 N/A 11/19/2001 REV-CLINPHARM-01(General Review) Original-1 (Type 1 NME and Type 4 New Combination) Archive

Table:	**Mean (SD) Pharmacokinetic Parameters in Healthy Female Volunteers Following Application of an EVRA™ Contraceptive Patch of 17d-NGM and EE Under Conditions Found in a Health Club (Study NRGEEP-PHI-015)**					
Parameter	Combination	Cool Water	Normal	Sauna	Treadmill	Whirlpool
EE						
t_{max} (h)	42.9 (17.6)	84.0 (48.1)	86.9 (48.5)	65.4 (35.3)	60.9 (36.8)	76.5 (52.0)
C_{max} (pg/mL)	89.9 (32.2)	63.9 (18.1)	64.5 (21.6)	85.4 25.8	81.3 21.2	80.8 (39.8)
C^{ss} (pg/mL)	59.3 (19.0)	52.3 (16.8)	53.0 (18.7)	61.7 (20.0)	60.8 (17.0)	55.2 (16.8)
$AUC_{0\text{-}168h}$ (pg·h/mL)	10343 (3293)	8186 (2458)	8237 (3047)	10172 (3428)	10378 (2534)	8987 (2749)
$AUC_{0\text{-}240h}$ (pg·h/mL)	11132 (3600)	9109 (2796)	9055 (3377)	11155 (3631)	11246 (3034)	9716 (2865)
$AUC_{0\text{-}\infty}$ (pg·h/mL)	11229 (3612)	9225 (2727)	9416 (3131)	11679 (3867)	11345 (3026)	9807 (2875)
$t_{½}$ (h)	15.2 (3.48)	14.9 (3.58)	15.0 (2.67)	25.7 (30.9)	17.7 (9.51)	18.0 (7.34)
N	12	12	29	12	12	11

Table:	**Mean (SD) Pharmacokinetic Parameters Obtained from 36 Women Wearing the 20-cm^2 Seven-Day EVRA™ Patch at Different Application Sites (Study NRGEEP-PHI-004)**			
Parameter	Abdomen	Arm	Buttock	Torso
EE				
C_{max} (pg/mL)	58.7 (19.9)	69.5 (20.6)	66.3 (23.9)	71.2 (32.2)
t_{max} (h)	56 (27.3)	57.8 (32.7)	52.7 (32.4)	56.2 (26.6)
C^{ss} (pg/mL)	46.6 (14.0)	57.0 (14.9)	54.0 (16.5)	57.1 (20.3)
$AUC_{0\text{-}168h}$ (pg·h/mL)	7163 (2211)	8751 (2272)	8391 (2622)	8599 (3161)
$AUC_{0\text{-}240h}$ (pg·h/mL)	7766 (2332)	9540 (2437)	9189 (2755)	9523 (3354)
$t_{½}$ (h)	16.1 (3.02)	16.4 (3.47)	18.1 (6.43)	17.1 (3.81)

- The 90% CI's for the least squares geometric means of LnUC0-t, Ln AUC∞ and LnCmax calculated by the reviewer agree with the firm's calculations and meet the criteria for BE.

Was the fasting bioequivalence study acceptable?
Incomplete due to the deficiency stated in the Deficiency Section (3.10).

Table 19. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

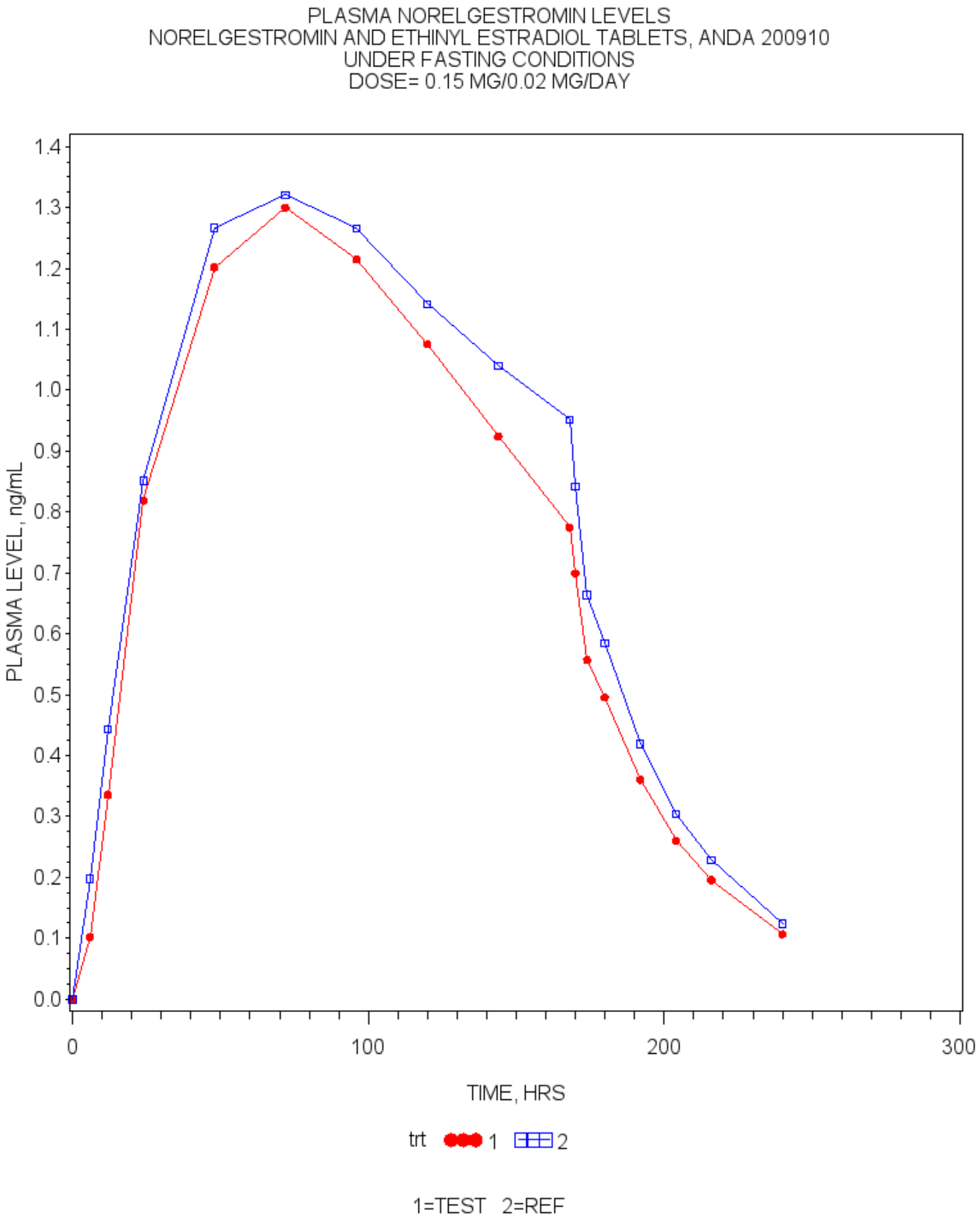
Norelgestromin

	Test (n=21)		Reference (n=21)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
6.00	0.10	74.45	0.20	63.91	0.52
12.00	0.34	39.16	0.44	39.63	0.76
24.00	0.82	25.04	0.85	36.83	0.96
48.00	1.20	19.09	1.27	24.42	0.95
72.00	1.30	17.94	1.32	22.00	0.98
96.00	1.22	22.29	1.27	22.83	0.96
120.00	1.08	25.21	1.14	21.37	0.94
144.00	0.92	26.45	1.04	25.45	0.89
168.00	0.78	24.77	0.95	26.14	0.81
170.00	0.70	28.19	0.84	26.16	0.83
174.00	0.56	29.25	0.66	27.17	0.84
180.00	0.50	32.95	0.59	27.62	0.85
192.00	0.36	35.84	0.42	32.26	0.86
204.00	0.26	44.05	0.30	35.82	0.86
216.00	0.20	49.26	0.23	40.07	0.86
240.00	0.11	60.67	0.12	52.25	0.86

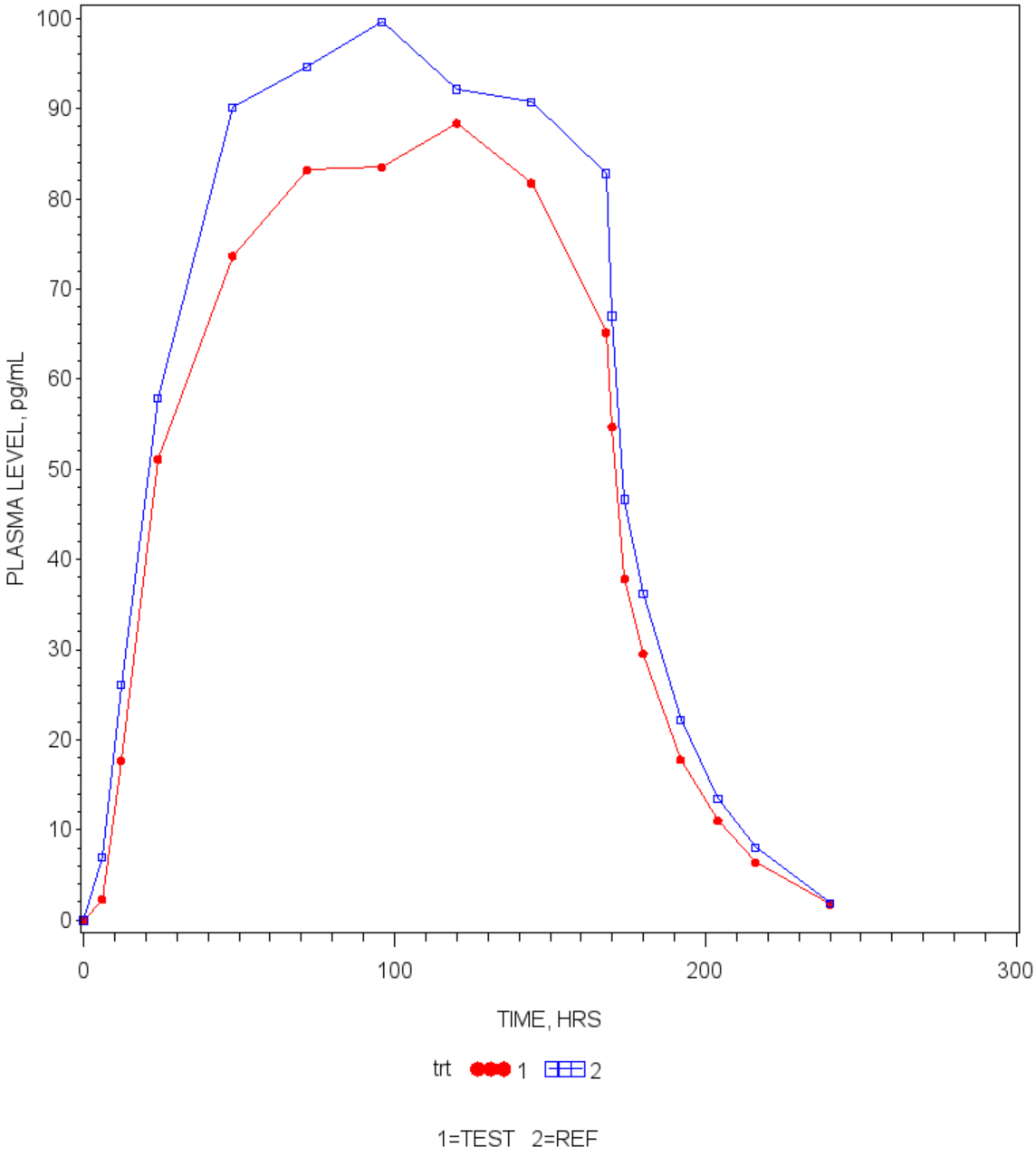
Ethinyl Estradiol

	Test (n=21)		Reference (n=21)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
6.00	2.28	146.34	7.00	95.34	0.33
12.00	17.68	49.63	26.07	44.48	0.68
24.00	51.14	28.23	57.92	38.64	0.88
48.00	73.66	18.46	90.12	23.94	0.82
72.00	83.23	27.10	94.64	25.32	0.88
96.00	83.54	21.82	99.65	25.62	0.84
120.00	88.40	27.97	92.19	30.44	0.96
144.00	81.77	29.17	90.79	33.48	0.90
168.00	65.20	34.31	82.85	34.34	0.79
170.00	54.70	39.68	67.03	36.09	0.82
174.00	37.83	42.12	46.67	37.32	0.81
180.00	29.54	42.91	36.26	38.19	0.81
192.00	17.79	49.51	22.19	42.76	0.80
204.00	11.02	55.26	13.48	54.09	0.82
216.00	6.36	72.88	8.07	58.97	0.79
240.00	1.70	171.89	1.92	147.81	0.88

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



PLASMA ETHINYL ESTRADIOL LEVELS
NORELGESTROMIN AND ETHINYL ESTRADIOL TABLETS, ANDA 200910
UNDER FASTING CONDITIONS
DOSE= 0.15 MG/0.02 MG/DAY



4.2 Formulation Data

Ingredient	Amount (mg) / Patch	Amount (%) / Patch	Function
Components of the Adhesive Matrix			
Norelgestromin	4.86	2.31	Active
Ethinyl Estradiol USP (b) (4)	0.53	0.25	Active
Polyisobutene Adhesive			
Oleyl Alcohol, NF			
Dipropylene Glycol			
(b) (4) Mineral Oil, NF			
Crospovidone, NF			
(b) (4)			
Total (Theoretical Matrix Weight)	**210.00**	**100.00**	
Other Components			
Polyethylene/Polyester Film			
Brown Ink			
Nonwoven Polyester			
Fluoropolymer Coated Polyester Film			

(b) (4)

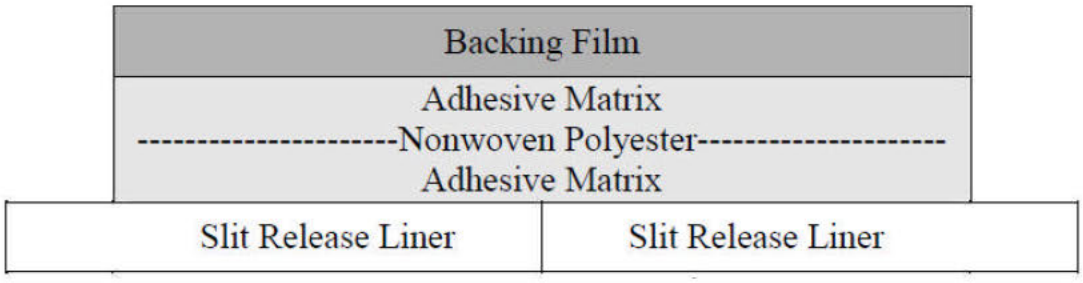
(b) (4)

(b) (4)

Following this page, 1 Page Withheld in Full as (b)(4)

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	No (See Comments Below)
If no, are they all above/within IIG (per day) limits?	
If no, are additional data or Pharm/Tox consult necessary?	Yes
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	N/A
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	N/A
Are all strengths of the RLD product dose-proportional?	N/A
Are all strengths of the test formulation acceptable?	NO
Additional Attachment for Formulation Calculations	N/A

Description of Drug Product



Mylan's Norelgestromin and Ethinyl Estradiol Transdermal System contain three layers. The outermost backing film layer is a pigmented polyethylene / polyester film. The middle layer is the polyisobutene adhesive matrix containing the two active pharmaceutical ingredients, norelgestromin and ethinyl estradiol. It also contains several inactive ingredients, namely oleyl alcohol, dipropylene glycol, crospovidone, nonwoven polyester, and mineral oil. The third layer is a release liner that is slit near the middle to facilitate removal prior to use. This liner is a transparent, fluoropolymer coated polyester film and both pieces are removed from the patch and discarded prior to use.

Reviewer's Comments:

- The test product is a 14 cm^2 square patch with round corners that contains 4.86 mg norelgestromin and 0.53 mg ethinyl estradiol. Whereas, the RLD product, Ortho Evra® is a transdermal patch with a contact surface area of 20 cm^2 containing 6 mg norelgestromin and 0.75 mg ethinyl estradiol[5]. Both the generic and RLD products are designed to deliver to the systemic circulation, 0.15 mg norelgestromin and 0.02 mg ethinyl estradiol daily.

- Based on Control 07-0512[18], the following are the general considerations for Transdermal Drug Delivery Systems: "*Transdermal products are considered as extended release drug products. The strength of a transdermal product is related to the amount of active ingredient that is delivered into the blood stream over a defined period of time, and not to amount of active ingredient initially in the patch. The amount of active ingredient in the generic product may differ from the amount of active ingredient in the RLD as long as the amount of the active ingredient absorbed into the blood stream in both products is equivalent. The difference in the amount of the active ingredient in the proposed generic compared to the RLD would have to be justified, regardless of equivalent pharmacokinetic and bioequivalence data*".

- Even though there are differences in the amounts of the active ingredients in the patch, both the test and reference products deliver the same amounts of active ingredients (6 mg norelgestromin and 0.75 mg ethinyl estradiol) to the systemic circulation.

- Although there are differences in the formulation design and amounts of the active ingredients in the patch between the test and reference products, the BE study (ORTH-0942) reveals that the 90% confidence intervals are with in the acceptance range of 80% and 125% for LnAUC0-t, LnAUCi and LnCmax. The study demonstrates that the test product is bioequivalent to the reference product.

- The fluoropolymer coated polyester film is not listed in the current IIG database[19]. (b) (4) Therefore the amount of fluoropolymer coated polyester film (b) (4) in the test product is (b) (4) the IIG limit of the approved drug product. In addition, the fluoropolymer coated polyester film is used to protect the patch during storage and is removed from the patch and discarded prior to use. Therefore, it is not expected that the above inactive ingredient will come in contact with the skin.

- The (b) (4) Brown Ink is not listed in the IIG database. However, the firm stated that the ink is approved for other Mylan commercial transdermal products. (b) (4)

[18] V:\firmsam\Mylan\Controls\070512C0407.doc
[19] (b) (4)

4.3 Dissolution Data

Dissolution Review Path	DARRTS: CHERSTNIAKOVA, SVETLANA A 07/30/2010 N/A 07/30/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Not Applicable) Archive and Current Review

Table 33. Dissolution Data

Firm's Proposed Method

Dissolution Conditions	**Apparatus:**	USP – V(Paddle over disk)
	Sinker:	No
	Speed of Rotation:	50 rpm
	Medium:	0.25% Tween 20 in water
	Volume:	900 mL
	Temperature:	32°C ± 0.5 °C
Firm's Proposed Specifications	Ethinyl Estradiol: Norelgestromin:	(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 & Form**	**No. of Dosage Units**		**Collection Times (hrs)** Norelgestromin (b) (4)				**Study Report Location**
N/A	Nov 2009	Norelgestromin/Ethinyl Estradiol Transdermal System 14 cm^2 Batch # R6A0014 Mfg date: May 2009	4.86 mg	12	Mean	9	22	54	97	3.2.P.5.4 Batch Analysis
					Range	(b) (4)				
					%CV	3.4	4.8	2.6	0.8	
	Dec 2009	Ortho Evra® Transdermal System 20 cm^2 Batch # 8HM6015P1 Exp. Date: July 2010	6.00 mg	12	Mean	9	26	63	97	
					Range	(b) (4)				
					%CV	5.7	3.4	2.9	1.1	

Dissolution Conditions	**Apparatus:**	USP – V(Paddle over disk)
	Sinker:	No
	Speed of Rotation:	50 rpm
	Medium:	0.25% Tween 20 in water
	Volume:	900 mL
	Temperature:	32°C ± 0.5 °C
Firm's Proposed Specifications	Ethinyl Estradiol: Norelgestromin:	(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 & Form**	**No. of Dosage Units**		**Collection Times (hrs)**				**Study Report Location**
						Ethinyl Estradiol				
						(b) (4)				
N/A	Nov 2009	Norelgestromin/Ethinyl Estradiol Transdermal System 14 cm^2 Batch # R6A0014 Mfg date: May 2009	0.53 mg	12	Mean	11	27	60	97	3.2.P.5.4 Batch Analysis
					Range	(b) (4)				
					%CV	2.9	3.5	2.7	0.8	
	Dec 2009	Ortho Evra® Transdermal System 20 cm^2 Batch # 8HM6015P1 Exp. Date: July 2010	0.75 mg	12	Mean	11	29	65	98	
					Range	(b) (4)				
					%CV	3.5	3.1	2.7	1.0	

[Note: The dissolution data submitted for the reference product was not on the bio-lot]

% Drug Release= $(m_i)(100)/L$ where m_i= Total amount of ethinyl estradiol or norelgestromin (in mg) released from patch at a given time interval and L is label claim (mg/patch)

FDA-Recommended Method

Dissolution Conditions	**Apparatus:**	USP – V(Paddle over disk)
	Sinker:	No
	Speed of Rotation:	50 rpm
	Medium:	0.1% Hydroxypropyl-beta-cyclodextrin in water
	Volume:	900 mL
	Temperature:	32°C ± 0.5 °C
Firm's Proposed Specifications	N/A	
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 & Form	No. of Dosage Units		Collection Times (hrs)					Study Report Location
						[redacted]					
N/A	Dec 2009	Norelgestromin/Ethinyl Estradiol Transdermal System 14 cm^2 Batch # R6A0014 Mfg date: May 2009	NGMN 4.86 mg	12	Mean	15	38	72	98	100	3.2.P.5.4 Batch Analysis
					Range	[redacted]					
					%CV	4.5	3.2	2.3	0.9	0.9	
			EE 0.53 mg		Mean	18	43	82	97	99	
					Range	[redacted]					
					%CV	3.7	3.9	2.6	0.8	0.7	
	Dec 2009	Ortho Evra® Transdermal System 20 cm^2 Batch # 8HM6015P1 Exp. Date: July 2010	NGMN 6.00 mg	12	Mean	14	33	63	81	92	
					Range	[redacted]					
					%CV	4.7	3.4	2.1	3.7	2.9	
			EE 0.75 mg		Mean	16	35	66	84	95	
					Range	[redacted]					
					%CV	5.6	3.8	2.4	3.7	2.4	

Additional Media- pH 4.5

Dissolution Conditions	**Apparatus:**	USP – V(Paddle over disk)
	Sinker:	No
	Speed of Rotation:	50 rpm
	Medium:	pH 4.5 with 0.25% Tween 20
	Volume:	900 mL
	Temperature:	32°C ± 0.5 °C
Firm's Proposed Specifications	N/A	
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 & Form	No. of Dosage Units		Collection Times (hrs)				Study Report Location
						[redacted] (b) (4)				
N/A	Dec 2009	Norelgestromin/Ethinyl Estradiol Transdermal System 14 cm^2 Batch # R6A0014 Mfg date: May 2009	NGMN 4.86 mg	12	Mean	6	18	46	90	3.2.P.5.4 Batch Analysis
					Range	[redacted] (b) (4)				
					%CV	7.5	3.6	4.2	1.6	
			EE 0.53 mg		Mean	8	22	52	94	
					Range	[redacted] (b) (4)				
					%CV	4.9	3.0	3.5	3.3	
	Dec 2009	Ortho Evra® Transdermal System 20 cm^2 Batch # 8HM6015P1 Exp. Date: July 2010	NGMN 6.00 mg	12	Mean	5	16	44	87	
					Range	[redacted] (b) (4)				
					%CV	0.0	4.2	3.1	1.2	
			EE 0.75 mg		Mean	7	20	50	94	
					Range	[redacted] (b) (4)				
					%CV	6.5	2.9	2.7	1.2	

Additional Media- pH 6.8

Dissolution Conditions	**Apparatus:**	USP – V(Paddle over disk)
	Sinker:	No
	Speed of Rotation:	50 rpm
	Medium:	pH 6.8 with 0.25% Tween 20
	Volume:	900 mL
	Temperature:	32°C ± 0.5 °C
Firm's Proposed Specifications	N/A	
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 & Form	No. of Dosage Units		Collection Times (hrs) (b) (4)				Study Report Location
N/A	Nov 2009	Norelgestromin/Ethinyl Estradiol Transdermal System 14 cm^2 Batch # R6A0014 Mfg date: May 2009	NGMN 4.86 mg	12	Mean	7	18	47	91	3.2.P.5.4 Batch Analysis
					Range	(b) (4)				
					%CV	5.6	5.4	6.6	2.4	
			EE 0.53 mg		Mean	8	21	53	95	
					Range	(b) (4)				
					%CV	0.0	4.3	5.5	2.2	
	Nov 2009	Ortho Evra® Transdermal System 20 cm^2 Batch # 8HM6015P1 Exp. Date: July 2010	NGMN 6.00 mg	12	Mean	5	16	40	78	
					Range	(b) (4)				
					%CV	5.8	5.0	6.1	4.0	
			EE 0.75 mg		Mean	7	19	46	89	
					Range	(b) (4)				
					%CV	6.5	4.2	4.3	3.6	

Additional Media- pH 1.2

Dissolution Conditions	**Apparatus:**	USP – V(Paddle over disk)
	Sinker:	No
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl with 0.25% Tween 20
	Volume:	900 mL
	Temperature:	32°C ± 0.5 °C
Firm's Proposed Specifications	N/A	
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 & Form	No. of Dosage Units		Collection Times (hrs) (b) (4)				Study Report Location
N/A	Nov 2009	Norelgestromin/Ethinyl Estradiol Transdermal System 14 cm^2 Batch # R6A0014 Mfg date: May 2009	NGMN 4.86 mg	12	Mean	35	70	96	95	3.2.P.5.4 Batch Analysis
					Range	(b) (4)				
					%CV	8.6	5.3	3.9	4.1	
			EE 0.53 mg		Mean	11	27	78	90	
					Range	(b) (4)				
					%CV	6.1	4.6	4.3	4.0	
	Nov 2009	Ortho Evra® Transdermal System 20 cm^2 Batch # 8HM6015P1 Exp. Date: July 2010	NGMN 6.00 mg	12	Mean	26	56	91	86	
					Range	(b) (4)				
					%CV	7.1	3.8	4.7	6.8	
			EE 0.75 mg		Mean	7	24	62	80	
					Range	(b) (4)				
					%CV	12.9	5.2	8.6	15.2	

Following this page, 1 Page Withheld in Full as (b)(4)

FDA-Recommended Method:

Medium: 0.1% Hydroxypropyl-beta-cyclodextrin in water
Apparatus: USP – V (Paddle over disk)
Speed/RPMs: 50 rpm
Volume: 900 mL

Firm's Proposed Method:

Medium: 0.25% Tween 20 in water
Apparatus: USP – V (Paddle over disk)
Speed/RPMs: 50 rpm
Volume: 900 mL
Sampling Times: (b) (4) hours

- The firm did not provide any justification for adopting their in-house method for dissolution testing of Norelgestromin and Ethinyl Estradiol Transdermal System.

- Using the in-house method, the firm measured % release of norelgestromin and ethinyl estradiol at sampling times of (b) (4) hours. The dissolution data submitted suggests that the above sampling time points are insufficient. The % drug release of norelgestromin and ethinyl estradiol at 8 hrs is (b) (4) % respectively. And at the next sampling time point i.e. (b) (4) hrs, the % drug release is (b) (4) % for both the components. Based on the dissolution data submitted using the firm's proposed method, the specifications cannot be set, as the firm did not demonstrate complete drug release profile.

- The reviewer consulted the DBI Dissolution Focal Point, Dr. Wayne Dehaven for an opinion regarding the dissolution method for this test product. Dr. Dehaven concurs with the reviewer that the sampling time points for the firm's proposed method is inadequate (see Section 4.6 Additional Attachments).

- The firm's proposed method gave profiles with more gradual slopes, compared with the FDA method, for both the test and reference products, and therefore, demonstrated superiority. However, the firm's dissolution testing is inadequate due to insufficient sampling time points used in characterizing the more gradual release profiles, The firm is asked to conduct additional dissolution testing using its method on fresh test lot and unexpired reference lot, using the time points of 0.5, 2, 6, 8, 14, 20 and 24 hours.

- In the original submission (dated 12/31/2009), the firm also provided the comparative dissolution profiles of the test and reference product in two additional dissolution media: pH 4.5 buffer with 0.25% tween 20, pH 6.8 buffer with 0.25% tween 20. Based on the data submitted, there is no evidence of dose dumping.

- In the deficiency letter sent to the firm on 7/30/2012, the firm was asked to submit comparative dissolution testing in pH 1.2 dissolution media[23]. In the amendment dated 10/8/2010, the firm provided following response:

  "As requested by the agency, mylan is providing dissolution (drug release) profiles on 12 dosage units of test and reference products generated in pH 1.2 media (containing 0.25% tween 20). Norelgestromin is not stable in the presence of acid, degrading continuously into (b) (4) *in standards and samples over the course of test. This degradation resulted in specificity issues when generating the norelgestromin release profile. This degradation was observed for both test and reference products. In order to provide a dug release profile for the norelgestromin active, the peak areas of norelgestromin were summed with the peal area of the primary degradation product"*.

  Based on the data submitted, there is no evidence of dose dumping in pH 1.2 buffer.

- **The firm's dissolution testing is incomplete.**

[23] DARRTS for ANDA 200910: RAMSON, TERESA V 07/30/2010 FAX 07/30/2010 COR-ANDADE-01(Bio Incomplete Deficiencies) Original-1 (Not Applicable) Archive

4.4 Review of Office of Scientific Investigations (OSI) Inspection Report

Clinical Site:
The clinical study for the current application was conducted at Cetero Research, 625 Demers Avenue, East Grand Forks, MN 56721, USA. The clinical site was inspected by OSI for NDA 022503 (routine) on 04/22/2010 and the outcome was NAI (No Action Indicated)[2].

Analytical Site:

		(b) (4)	ANDA 200462	ANDA 200245
Analytical Dates	Fast		17 -24 June 2009	19 May to 24 June 2009
	Fed		22 June to 06 July 2009	16 July to 10 August 2009

OSI conducted an audit of the analytical portions (August 18-26, 2010) of the BE studies for both ANDAs 200462/200245 and following the inspection a form 483 was issued to the Mylan Pharmaceuticals Inc. Bioanalytical Department, 3711 Collins Ferry Rd, Morgantown, WV 26505. The analytical site of ANDAs 200462/200245 is same as the analytical site of the fasting BE study in the current application. The firm submitted it's responses to the OSI findings on September 9, 2010. The outcome of the OSI inspection of the analytical site for ANDA ANDAs 200462/200245 (Routine) was Voluntary Action Indicated (VAI). The OSI concluded that the analytical data of the fast and fed studies can be accepted for the review[3]. The firm's response was attached to the OSI report.

The firm will be asked to address the following OSI findings at the analytical site (based on ANDA 200245) in order to determine whether or not the findings will have an impact the outcome of the current ANDA 200910.

OSI Finding # 1: Stability of processed samples was determined with only mid level QCs during pre-study validation for the audited studies. Processed stability was not evaluated with low and high QC concentrations.

OSI Finding # 2: Failure to document all aspects of study conduct. No documentation was maintained for identity of the weighing scales used for quarterly qualification for pipettes during the audited studies.

In addition to the above two findings, the form 483 also contains one additional finding on incurred sample reproducibility (ISR) *"Only 5% of samples were repeated for ISR. The firm's SOP L-324-01 for ISR effective date March 10, 2009, requires a fixed percentage of the total samples to be reanalyzed irrespective of sample size"*. For the current application, the firm has provided IST data. The reviewer notes that similar to the OSI observation, only 5% of the samples were reanalyzed for ISR in the current application. Currently, DB does not have any specific criteria to assess incurred sample reproducibility (ISR) in bioequivalence studies for ANDA submissions. So this OSI finding does not have any impact on the outcome of the current fasting BE study.

4.5 SAS Output

4.5.1 Fasting Study Data

Norelgestromin

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
1	1	4	1	1	B	0	0.19070	0.4129	0.8214	1.1940	1.3220	1.4300	1.2180	1.1500	0.9875	0.8526	0.6610	0.5394	0.4010
2	1	4	2	1	A	0	0.10770	0.4160	0.8214	1.1950	1.2730	1.1190	1.1970	1.0960	0.8560	0.8846	0.6956	0.5900	0.4386
3	2	1	1	1	A	0	0.00000	0.1865	0.7109	1.0160	1.1700	1.2020	0.9824	0.8427	0.6377	0.5818	0.4525	0.4178	0.2778
4	2	1	2	1	B	0	0.06714	0.2517	0.6600	0.9272	0.9743	0.9253	0.9175	0.7694	0.6496	0.6082	0.5070	0.4479	0.3175
5	3	3	1	1	A	0	0.00000	0.1474	0.6305	1.1320	1.4130	1.3730	1.2850	1.1870	0.9718	0.9630	0.7344	0.6508	0.4758
6	3	3	2	1	B	0	0.22770	0.5256	1.2600	1.6970	1.8660	1.7720	1.4020	1.2110	0.9803	0.9596	0.7422	0.7039	0.4595
7	4	2	1	1	B	0	0.19510	0.4806	0.9546	1.5300	1.2320	0.9552	0.7698	0.6452	0.6430	0.5708	0.4593	0.3933	0.2384
8	4	2	2	1	A	0	0.04041	0.2052	0.7442	1.2630	1.2370	0.9934	0.7037	0.5912	0.4697	0.4017	0.3412	0.2912	0.1989
9	5	1	1	1	A	0	0.18120	0.4290	1.0460	1.6620	1.7510	1.6200	1.4390	1.2200	0.9054	0.8126	0.6713	0.6406	0.4912
10	5	1	2	1	B	0	0.13260	0.3281	0.6730	1.1790	1.3520	1.4250	1.4440	1.4080	1.3040	1.1070	0.9577	0.8354	0.5812
11	6	3	1	1	A	0	0.25450	0.5491	1.1670	1.3810	1.2610	1.1580	0.9920	0.9082	0.7151	0.5970	0.4877	0.4676	0.3088
12	6	3	2	1	B	0	0.22990	0.3620	0.8559	1.2310	1.2420	1.1420	1.0500	0.9009	0.7626	0.7237	0.6236	0.5478	0.3690
13	7	2	1	1	B	0	0.47630	0.7284	1.2480	1.5200	1.3210	1.1330	1.0060	1.0260	0.9703	0.7630	0.6535	0.5455	0.3538
14	7	2	2	1	A	0	0.10830	0.4168	1.0640	1.6350	1.5450	1.2010	0.8337	0.7099	0.6269	0.5628	0.4007	0.3341	0.1916
15	8	4	1	1	B	0	0.06446	0.2662	0.5644	0.8715	1.0090	1.0810	1.0770	0.9927	0.9164	0.8035	0.6063	0.6015	0.4473
16	8	4	2	1	A	0	0.09772	0.2887	0.6422	0.9498	1.0920	1.1020	1.1450	0.9055	0.7904	0.7312	0.5858	0.5545	0.4490
17	10	4	1	1	B	0	0.06151	0.2917	0.5992	0.9671	1.2220	1.2640	1.1790	1.0360	1.0710	1.0340	0.7812	0.6664	0.5364
18	10	4	2	1	A	0	0.00000	0.1765	0.5385	0.8612	0.9250	1.0550	0.9491	0.9163	0.8832	0.8529	0.6687	0.5863	0.4835
19	12	2	1	1	B	0	0.21740	0.5557	0.9694	1.3150	1.1640	0.9215	0.7321	0.4921	0.4379	0.3544	0.2555	0.2295	0.1208
20	12	2	2	1	A	0	0.04295	0.2444	0.5741	0.9201	0.9341	0.7087	0.6137	0.4712	0.4742	0.3837	0.2533	0.2051	0.1414
21	13	4	1	1	B	0	0.18200	0.3342	0.0000	1.0420	1.1570	1.1120	1.1590	0.8995	0.7238	0.6863	0.5306	0.4682	0.3283
22	13	4	2	1	A	0	0.07585	0.2360	0.7848	1.0880	1.1860	1.0940	0.9636	0.8198	0.6562	0.6207	0.4877	0.4737	0.3024

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
23	14	2	1	1	B	0	0.41430	0.7296	1.3210	1.7290	1.8790	1.8480	1.6120	1.5530	1.5110	1.3420	1.0570	0.9529	0.7400
24	14	2	2	1	A	0	0.10380	0.2410	0.6449	1.0100	1.2630	1.2890	1.0830	0.9471	0.7663	0.6866	0.6323	0.5626	0.3948
25	15	1	1	1	A	0	0.14610	0.4568	0.8757	1.1180	1.1390	1.0660	0.9131	0.7702	0.6007	0.5187	0.3946	0.3506	0.2567
26	15	1	2	1	B	0	0.24530	0.6173	0.9580	1.2520	1.2630	1.3740	1.2250	1.1390	1.0390	0.8703	0.6698	0.5279	0.4653
27	16	3	1	1	A	0	0.18310	0.4746	0.9568	1.4360	1.5190	1.4780	1.2790	1.1460	0.9626	0.9425	0.7502	0.6725	0.4896
28	16	3	2	1	B	0	0.21090	0.4204	0.7813	1.1080	1.3010	1.0970	1.0370	0.8849	0.7425	0.7117	0.5821	0.5399	0.4050
29	17	3	1	1	A	0	0.16710	0.4035	1.0000	1.3550	1.4190	1.3630	1.2450	0.9825	0.9262	0.7877	0.6835	0.6005	0.4663
30	17	3	2	1	B	0	0.27770	0.5773	1.0280	1.4620	1.4530	1.4190	1.3020	1.3940	1.1730	1.0350	0.8642	0.7268	0.5286
31	18	2	1	1	B	0	0.07028	0.3110	0.7031	0.9387	0.9375	0.8721	0.7511	0.6845	0.7613	0.6021	0.4554	0.3993	0.2661
32	18	2	2	1	A	0	0.07951	0.3259	0.6840	1.1800	1.4370	1.0910	0.9466	0.7626	0.7510	0.5757	0.4889	0.3451	0.3054
33	19	4	1	1	B	0	0.08369	0.3263	0.7946	1.0400	1.1280	1.2820	1.1070	1.0840	0.9871	0.8642	0.5758	0.4993	0.3152
34	19	4	2	1	A	0	0.09370	0.3349	0.7291	0.9950	1.0580	0.9314	0.8613	0.7211	0.5941	0.5334	0.3718	0.3138	0.1833
35	20	1	1	1	A	0	0.00000	0.1865	0.6335	1.1170	1.3620	1.2700	1.2810	1.2190	0.9783	0.8608	0.6733	0.6184	0.4125
36	20	1	2	1	B	0	0.00000	0.1799	0.5894	1.1070	1.2670	1.3260	1.2260	1.1450	1.1830	1.0160	0.7939	0.7234	0.4726
37	21	2	1	1	B	0	0.37720	0.5841	1.2240	1.9600	1.8600	1.7080	1.4140	1.2420	1.0320	0.9282	0.7275	0.6450	0.4645
38	21	2	2	1	A	0	0.16960	0.4446	0.9272	1.1750	1.4010	1.2910	0.9626	0.7185	0.6024	0.5101	0.4279	0.3401	0.2612
39	24	1	1	1	A	0	0.06593	0.2769	0.7438	1.1860	1.1280	1.0840	1.0580	0.9567	0.8659	0.7467	0.6092	0.5206	0.4229
40	24	1	2	1	B	0	0.10510	0.2615	0.6560	0.9356	1.0280	0.9522	0.9125	0.9506	0.9401	0.8174	0.6570	0.6005	0.4347
41	25	2	1	1	B	0	0.33210	0.7721	1.2260	1.6080	1.7720	1.5590	1.4310	1.2540	1.1660	1.0320	0.7892	0.6988	0.5585
42	25	2	2	1	A	0	0.23730	0.6041	1.2900	1.5670	1.7980	2.0320	1.8540	1.5200	1.2440	1.1380	0.8938	0.8764	0.6224

Obs	c15	c16	c17	KE_FIRST	KE_LAST	trt	c18	c19	i
1	0.29960	0.18210	0.08767	12	16	2	0	0	20
2	0.28420	0.18130	0.11680	12	16	1	0	0	20
3	0.21940	0.15700	0.07897	12	16	1	0	0	20
4	0.25100	0.16810	0.07971	12	16	2	0	0	20
5	0.31410	0.22800	0.12260	12	16	1	0	0	20
6	0.34100	0.25870	0.14030	12	16	2	0	0	20
7	0.16010	0.11530	0.05441	12	16	2	0	0	20

8	0.13030	0.09495	0.04809	12	16	1	0	0	20
9	0.32330	0.27020	0.15430	12	16	1	0	0	20
10	0.39320	0.32360	0.17690	12	16	2	0	0	20
11	0.23130	0.16790	0.08603	12	16	1	0	0	20
12	0.24840	0.17670	0.09823	12	16	2	0	0	20
13	0.22130	0.16980	0.06310	12	16	2	0	0	20
14	0.13550	0.08535	0.04247	12	16	1	0	0	20
15	0.33780	0.27400	0.17870	12	16	2	0	0	20
16	0.33290	0.24440	0.13550	12	16	1	0	0	20
17	0.35490	0.32600	0.19880	12	16	2	0	0	20
18	0.33330	0.27250	0.17490	12	16	1	0	0	20
19	0.07208	0.03912	0.00000	12	16	2	0	0	20
20	0.06557	0.04156	0.00000	12	16	1	0	0	20
21	0.23960	0.17400	0.08660	12	16	2	0	0	20
22	0.22460	0.17380	0.08468	12	16	1	0	0	20
23	0.54220	0.39910	0.23300	12	16	2	0	0	20
24	0.31040	0.24290	0.15540	12	16	1	0	0	20
25	0.14860	0.10310	0.06133	12	16	1	0	0	20
26	0.28980	0.21030	0.10320	12	16	2	0	0	20
27	0.41690	0.33030	0.18520	12	16	1	0	0	20
28	0.32510	0.24790	0.15490	12	16	2	0	0	20
29	0.31840	0.24050	0.12460	12	16	1	0	0	20
30	0.35420	0.27020	0.14190	12	16	2	0	0	20
31	0.20500	0.16890	0.08509	12	16	2	0	0	20
32	0.19960	0.14940	0.07025	12	16	1	0	0	20
33	0.19110	0.13190	0.05044	12	16	2	0	0	20
34	0.11050	0.07412	0.00000	12	16	1	0	0	20
35	0.31080	0.22050	0.10480	12	16	1	0	0	20
36	0.36100	0.24590	0.13770	12	16	2	0	0	20
37	0.31790	0.23690	0.11340	12	16	2	0	0	20
38	0.17450	0.13400	0.06276	12	16	1	0	0	20
39	0.32410	0.24560	0.17290	12	16	1	0	0	20
40	0.36720	0.25420	0.15430	12	16	2	0	0	20
41	0.51090	0.41990	0.27110	12	16	2	0	0	20
42	0.55630	0.45550	0.26720	12	16	1	0	0	20

Ethinyl Estradiol

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
1	1	4	1	1	B	0	5.663	21.140	60.54	101.50	111.00	126.30	94.22	95.72	111.70	101.20	75.50	55.76	33.050	19.760
2	1	4	2	1	A	0	0.000	26.360	65.70	91.09	83.88	91.12	107.60	116.90	118.80	122.00	85.73	67.68	45.410	25.950
3	2	1	1	1	A	0	0.000	9.548	55.87	67.18	69.79	101.70	89.37	77.26	56.92	46.02	31.12	24.93	13.870	12.060
4	2	1	2	1	B	0	0.000	12.890	52.75	68.49	62.97	61.47	63.55	68.25	69.78	54.89	37.59	29.43	18.940	11.580
5	3	3	1	1	A	0	0.000	5.268	26.40	66.69	66.19	86.26	95.90	87.51	69.18	57.75	37.10	30.79	15.430	9.023
6	3	3	2	1	B	0	7.630	39.120	75.63	91.55	87.31	83.20	80.03	92.41	82.01	67.71	45.62	33.61	17.070	11.880
7	4	2	1	1	B	0	7.383	24.550	47.88	123.00	132.10	109.60	53.24	33.27	25.38	20.57	14.89	10.16	6.124	0.000
8	4	2	2	1	A	0	0.000	9.542	43.09	79.81	105.60	99.30	85.33	56.25	33.49	25.74	21.13	15.48	8.033	4.894
9	5	1	1	1	A	0	7.060	22.330	54.89	71.35	72.58	83.89	93.72	78.81	47.44	38.21	26.82	24.00	13.940	8.424
10	5	1	2	1	B	0	4.199	16.380	36.34	60.95	72.50	112.30	157.70	143.90	118.80	92.83	66.61	49.55	26.710	15.690
11	6	3	1	1	A	0	8.431	31.560	72.31	76.80	67.82	67.38	77.85	84.92	71.69	52.03	37.20	32.31	16.950	9.792
12	6	3	2	1	B	0	9.653	20.800	59.74	87.23	75.05	71.78	75.27	79.43	74.35	62.86	45.53	35.54	18.250	11.560
13	7	2	1	1	B	0	18.000	39.600	77.98	132.30	120.30	106.60	70.98	47.03	33.89	24.79	18.42	13.26	6.870	0.000
14	7	2	2	1	A	0	0.000	14.340	49.00	83.94	125.40	90.49	55.37	35.17	19.30	17.37	10.93	8.81	5.106	0.000
15	8	4	1	1	B	0	0.000	13.530	30.25	52.03	53.72	54.73	52.39	44.39	41.02	29.54	20.42	16.06	10.370	6.514
16	8	4	2	1	A	0	0.000	15.220	50.01	62.24	69.34	54.71	50.68	54.63	41.81	38.04	24.40	19.86	11.500	8.825
17	10	4	1	1	B	0	0.000	12.770	33.63	66.57	72.31	72.81	67.50	63.47	82.64	72.96	46.33	37.32	26.720	12.400
18	10	4	2	1	A	0	0.000	5.380	29.86	48.09	42.33	54.76	52.20	53.63	55.28	53.80	32.58	24.91	17.380	8.940
19	12	2	1	1	B	0	7.230	31.180	60.39	91.84	94.74	86.83	82.20	69.97	54.41	43.76	29.40	25.63	11.660	7.345
20	12	2	2	1	A	0	0.000	9.174	26.74	66.56	87.95	74.20	99.07	65.00	40.09	34.47	22.16	17.59	10.130	4.867
21	13	4	1	1	B	0	5.810	16.760	0.00	69.32	68.21	74.26	85.68	68.10	74.33	61.22	40.21	33.77	21.900	12.450
22	13	4	2	1	A	0	0.000	8.892	44.01	60.76	69.06	63.24	61.48	60.00	55.71	46.26	28.79	23.16	13.500	7.255
23	14	2	1	1	B	0	22.390	45.170	98.13	110.80	113.70	107.50	103.50	111.00	122.00	93.93	66.62	55.80	38.930	25.400
24	14	2	2	1	A	0	0.000	13.890	39.38	63.81	99.73	99.84	98.58	96.23	72.35	55.36	41.57	35.49	21.240	13.760
25	15	1	1	1	A	0	5.891	29.340	69.44	78.32	83.17	82.02	79.11	82.30	81.89	60.93	44.05	30.00	19.320	10.290
26	15	1	2	1	B	0	11.270	39.620	81.40	105.30	111.30	107.10	99.33	106.20	105.30	79.09	58.55	42.04	30.980	14.480
27	16	3	1	1	A	0	6.544	29.440	67.08	93.18	89.59	78.07	80.25	90.39	81.22	73.37	47.75	35.49	21.340	15.020

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
28	16	3	2	1	B	0	7.045	23.720	50.03	70.07	76.47	92.05	111.80	129.90	108.40	92.08	65.64	52.71	32.640	21.140
29	17	3	1	1	A	0	7.147	22.620	63.87	77.29	85.41	103.90	102.10	121.40	84.86	69.41	54.68	40.82	23.760	16.310
30	17	3	2	1	B	0	13.280	35.880	68.01	91.68	82.60	85.15	69.39	95.75	78.60	63.31	46.15	31.69	20.000	11.010
31	18	2	1	1	B	0	0.000	31.230	77.24	86.36	122.10	128.80	117.30	105.40	93.29	66.40	48.96	40.40	27.750	18.730
32	18	2	2	1	A	0	0.000	23.310	45.62	98.28	142.80	115.30	127.40	108.00	84.37	59.69	42.54	30.12	20.540	13.650
33	19	4	1	1	B	0	0.000	18.260	57.19	67.19	70.14	91.37	78.02	88.00	83.92	67.46	39.49	26.28	13.480	7.913
34	19	4	2	1	A	0	0.000	15.860	40.99	51.22	55.64	63.05	71.87	77.17	65.93	51.63	29.18	20.43	10.140	4.479
35	20	1	1	1	A	0	0.000	7.529	40.44	59.86	67.58	68.17	94.00	106.60	85.68	69.93	50.01	34.35	17.780	10.910
36	20	1	2	1	B	0	0.000	8.711	40.20	104.30	111.60	118.00	116.10	132.70	126.20	105.20	66.46	50.73	24.390	14.030
37	21	2	1	1	B	0	17.110	36.470	81.73	113.10	115.00	123.70	96.57	91.15	63.46	48.80	30.12	25.26	15.130	11.360
38	21	2	2	1	A	0	6.801	29.650	58.04	85.83	83.55	74.31	75.14	55.35	54.48	40.43	27.36	18.93	11.870	6.778
39	24	1	1	1	A	0	0.000	17.230	58.97	86.48	93.21	86.49	105.80	101.70	83.73	75.32	51.65	45.12	28.790	19.810
40	24	1	2	1	B	0	0.000	15.850	50.78	104.10	108.20	122.60	115.80	120.20	102.70	87.72	59.38	53.02	33.090	28.340
41	25	2	1	1	B	0	10.280	43.840	76.49	94.79	126.20	156.40	145.40	120.40	87.70	71.26	58.19	43.48	31.850	21.600
42	25	2	2	1	A	0	6.034	24.890	72.20	78.09	87.27	116.10	153.50	108.00	65.02	60.93	47.77	40.09	27.520	20.440

Obs	c16	c17	KE_FIRST	KE_LAST	trt	c18	c19	i
1	10.880	5.019	12	17	2	0	0	20
2	17.860	8.851	12	17	1	0	0	20
3	7.270	0.000	12	16	1	0	0	20
4	7.076	0.000	12	16	2	0	0	20
5	5.807	0.000	12	16	1	0	0	20
6	7.207	0.000	12	16	2	0	0	20
7	0.000	0.000	10	14	2	0	0	20
8	0.000	0.000	12	15	1	0	0	20
9	4.923	0.000	12	16	1	0	0	20
10	10.370	4.441	12	17	2	0	0	20
11	5.717	0.000	12	16	1	0	0	20

12	6.553	0.000	12	16	2	0	0	20
13	0.000	0.000	10	14	2	0	0	20
14	0.000	0.000	10	14	1	0	0	20
15	4.341	0.000	12	16	2	0	0	20
16	4.688	0.000	12	16	1	0	0	20
17	10.060	0.000	12	16	2	0	0	20
18	6.342	0.000	12	16	1	0	0	20
19	0.000	0.000	12	15	2	0	0	20
20	0.000	0.000	12	15	1	0	0	20
21	7.455	0.000	12	16	2	0	0	20
22	4.246	0.000	12	16	1	0	0	20
23	16.150	6.673	12	17	2	0	0	20
24	9.080	4.542	12	17	1	0	0	20
25	6.511	0.000	12	16	1	0	0	20
26	9.527	0.000	12	16	2	0	0	20
27	8.076	0.000	12	16	1	0	0	20
28	12.300	5.096	12	17	2	0	0	20
29	9.114	4.345	12	17	1	0	0	20
30	7.099	0.000	12	16	2	0	0	20
31	12.820	5.576	12	17	2	0	0	20
32	8.551	4.092	12	17	1	0	0	20
33	4.160	0.000	12	16	2	0	0	20
34	0.000	0.000	12	15	1	0	0	20
35	4.894	0.000	12	16	1	0	0	20
36	7.700	0.000	12	16	2	0	0	20
37	6.011	0.000	12	16	2	0	0	20
38	4.263	0.000	12	16	1	0	0	20
39	11.770	7.511	12	17	1	0	0	20
40	14.610	7.337	12	17	2	0	0	20
41	15.230	6.170	12	17	2	0	0	20
42	14.530	6.282	12	17	1	0	0	20

Fasting-Reviewer-Calculated Pharmacokinetic Dataset

Norelgestromin

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
1	1	1	4	2	1	196.204	196.722	1.2730	72	3.07761	0.22522
2	1	2	4	1	1	207.473	208.154	1.4300	96	5.38364	0.12875
3	2	1	1	1	1	165.387	.	1.2020	96	.	0.00000
4	2	2	1	2	1	150.517	150.879	0.9743	72	3.14719	0.22024
5	3	1	3	1	1	206.141	.	1.4130	72	.	0.00000
6	3	2	3	2	1	261.144	262.150	1.8660	72	4.97170	0.13942
7	4	1	2	2	1	148.279	148.456	1.2630	48	2.55946	0.27082
8	4	2	2	1	1	169.270	169.632	1.5300	48	4.61317	0.15025
9	5	1	1	1	1	248.203	249.277	1.7510	72	4.82550	0.14364
10	5	2	1	2	1	231.475	232.647	1.4440	120	4.59047	0.15100
11	6	1	3	1	1	192.550	193.221	1.3810	48	5.40831	0.12816
12	6	2	3	2	1	185.526	186.825	1.2420	72	9.16054	0.07567
13	7	1	2	2	1	186.563	186.752	1.6350	48	3.08591	0.22462
14	7	2	2	1	1	209.816	210.707	1.5200	48	9.79016	0.07080
15	8	1	4	2	1	175.204	175.954	1.1450	120	3.83915	0.18055
16	8	2	4	1	1	172.957	173.713	1.0810	96	2.93250	0.23637
17	10	1	4	2	1	163.706	.	1.0550	96	.	0.00000
18	10	2	4	1	1	195.692	196.458	1.2640	96	2.67190	0.25942
19	12	1	2	2	1	113.499	113.643	0.9341	72	2.39185	0.28979
20	12	2	2	1	1	147.396	147.646	1.3150	48	4.43146	0.15641
21	13	1	4	2	1	167.902	168.350	1.1860	72	3.66397	0.18918
22	13	2	4	1	1	162.289	163.144	1.1590	120	6.84327	0.10129
23	14	1	2	2	1	183.556	184.663	1.2890	96	4.93735	0.14039
24	14	2	2	1	1	302.631	305.101	1.8790	72	7.34907	0.09432
25	15	1	1	1	1	162.851	163.173	1.1390	72	3.64829	0.18999
26	15	2	1	2	1	212.647	213.317	1.3740	96	4.50645	0.15381
27	16	1	3	1	1	231.375	232.542	1.5190	72	4.36656	0.15874
28	16	2	3	2	1	184.021	185.369	1.3010	72	6.02892	0.11497
29	17	1	3	1	1	213.848	214.696	1.4190	72	4.71751	0.14693
30	17	2	3	2	1	240.462	241.625	1.4620	48	5.68293	0.12197
31	18	1	2	2	1	172.368	172.666	1.4370	72	2.94808	0.23512
32	18	2	2	1	1	143.578	143.922	0.9387	48	2.79625	0.24788
33	19	1	4	2	1	144.280	144.629	1.0580	72	3.26511	0.21229
34	19	2	4	1	1	184.978	185.201	1.2820	96	3.05643	0.22678
35	20	1	1	1	1	201.196	.	1.3620	72	.	0.00000
36	20	2	1	2	1	202.921	.	1.3260	96	.	0.00000
37	21	1	2	2	1	177.818	178.209	1.4010	72	4.31539	0.16062
38	21	2	2	1	1	266.625	268.181	1.9600	48	9.51044	0.07288
39	24	1	1	1	1	182.869	183.592	1.1860	48	2.89805	0.23918
40	24	2	1	2	1	168.899	169.914	1.0280	72	4.56257	0.15192
41	25	1	2	2	1	298.077	299.793	2.0320	96	4.45079	0.15574
42	25	2	2	1	1	266.119	268.047	1.7720	72	4.92947	0.14061

Ethinyl Estradiol

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
1	1	1	4	2	1	17426.18	.	122.00	170	.	0.00000
2	1	2	4	1	1	17528.55	17551.41	126.30	96	3.15733	0.21954
3	2	1	1	1	1	12431.56	.	101.70	96	.	0.00000
4	2	2	1	2	1	10792.36	.	69.78	168	.	0.00000
5	3	1	3	1	1	12047.29	.	95.90	120	.	0.00000
6	3	2	3	2	1	14377.69	14404.15	92.41	144	2.54437	0.27242
7	4	1	2	2	1	11975.78	.	105.60	72	.	0.00000
8	4	2	2	1	1	12550.41	.	132.10	72	.	0.00000
9	5	1	1	1	1	12219.11	12244.76	93.72	120	3.61175	0.19191
10	5	2	1	2	1	17313.78	17333.35	157.70	120	3.05527	0.22687
11	6	1	3	1	1	12550.74	12576.73	84.92	144	3.15073	0.22000
12	6	2	3	2	1	12750.36	12801.57	87.23	48	5.41744	0.12795
13	7	1	2	2	1	10847.53	.	125.40	72	.	.
14	7	2	2	1	1	14088.68	.	132.30	48	.	0.00000
15	8	1	4	2	1	9265.98	.	69.34	72	.	0.00000
16	8	2	4	1	1	7937.68	.	54.73	96	.	0.00000
17	10	1	4	2	1	8231.16	.	55.28	168	.	0.00000
18	10	2	4	1	1	11334.64	.	82.64	168	.	0.00000
19	12	1	2	2	1	11035.06	.	99.07	120	.	0.00000
20	12	2	2	1	1	13025.21	13055.36	94.74	72	2.84555	0.24359
21	13	1	4	2	1	9911.10	.	69.06	72	.	0.00000
22	13	2	4	1	1	11071.24	11166.16	85.68	120	3.92564	0.17657
23	14	1	2	2	1	14102.24	.	99.84	96	.	0.00000
24	14	2	2	1	1	19269.04	19326.08	122.00	168	5.92587	0.11697
25	15	1	1	1	1	13399.40	13423.73	83.17	72	2.59036	0.26759
26	15	2	1	2	1	17470.88	17516.35	111.30	72	3.30808	0.20953
27	16	1	3	1	1	14186.09	14218.31	93.18	48	2.76557	0.25063
28	16	2	3	2	1	16099.19	16124.38	129.90	144	3.42577	0.20233
29	17	1	3	1	1	15807.74	15830.37	121.40	144	3.60970	0.19202
30	17	2	3	2	1	13958.86	14001.72	95.75	144	4.18432	0.16565
31	18	1	2	2	1	17606.63	.	142.80	72	.	0.00000
32	18	2	2	1	1	17986.23	.	128.80	96	.	0.00000
33	19	1	4	2	1	10025.66	.	77.17	144	.	0.00000
34	19	2	4	1	1	12676.03	.	91.37	96	.	0.00000
35	20	1	1	1	1	12561.20	.	106.60	144	.	0.00000
36	20	2	1	2	1	18039.11	.	132.70	144	.	0.00000
37	21	1	2	2	1	11718.75	11736.12	85.83	48	2.82458	0.24540
38	21	2	2	1	1	16553.78	16601.43	123.70	96	5.49516	0.12614
39	24	1	1	1	1	15448.82	.	105.80	120	.	0.00000
40	24	2	1	2	1	18218.81	.	122.60	96	.	0.00000
41	25	1	2	2	1	17131.01	17157.61	153.50	120	2.93488	0.23618
42	25	2	2	1	1	20295.35	20320.87	156.40	96	2.86751	0.24172

4.5.2 Fasting Study Codes

```
****** STEP 1:  LOCATION OF MACRO FILE (MACROLIB.SAS). CHANGE LOCATION IF
APPLICABLE ********;
%INCLUDE "C:\SAS\BEPRG\NEW\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 2:  ASSIGN FLAG FROM ABOVE FOR TREAT*GROUP INTERACTION*****;
%let trtgroup=;

*****STEP 3: ENTER ANDA INFORMATION *****;
%let level = NORELGESTROMIN;
%let drug= NORELGESTROMIN AND ETHINYL ESTRADIOL TABLETS;
%let dose= 0.15 MG/0.02 MG/DAY;
%let anda=200910;
%let studytype=FASTING;

***** STEP 4: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
%let studydir=C:\Documents and Settings\DANDAMUDI\My
Documents\suman\Transdermal\SAS\Norlegestromin;

*****STEP 5: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = ng hr/mL;
%let cmaxunit = ng/mL;
%let timeunit = hr;

**** DO NOT CHANGE: NAME OF MS WORD STATISTICAL OUTPUT FILE ****;
%LET ODSFILE=&studydir\&anda._&studytype._stat_&level.ACTUAL.doc;

**** DO NOT CHANGE: NAME OF MS WORD REVIEW TABLES OUTPUT FILE ****;
%LET ODSFILE1=&studydir\&anda._&studytype._table_&level.ACTUAL.doc;

**** DO NOT CHANGE: NAME OF PLASMA CONCENTRATION PLOT IN CGM GRAPHIC
FILE****;
%LET PLOTFILE=&studydir\&anda._&studytype._plot_&level.ACTUAL.png;

**** 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 6: SELECT TYPE OF ANALYSIS FROM BOTTOM******;
```

```
/***NOTE:  THE CURRENT PROGRAM DOES NOT INCLUDE CONTINU OR CONTINU2
OPTIONS********
*******SELECT TWOWAYCALCKE07MAR2009.SAS IF YOU WANT TO CALCULATE KE AND OTHER
PARAMETERS ***/
/***SELECT TWOWAYCONTINU(2)07MAR2009.SAS IF YOU DO NOT WANT TO RECALCULATE
KE.
FOR TWOWAYCONTINU(2)07MAR2009.SAS, SPONSOR'S KE WILL BE USED FOR CALCULATION
OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR SUPPLIED PARAMETERS (CONTINU).
OR WITH STATISTICS ON CALCULATED PARAMETERS (CONTINU2) ***/

%LET FNAME=%QUOTE(V:\DIVISION\BIO\SAS Programs\Macros\CALCKE.SAS);
/*** WRITE DATA FILE NAMES  ***/

***** STEP 7:  ENTER THE NAME OF THE DATASET FILE (EXCEL FILE) *****;
/*** 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:R43C24';
* FILENAME ORGPLASM "&studydir.\&plasmadata";
 *%LET FIRSTOBS=1; /* FIRST OBSERVATION */
 *%LET VARPLASM=SUB SEQ PER TRT c1-c22;  /* VARIABLE LIST FOR THE PLASMA DATA
FILE */
%LET PLASMLS=900;   /* INCREASE LINE SIZE IF NEEDED */
 *%READDATA(ORGPLASM,PLASMA,&FIRSTOBS,&VARPLASM,&PLASMLS)
 *RUN;

***** NOTE:  THE FIRST ROW OF THE EXCEL FILE SHOULD CONTAIN PROPER NAMES OF
THE VARIALBES ***;
***** STANDARD NAMES:  SUB SEQ PER GRP TRT C1 C2 C3... KE_FIRST KE_LAST
******;
***** EXCEL FILE DOES NOT NEED TO BE OPEN WHEN RUNNING THIS PROGRAM *****;
* %let excelfile = &studydir\fed.xls;

***** ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING CONCENTRATION
DATA *****;
* %let sheetname = conc;
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST SPECIFYING
DATA POINTS TO BE USED FOR CALCULATION OF KE **;
*** STANDARD NAMES:  SUB SEQ PER GRP TRT c1-c23  ****;
/*
proc import datafile="&excelfile"
            out=plasma
            dbms=excel replace;
                  sheet="&sheetname";
                  getnames=yes;
                  mixed=yes;
run;
*/

LIBNAME libdata "&studydir";

** STEP 8:  ENSURE TREATMENT AND OTHER VARIABLES ARE PROPERLY FORMATTED..CHAR
OR NUMERIC **;
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST SPECIFYING
DATA POINTS TO BE USED FOR CALCULATION OF KE **;
DATA PLASMA;
  * SET PLASMA;
```

```
  infile ORGPLASM;
  input sub seq per GRP treat $ c1-c17 KE_FIRST KE_LAST;

  if treat = "A" then trt=1;
  else trt=2;

RUN;

data plasma;
  set plasma;

  array conc{*} c1-c19;

  do i=1 to 19;
    if conc{i} < 0 then conc{i} = 0;
  end;
run;

proc print data=plasma;
run;

%SORTDS(PLASMA, &VARSORT)
RUN;

*****ACTIVATE THIS STEP AND STEP 9A BELOW ONLY IF USING CONTINU.SAS OR
CONTINU2.SAS*********
****PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE LIST
*****;

***** STEP 9:  ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING PK STUDY
DATA *****;
/***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:R43C11';
* FILENAME ORGPARAM "&studydir.\&pkdata";
*%LET FIRSTOBS=1; /* FIST OBSERVATION */
*%LET VARPARAM=SUB SEQ PER TRT $ TMAX CMAX AUCT AUCI KE THALF; /* VARIABLE
LIST */
%LET PARAMLS=500;  /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGPARAM,PARAME,&FIRSTOBS,&VARPARAM,&PARAMLS)
RUN;

/*
***** ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING PK STUDY DATA
*****;
*%let pksheetname = pk;

proc import datafile="&excelfile"
            out=parame
            dbms=excel replace;
                  sheet="&pksheetname";
                  getnames=yes;
                  mixed=yes;
run;
*/
```

```
** STEP 10:  ENSURE TREATMENT AND OTHER VARIABLES ARE PROPERLY
FORMATTED..CHAR OR NUMERIC **;
DATA PARAME;
  * set parame;

   infile ORGPARAM ls=&paramls;
   input sub seq per GRP treat $ AUCT AUCI CMAX TMAX KE THALF;

 if treat = "A" then trt=1;
  else trt=2;
RUN;

%SORTDS(PARAME, &VARSORT)
RUN;

*****STEP 11: 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);


/***STEP 12: 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***/
DATA TIME
%LET TIME=%STR(T1=0; T2=6; T3=12; T4=24; T5=48;
T6=72; T7=96; T8=120; T9=144; T10=168; T11=170; T12=174;
T13=180; T14=192; T15=204; T16=216; T17=240);

/*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 SUB TRT SEQ PER GRP T1-T27;
*KEEP SUB TRT SEQ PER GRP T1-T27;

/*PROC PRINT DATA=TIME;RUN;*/

*****STEP 13: WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS *****;
%LET NO_ASSAY=17;

*****INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF THESE ARE NOT
IN THE DATA SUBMITTED. *****;
** DO NOT CHANGE SINCE KE_FIRST AND KE_LAST VALUES ARE IN CONC DATASET **;
* %LET KE_FIRST=20;
* %LET KE_LAST=27;

*****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^=1);

*****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 );*/

DATA ORIGIN;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
SET PLASMA;
*SET TIME;
* SET PARAME;
*SET MERGED;
&TIME;
*KE_FIRST=0;
*KE_LAST=0;
CLAST=C&NO_ASSAY;
NEWCMAX=MAX(&CONCENT);

/***DO NOT CHANGE: TITLES FOR TABLES***/
%LET TITLE1=MEAN PLASMA &level LEVELS;
%LET TITLE2=MEAN PLASMA &level LEVELS FOR TEST AND REFERENCE PRODUCTS;

/*** DESCRIBE TITLES, FOOTNOTES AND LABELS FOR GRAPH ***/
%LET TITLE3=PLASMA &level LEVELS;
%LET TITLE4= &drug, ANDA &anda;
%LET TITLE5=UNDER &STUDYTYPE CONDITIONS;
%LET TITLE6=DOSE= &dose;
%LET FOOTNOT1=1=TEST   2=REF;
%LET FOOTNOT2=Tmax values are presented as median, range.;
%LET FOOTNOT3=;
%LET FOOTNOT4=;
%LET FOOTNOT5=;
%LET LABEL1=PLASMA LEVEL, &cmaxunit;
%LET LABEL2=TIME, HRS;
%LET LABEL3=TEST;
%LET LABEL4=REFERENCE;

%COPYDS(ORIGIN, NEW)
RUN;

proc print data=origin;
run;

*****STEP 15: OPEN IF YOU WANT TO REMOVE, ADD OR EDIT*****;
*%REMUVSUB(NEW, NEW)
RUN;
```

4.5.3 Fasting Study Output

Norelgestromin

FASTING STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
sub	21	1 2 3 4 5 6 7 8 10 12 13 14 15 16 17 18 19 20 21 24 25
trt	2	1 2
per	2	1 2
seq	4	1 2 3 4

Number of Observations Read	42
Number of Observations Used	42

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	22	1.44525452	0.06569339	3.73	0.0026
Error	19	0.33473611	0.01761769		
Corrected Total	41	1.77999063			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.811945	2.527015	0.132732	5.252507

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	3	0.15949511	0.05316504	3.02	0.0553
sub(seq)	17	1.18408613	0.06965213	3.95	0.0025
per	1	0.04912873	0.04912873	2.79	0.1113
trt	1	0.05254455	0.05254455	2.98	0.1004

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	3	0.15949511	0.05316504	3.02	0.0553
sub(seq)	17	1.18408613	0.06965213	3.95	0.0025
per	1	0.03483078	0.03483078	1.98	0.1758
trt	1	0.05254455	0.05254455	2.98	0.1004

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**

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	3	0.15949511	0.05316504	0.76	0.5301

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.07147376	0.04138636	-1.73	0.1004

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	22	1.55321921	0.07060087	4.11	0.0014
Error	19	0.32627935	0.01717260		
Corrected Total	41	1.87949856			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.826401	2.483389	0.131044	5.276831

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	3	0.15607869	0.05202623	3.03	0.0547
sub(seq)	17	1.29195477	0.07599734	4.43	0.0012
per	1	0.05028534	0.05028534	2.93	0.1033
trt	1	0.05490041	0.05490041	3.20	0.0897

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	3	0.15607869	0.05202623	3.03	0.0547
sub(seq)	17	1.29195477	0.07599734	4.43	0.0012
per	1	0.03552144	0.03552144	2.07	0.1666
trt	1	0.05490041	0.05490041	3.20	0.0897

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	3	0.15607869	0.05202623	0.68	0.5737

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.07305847	0.04086023	-1.79	0.0897

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	22	1.10784416	0.05035655	2.24	0.0399
Error	19	0.42631064	0.02243740		
Corrected Total	41	1.53415480			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.722120	51.50080	0.149791	0.290852

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	3	0.31793568	0.10597856	4.72	0.0126
sub(seq)	17	0.74027030	0.04354531	1.94	0.0823
per	1	0.04386561	0.04386561	1.96	0.1782
trt	1	0.00577257	0.00577257	0.26	0.6178

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	3	0.31793568	0.10597856	4.72	0.0126
sub(seq)	17	0.74027030	0.04354531	1.94	0.0823
per	1	0.03858832	0.03858832	1.72	0.2053
trt	1	0.00577257	0.00577257	0.26	0.6178

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	3	0.31793568	0.10597856	2.43	0.1003

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.02369012	0.04670561	-0.51	0.6178

FASTING STATISTICAL OUTPUT

The GLM Procedure
Least Squares Means

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: AUCT				
i/j	1	2	3	4
1		-0.53579 0.5983	-1.61641 0.1225	1.235456 0.2317

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: AUCT				
i/j	1	2	3	4
2	0.535786 0.5983		-1.22945 0.2339	1.87023 0.0769
3	1.616412 0.1225	1.229449 0.2339		2.781211 0.0119
4	-1.23546 0.2317	-1.87023 0.0769	-2.78121 0.0119	

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: AUCI				
i/j	1	2	3	4
1		-0.54958 0.5890	-1.62988 0.1196	1.219189 0.2377
2	0.549584 0.5890		-1.23098 0.2334	1.866459 0.0775
3	1.629882 0.1196	1.230976 0.2334		2.779345 0.0119
4	-1.21919 0.2377	-1.86646 0.0775	-2.77934 0.0119	

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: CMAX				
i/j	1	2	3	4
1		-2.48914 0.0222	-1.73848 0.0983	0.916145 0.3711
2	2.489142 0.0222		0.464725 0.6474	3.478692 0.0025
3	1.738483 0.0983	-0.46473 0.6474		2.602233 0.0175
4	-0.91615 0.3711	-3.47869 0.0025	-2.60223 0.0175	

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: LAUCT				
i/j	1	2	3	4
1		-0.04647 0.9634	-1.77321 0.0922	1.30762 0.2066
2	0.04647 0.9634		-1.85438 0.0793	1.458861 0.1609
3	1.773213 0.0922	1.854385 0.0793		3.006048 0.0073

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: LAUCT				
i/j	1	2	3	4
4	-1.30762 0.2066	-1.45886 0.1609	-3.00605 0.0073	

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: LAUCI				
i/j	1	2	3	4
1		0.009988 0.9921	-1.79481 0.0886	1.287202 0.2135
2	-0.00999 0.9921		-1.93025 0.0686	1.380349 0.1835
3	1.794814 0.0886	1.930247 0.0686		3.0084 0.0072
4	-1.2872 0.2135	-1.38035 0.1835	-3.0084 0.0072	

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: LCMAX				
i/j	1	2	3	4
1		-2.30122 0.0329	-1.86796 0.0773	0.895144 0.3819
2	2.301219 0.0329		0.150592 0.8819	3.268084 0.0040
3	1.867962 0.0773	-0.15059 0.8819		2.711912 0.0138
4	-0.89514 0.3819	-3.26808 0.0040	-2.71191 0.0138	

Ethinyl Estradiol

FASTING STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	21	1 2 3 4 5 6 7 8 10 12 13 14 15 16 17 18 19 20 21 24 25
trt	2	1 2
per	2	1 2
seq	4	1 2 3 4

Number of Observations Read	42
Number of Observations Used	42

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	22	1.94897282	0.08858967	6.35	<.0001
Error	19	0.26521916	0.01395890		
Corrected Total	41	2.21419198			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.880219	1.241962	0.118148	9.512996

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	3	0.51353240	0.17117747	12.26	0.0001
sub(seq)	17	1.21534435	0.07149084	5.12	0.0005
per	1	0.00990045	0.00990045	0.71	0.4102
trt	1	0.21019561	0.21019561	15.06	0.0010

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	3	0.51353240	0.17117747	12.26	0.0001
sub(seq)	17	1.21534435	0.07149084	5.12	0.0005
per	1	0.00108798	0.00108798	0.08	0.7831
trt	1	0.21019561	0.21019561	15.06	0.0010

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	3	0.51353240	0.17117747	2.39	0.1042

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.14295343	0.03683905	-3.88	0.0010

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	22	1.92608702	0.08754941	6.28	<.0001
Error	19	0.26474047	0.01393371		
Corrected Total	41	2.19082749			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.879160	1.239422	0.118041	9.523886

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	3	0.50258863	0.16752954	12.02	0.0001
sub(seq)	17	1.20281237	0.07075367	5.08	0.0005
per	1	0.01026871	0.01026871	0.74	0.4013
trt	1	0.21041732	0.21041732	15.10	0.0010

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	3	0.50258863	0.16752954	12.02	0.0001
sub(seq)	17	1.20281237	0.07075367	5.08	0.0005
per	1	0.00120860	0.00120860	0.09	0.7716
trt	1	0.21041732	0.21041732	15.10	0.0010

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	3	0.50258863	0.16752954	2.37	0.1068

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.14302881	0.03680579	-3.89	0.0010

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	22	2.25621095	0.10255504	3.74	0.0026
Error	19	0.52093471	0.02741762		
Corrected Total	41	2.77714565			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.812421	3.580368	0.165583	4.624739

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	3	0.95237101	0.31745700	11.58	0.0002
sub(seq)	17	1.18992258	0.06999545	2.55	0.0257
per	1	0.00405786	0.00405786	0.15	0.7047
trt	1	0.10985950	0.10985950	4.01	0.0598

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	3	0.95237101	0.31745700	11.58	0.0002
sub(seq)	17	1.18992258	0.06999545	2.55	0.0257
per	1	0.00024642	0.00024642	0.01	0.9255
trt	1	0.10985950	0.10985950	4.01	0.0598

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	3	0.95237101	0.31745700	4.54	0.0164

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.10334788	0.05162946	-2.00	0.0598

FASTING STATISTICAL OUTPUT

The GLM Procedure
Least Squares Means

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: AUCT				
i/j	1	2	3	4
1		-0.12015 0.9056	1.059378 0.3027	4.466587 0.0003
2	0.120147 0.9056		1.24605 0.2279	4.944613 <.0001
3	-1.05938 0.3027	-1.24605 0.2279		3.151761 0.0053
4	-4.46659 0.0003	-4.94461 <.0001	-3.15176 0.0053	

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: AUCI				
i/j	1	2	3	4
1		-0.0707 0.9444	1.082621 0.2925	4.462701 0.0003
2	0.070698 0.9444		1.224731 0.2356	4.890966 0.0001
3	-1.08262 0.2925	-1.22473 0.2356		3.124854 0.0056

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: AUCI				
i/j	1	2	3	4
4	-4.4627 0.0003	-4.89097 0.0001	-3.12485 0.0056	

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: CMAX				
i/j	1	2	3	4
1		-1.89824 0.0730	1.067511 0.2991	3.381705 0.0031
2	1.898241 0.0730		2.915848 0.0089	5.5509 <.0001
3	-1.06751 0.2991	-2.91585 0.0089		2.120791 0.0473
4	-3.38171 0.0031	-5.5509 <.0001	-2.12079 0.0473	

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: LAUCT				
i/j	1	2	3	4
1		-0.01498 0.9882	0.80401 6 0.4313	5.060883 <.0001
2	0.014981 0.9882		0.8745 0.3928	5.481359 <.0001
3	-0.80402 0.4313	-0.8745 0.3928		3.967431 0.0008
4	-5.06088 <.0001	-5.48136 <.0001	-3.96743 0.0008	

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: LAUCI				
i/j	1	2	3	4
1		0.036877 0.9710	0.82661 5 0.4187	5.039526 <.0001
2	-0.03688 0.9710		0.85024 1 0.4058	5.406433 <.0001
3	-0.82661 0.4187	-0.85024 0.4058		3.924696 0.0009
4	-5.03953 <.0001	-5.40643 <.0001	-3.9247 0.0009	

Least Squares Means for Effect seq t for H0: LSMean(i)=LSMean(j) / Pr > |t| Dependent Variable: LCMAX				
i/j	1	2	3	4
1		-1.78118 0.0909	0.861617 0.3996	3.742843 0.0014
2	1.781183 0.0909		2.586133 0.0181	5.823915 <.0001
3	-0.86162 0.3996	-2.58613 0.0181		2.667169 0.0152
4	-3.74284 0.0014	-5.82392 <.0001	-2.66717 0.0152	

Fasting Firm to Reviewer Ratio

Norelgestromin

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	4	1	1	2	207.473	208.154	1.4300	B	207.441	210.314	1.4300	0.99984	1.01037	1
2	1	4	2	1	1	196.204	196.722	1.2730	A	196.204	200.202	1.2730	1.00000	1.01769	1
3	2	1	1	1	1	165.387	.	1.2020	A	165.387	168.166	1.2020	1.00000	.	1
4	2	1	2	1	2	150.517	150.879	0.9743	B	150.517	153.027	0.9743	1.00000	1.01424	1
5	3	3	1	1	1	206.141	.	1.4130	A	206.141	210.840	1.4130	1.00000	.	1
6	3	3	2	1	2	261.144	262.150	1.8660	B	261.144	266.833	1.8660	1.00000	1.01786	1
7	4	2	1	1	2	169.270	169.632	1.5300	B	169.270	171.051	1.5300	1.00000	1.00837	1
8	4	2	2	1	1	148.279	148.456	1.2630	A	148.279	150.010	1.2630	1.00000	1.01046	1
9	5	1	1	1	1	248.203	249.277	1.7510	A	248.203	254.781	1.7510	1.00000	1.02208	1
10	5	1	2	1	2	231.475	232.647	1.4440	B	231.475	238.227	1.4440	1.00000	1.02398	1
11	6	3	1	1	1	192.550	193.221	1.3810	A	192.550	195.675	1.3810	1.00000	1.01270	1
12	6	3	2	1	2	185.526	186.825	1.2420	B	185.532	189.372	1.2420	1.00003	1.01363	1
13	7	2	1	1	2	209.816	210.707	1.5200	B	209.816	211.619	1.5200	1.00000	1.00432	1
14	7	2	2	1	1	186.563	186.752	1.6350	A	186.563	187.901	1.6350	1.00000	1.00615	1
15	8	4	1	1	2	172.957	173.713	1.0810	B	172.957	183.050	1.0810	1.00000	1.05375	1
16	8	4	2	1	1	175.204	175.954	1.1450	A	175.204	180.627	1.1450	1.00000	1.02656	1
17	10	4	1	1	2	195.692	196.458	1.2640	B	195.692	205.311	1.2640	1.00000	1.04506	1
18	10	4	2	1	1	163.706	.	1.0550	A	163.706	173.427	1.0550	1.00000	.	1
19	12	2	1	1	2	147.396	147.646	1.3150	B	147.371	148.177	1.3150	0.99983	1.00359	1
20	12	2	2	1	1	113.499	113.643	0.9341	A	113.499	114.437	0.9341	1.00000	1.00699	1
21	13	4	1	1	2	162.289	163.144	1.1590	B	172.543	175.645	1.1590	1.06318	1.07663	1
22	13	4	2	1	1	167.902	168.350	1.1860	A	167.951	170.971	1.1860	1.00029	1.01557	1
23	14	2	1	1	2	302.631	305.101	1.8790	B	302.878	312.675	1.8790	1.00082	1.02483	1
24	14	2	2	1	1	183.556	184.663	1.2890	A	183.556	191.559	1.2890	1.00000	1.03734	1
25	15	1	1	1	1	162.851	163.173	1.1390	A	162.851	165.389	1.1390	1.00000	1.01358	1
26	15	1	2	1	2	212.647	213.317	1.3740	B	212.647	216.227	1.3740	1.00000	1.01364	1
27	16	3	1	1	1	231.375	232.542	1.5190	A	231.356	239.492	1.5190	0.99992	1.02989	1
28	16	3	2	1	2	184.021	185.369	1.3010	B	184.025	191.696	1.3010	1.00002	1.03413	1
29	17	3	1	1	1	213.848	214.696	1.4190	A	213.848	218.595	1.4190	1.00000	1.01816	1
30	17	3	2	1	2	240.462	241.625	1.4620	B	240.470	246.010	1.4620	1.00003	1.01815	1
31	18	2	1	1	2	143.578	143.922	0.9387	B	143.578	146.984	0.9387	1.00000	1.02128	1
32	18	2	2	1	1	172.368	172.666	1.4370	A	172.374	174.704	1.4370	1.00004	1.01180	1
33	19	4	1	1	2	184.978	185.201	1.2820	B	184.978	186.307	1.2820	1.00000	1.00598	1
34	19	4	2	1	1	144.280	144.629	1.0580	A	144.280	146.151	1.0580	1.00000	1.01052	1
35	20	1	1	1	1	201.196	.	1.3620	A	201.196	204.654	1.3620	1.00000	.	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
36	20	1	2	1	2	202.921	.	1.3260	B	202.921	208.206	1.3260	1.00000	.	1
37	21	2	1	1	2	266.625	268.181	1.9600	B	266.625	270.548	1.9600	1.00000	1.00883	1
38	21	2	2	1	1	177.818	178.209	1.4010	A	177.818	180.020	1.4010	1.00000	1.01016	1
39	24	1	1	1	1	182.869	183.592	1.1860	A	182.869	191.822	1.1860	1.00000	1.04483	1
40	24	1	2	1	2	168.899	169.914	1.0280	B	168.922	175.873	1.0280	1.00014	1.03507	1
41	25	2	1	1	2	266.119	268.047	1.7720	B	266.147	281.470	1.7720	1.00011	1.05008	1
42	25	2	2	1	1	298.077	299.793	2.0320	A	298.065	311.014	2.0320	0.99996	1.03743	1

Ethinyl Estradiol

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	4	1	1	2	17528.55	17551.41	126.30	B	17525.20	17645.89	126.30	0.99981	1.00538	1
2	1	4	2	1	1	17426.18	.	122.00	A	17426.18	17723.30	122.00	1.00000	.	1
3	2	1	1	1	1	12431.56	.	101.70	A	12431.56	12648.92	101.70	1.00000	.	1
4	2	1	2	1	2	10792.36	.	69.78	B	10792.36	10964.84	69.78	1.00000	.	1
5	3	3	1	1	1	12047.29	.	95.90	A	12047.29	12189.90	95.90	1.00000	.	1
6	3	3	2	1	2	14377.69	14404.15	92.41	B	14377.69	14578.29	92.41	1.00000	1.01209	1
7	4	2	1	1	2	12550.41	.	132.10	B	12550.41	12677.11	132.10	1.00000	.	1
8	4	2	2	1	1	11975.78	.	105.60	A	11975.78	12074.40	105.60	1.00000	.	1
9	5	1	1	1	1	12219.11	12244.76	93.72	A	12219.11	12331.50	93.72	1.00000	1.00708	1
10	5	1	2	1	2	17313.78	17333.35	157.70	B	17313.78	17440.30	157.70	1.00000	1.00617	1
11	6	3	1	1	1	12550.74	12576.73	84.92	A	12550.74	12676.99	84.92	1.00000	1.00797	1
12	6	3	2	1	2	12750.36	12801.57	87.23	B	12751.27	12892.74	87.23	1.00007	1.00712	1
13	7	2	1	1	2	14088.68	.	132.30	B	14088.68	14214.06	132.30	1.00000	.	1
14	7	2	2	1	1	10847.53	.	125.40	A	10847.53	10967.00	125.40	1.00000	.	1
15	8	4	1	1	2	7937.68	.	54.73	B	7937.68	8055.09	54.73	1.00000	.	1
16	8	4	2	1	1	9265.98	.	69.34	A	9265.98	9389.06	69.34	1.00000	.	1
17	10	4	1	1	2	11334.64	.	82.64	B	11334.64	11595.48	82.64	1.00000	.	1
18	10	4	2	1	1	8231.16	.	55.28	A	8231.16	8390.56	55.28	1.00000	.	1
19	12	2	1	1	2	13025.21	13055.36	94.74	B	13023.19	13165.12	94.74	0.99984	1.00841	1
20	12	2	2	1	1	11035.06	.	99.07	A	11035.06	11125.97	99.07	1.00000	.	1
21	13	4	1	1	2	11071.24	11166.16	85.68	B	11687.75	11853.79	85.68	1.05569	1.06158	1
22	13	4	2	1	1	9911.10	.	69.06	A	9914.65	10002.73	69.06	1.00036	.	1
23	14	2	1	1	2	19269.04	19326.08	122.00	B	19223.71	19403.64	122.00	0.99765	1.00401	1
24	14	2	2	1	1	14102.24	.	99.84	A	14102.24	14251.10	99.84	1.00000	.	1
25	15	1	1	1	1	13399.40	13423.73	83.17	A	13399.40	13543.82	83.17	1.00000	1.00895	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
26	15	1	2	1	2	17470.88	17516.35	111.30	B	17470.88	17682.56	111.30	1.00000	1.00949	1
27	16	3	1	1	1	14186.09	14218.31	93.18	A	14184.58	14382.73	93.18	0.99989	1.01156	1
28	16	3	2	1	2	16099.19	16124.38	129.90	B	16100.26	16230.86	129.90	1.00007	1.00660	1
29	17	3	1	1	1	15807.74	15830.37	121.40	A	15807.74	15920.70	121.40	1.00000	1.00571	1
30	17	3	2	1	2	13958.86	14001.72	95.75	B	13959.65	14127.18	95.75	1.00006	1.00896	1
31	18	2	1	1	2	17986.23	.	128.80	B	17986.23	18153.09	128.80	1.00000	.	1
32	18	2	2	1	1	17606.63	.	142.80	A	17607.68	17729.23	142.80	1.00006	.	1
33	19	4	1	1	2	12676.03	.	91.37	B	12676.03	12758.37	91.37	1.00000	.	1
34	19	4	2	1	1	10025.66	.	77.17	A	10025.66	10097.72	77.17	1.00000	.	1
35	20	1	1	1	1	12561.20	.	106.60	A	12561.20	12652.58	106.60	1.00000	.	1
36	20	1	2	1	2	18039.11	.	132.70	B	18039.11	18199.39	132.70	1.00000	.	1
37	21	2	1	1	2	16553.78	16601.43	123.70	B	16553.78	16714.63	123.70	1.00000	1.00682	1
38	21	2	2	1	1	11718.75	11736.12	85.83	A	11718.75	11820.40	85.83	1.00000	1.00718	1
39	24	1	1	1	1	15448.82	.	105.80	A	15448.82	15693.82	105.80	1.00000	.	1
40	24	1	2	1	2	18218.81	.	122.60	B	18220.00	18447.50	122.60	1.00007	.	1
41	25	2	1	1	2	20295.35	20320.87	156.40	B	20298.63	20478.35	156.40	1.00016	1.00775	1
42	25	2	2	1	1	17131.01	17157.61	153.50	A	17130.25	17320.15	153.50	0.99996	1.00947	1

4.6 Additional Attachments

E-mail correspondence between the reviewer and dissolution focal point, Dr. Wayne Dehaven

From: Dehaven, Wayne
Sent: Thursday, May 09, 2013 5:40 PM
To: Dandamudi, Suman
Subject: RE: Dissolution Consult for ANDA 200910

Hi Suman:

Based on low variability, I concur. Sorry it took so long for me to respond.

Thanks,
Wayne

From: Dandamudi, Suman
Sent: Friday, May 03, 2013 3:48 PM
To: Dehaven, Wayne
Cc: Braddy, April
Subject: RE: Dissolution Consult for ANDA 200910

Hello Wayne,

Thank you for input on the dissolution testing for this drug product.

I will recommend the firm to either acknowledge the FDA-recommended method or conduct additional dissolution testing using the firm's proposed method with some additional sampling time points.

For the recommended method, based on the data submitted, I would like to recommend the following specifications.

Norelgestromin: (b) (4)

Ethinyl Estradiol

I would like to know your opinion on setting the dissolution specification for Norelgestromin/Ethinyl Estradiol Transdermal System.

Thanks,
Suman

From: Dehaven, Wayne
Sent: Wednesday, May 01, 2013 4:23 PM
To: Dandamudi, Suman
Subject: RE: Dissolution Consult for ANDA 200910

Hi Suman:

Thanks for the interesting consult. I have the following comments:

1. If I were to pick the more appropriate method based on the currently submitted data, I would pick the FDA-recommended method over the in-house method, simply because the limited data-points submitted allow for more appropriate specifications in the FDA-recommended method data-set.

2. That said, the firm can use their in-house method if they wish. But I agree with you, they should justify why they prefer their method over the FDA-recommended method. Also, I would agree with you that there should be additional time-points (b) (4) for their in-house method.

3. In contrast, if you ask them to acknowledge the FDA-recommended method, I think the data-set is limited, but sufficient to set appropriate specifications (at (b) (4) hours). I note that the variability is low for both analytes (see profiles below), and the data collected capture early, mid and late phases of release.

Please remember that these are just my opinions. Please consult with TL and management for further input.

Thanks,
Wayne

<< OLE Object: Microsoft Office Excel Chart >>

<< OLE Object: Microsoft Office Excel Chart >>

From: Dandamudi, Suman
Sent: Tuesday, April 30, 2013 9:47 AM
To: Dehaven, Wayne
Cc: Braddy, April
Subject: Dissolution Consult for ANDA 200910

Hello Wayne,

I'm currently working on ANDA 200910, Norelgestromin/Ethinyl Estradiol Transdermal Film Extended Release.

The firm submitted the dissolution data using both the FDA -recommended method and the in house method.

The firm did not provide any justification for conducting dissolution testing using its own proposed method.

For the in-house method, the firm measured % drug release at sampling times of (b) (4) hours. In my opinion, the number of sampling times used in the dissolution testing (both firm's and FDA methods) is not sufficient. The firm should conduct dissolution testing with additional sampling time points (b) (4) to get complete release profile.

I would like to know your opinion on the dissolution testing for this product.

Thanks,
Suman

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 200910

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch

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

1. The comparative dissolution testing conducted using your proposed method is considered inadequate. Your proposed method gave release profiles with more gradual slopes, compared with the FDA method, for both the test and reference products, and therefore, demonstrated superiority. However, the dissolution testing based on your method did not include sufficient sampling time points to characterize adequately the more gradual release profiles. Please conduct additional comparative dissolution testing using your method on a fresh test lot and unexpired reference lot, using the time points of 0.5, 2, 6, 8, 14, 20 and 24 hours. The fresh test lot should be manufactured using the same manufacturing conditions, specifications and formulation as the bio study test lot, and the Chemistry, Manufacturing and Controls records for the fresh test lot should be submitted to the Division of Chemistry for evaluation. The Certificate of Analysis for this fresh test lot should also be submitted to DBI for confirmation.

2. Following the inspection of the analytical site, Mylan Pharmaceuticals Inc. Bioanalytical Department, 3711 Collins Ferry Rd, Morgantown, WV, between August 18-26, 2010, by the Office of Scientific Investigations (OSI) for bioequivalence (BE) studies from another application, Form FDA- 483 was issued for the site.

   For considering the impact of similar study conduct and site practices by the same analytical facility on the fasting bioequivalence (BE) study of the current ANDA, the DBI reviewed the above OSI inspection report and found that the following objectionable findings by the OSI at the analytical site could potentially compromise the integrity of the study of current ANDA as well:

   - Stability of processed samples was determined with only mid level QCs during pre-study validation for the audited studies. Processed stability was not evaluated with low and high QC concentrations.

   - Failure to document all aspects of the study conduct.

     No documentation was maintained for identity of the weighing scales used for quarterly qualification for pipettes during the audited studies.

Please address the above specific findings by the OSI with respect to their impact on the fasting BE study of the current ANDA, providing any necessary supporting documents in your response.

3. During the fasting BE study (ORH-0942), two (2) study samples for norelgestromin were re-assayed for the reason of "Abnormal Internal Standard Response" as per Bioanalytical report (ORTH-0942_NORE), Table 5- Repeat Analysis Results for NORE in Human Plasma. However, in the table of Reanalysis of Study Samples, you have stated the reason for the re-assay as "Documented Sample Processing Error". Please be advised that for the future submissions, you should provide consistent information concerning repeat analyses throughout your submission.

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

4.7 Outcome Page

ANDA: 200910

Enter Review Productivity and Generate Report

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
19829	12/31/2009	Bioequivalence Study (REGULAR)	Fasting Study	1	1
19829	10/8/2010	Dissolution Data (REGULAR)	Dissolution Amendment	1	1
				Total:	2

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

/s/

SUMAN DANDAMUDI
06/05/2013

APRIL C BRADDY
06/05/2013

HOAINHON N CARAMENICO
06/07/2013

DALE P CONNER
06/11/2013

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	200910
Drug Product Name	Norelgestromin and Ethinyl Estradiol Transdermal System
Strength (s)	0.15 mg/24 hour and 0.02 mg/24 hour
Applicant Name	Mylan Technologies Inc.
Address	781 Chestnut Ridge Road, P.O. Box 4310, Morgantown, WV 26505
Applicant's Point of Contact	S. Wayne Talton, Vice President, Regulatory Affairs
Contact's Phone Number	(304) 599-2595, ext. 6551
Contact's Fax Number	(304) 285-6407
Submission Date(s)	December 31, 2009
First Generic	No
Reviewer	Svetlana Cherstniakova, Ph.D.
Study Number (s)	ORTH-0942
Study Type (s)	Pharmacokinetic Endpoints
Strength(s)	0.15 mg / 0.02 mg /24 hours
Clinical Site	Cetero Research
Clinical Site Address	625 Demers Avenue, East Grand Forks, MN 56721, USA 218-773-5560
Analytical Site	Mylan Pharmaceuticals Inc.
Analytical Address	Bioanalytical Department 3711 Collins Ferry Rd, Morgantown, WV 26505 800-826-9526
OUTCOME DECISION	INCOMPLETE

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing data with the FDA-recommended method are acceptable. In addition, the firm has submitted comparative dissolution testing of the test and RLD products using the dissolution media of pH 6.8 buffer, pH 4.5 buffer and water with 0.25% Tween® 20. The data showed no evidence of dose dumping in early time points. However, the firm did not submit comparative dissolution testing data in pH 1.2 dissolution medium.

The firm will be asked to submit the dissolution profiles on 12 dosage units each of test and reference products generated in pH 1.2 dissolution medium.

The Long Term Storage Stability data is not sufficient to cover the storage period of the study samples for the bioequivalence studies. The firm should provide Long Term Storage Stability data for at least 96 days for Norelgestromin and 60 days for Ethinyl Estradiol.

The DBE will review the bioequivalence with pharmacokinetic endpoints, adhesion and skin irritation and sensitization studies at a later date.

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.					

Dissolution Reference

Ethinyl Estradiol; Norelgestromin

Dosage Form: Film, Transdermal

Medium: 0.1% Hydroxypropyl-beta-cyclodextrin at 32° C

Apparatus: Modified USP Type V (Paddle-over-disk)

Speed/RPMs: 50

Modify Date:

Sampling Times: 0.25, 0.5, 1, 2, 4, 8, 12, 16, 20 and 24 hours

Volume: 900

Notes: Added by NT on 7/16/09 Source: N 21180,AR 2009)

Specification: EE (100%=0.75 mg/unit): (b) (4) (b) (4)

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Drug Release Conditions	**Apparatus:**	5 (paddle over disk – transdermal sandwich)
	Speed of Rotation:	50 rpm
	Medium:	0.1% Hydroxypropyl β-Cyclodextrin in Water
	Volume:	900 mL
	Temperature:	32 °C ± 0.5 °C
Firm's Proposed Specifications	N/A	
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
										(b) (4)	
						Hours	Hours	Hours	Hours	Hours	
N/A	Dec. 2009	Norelgestromin / Ethinyl Estradiol Transdermal System 14cm² Lot R6A0014 DOM – May 2009	NGMN 4.86mg	12	Mean (%)	15	38	72	98	100	3.2.P.5.4 Batch Analysis
					Range (%)	(b) (4)					
					%CV	4.5	3.2	2.3	0.9	0.9	
			EE 0.53mg	12	Mean (%)	18	43	82	97	99	
					Range (%)	(b) (4)					
					%CV	3.7	3.9	2.6	0.8	0.7	
N/A	Dec. 2009	Ortho Evra® 20cm² Lot 8HM6015P1 Exp. Date July 2010	NGMN 6.00mg	12	Mean (%)	14	33	63	81	92	
					Range (%)	(b) (4)					
					%CV	4.7	3.4	2.1	3.7	2.9	
			EE 0.75mg	12	Mean (%)	16	35	66	84	95	
					Range (%)	(b) (4)					
					%CV	5.6	3.8	2.4	3.7	2.4	

NEETS 14cm² - Norelgestromin

Dosage: NEETS 14 cm² [NGMN 4.86 mg / EE 0.53 mg]
Lot: R6A0014
Test Method: STM-0676
Drug Release Medium: 0.1% Hydroxypropyl β-Cyclodextrin in Water
Volume: 900 mL
Temperature: 32 °C ± 0.5 °C

	Quantity Of Norelgestromin Released, % of Claim				
Sample Number	(b) (4)				
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean, % of claim	15	38	72	98	100
RSD, %	4.5	3.2	2.3	0.9	0.9
Range, % of claim	(b) (4)				

NEETS 14cm² – Ethinyl Estradiol

	Quantity Of Ethinyl Estradiol Released, % of Claim				
Sample Number	(b) (4)				
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean, % of claim	18	43	82	97	99
RSD, %	3.7	3.9	2.6	0.8	0.7
Range, % of claim	(b) (4)				

Ortho Evra® - Norelgestromin

Dosage: Ortho Evra® (6.00 mg NGMN / 0.75 mg EE)
Lot: 8HM6015P1
Test Method: STM-0676
Drug Release Medium: 0.1% Hydroxypropyl β-Cyclodextrin in Water
Volume: 900 mL
Temperature: 32 °C ± 0.5 °C

	Quantity Of Norelgestromin Released, % of Claim				
Sample Number	(b) (4)				
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean, % of claim	14	33	63	81	92
RSD, %	4.7	3.4	2.1	3.7	2.9
Range, % of claim	(b) (4)				

Ortho Evra® – Ethinyl Estradiol

	Quantity Of Ethinyl Estradiol Released, % of Claim				
Sample Number	(b) (4)				
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean, % of claim	16	35	66	84	95
RSD, %	5.6	3.8	2.4	3.7	2.4
Range, % of claim	(b) (4)				

Norelgestromin / Ethinyl Estradiol Transdermal System 14 cm² [NGMN 4.86 mg / EE 0.53 mg]

Drug Release Conditions	**Apparatus:**	5 (paddle over disk – transdermal sandwich)
	Speed of Rotation:	50 rpm
	Medium:	0.25% Tween® 20 in Water
	Volume:	900 mL
	Temperature:	32 °C ± 0.5 °C
Firm's Proposed Specifications	Ethinyl Estradiol: [redacted] (b) (4) Norelgestromin:	
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
						[redacted] (b) (4)				
N/A	Nov. 2009	Norelgestromin / Ethinyl Estradiol Transdermal System 14cm² Lot R6A0014 DOM – May 2009	NGMN 4.86mg	12	Mean (%)	9	22	54	97	3.2.P.5.4 Batch Analysis
					Range (%)	[redacted] (b) (4)				
					%CV	3.4	4.8	2.6	0.8	
			EE 0.53mg	12	Mean (%)	11	27	60	97	
					Range (%)	[redacted] (b) (4)				
					%CV	2.9	3.5	2.7	0.8	
N/A	Nov. 2009	Ortho Evra® 20cm² Lot 8HM6015P1 Exp. Date July 2010	NGMN 6.00mg	12	Mean (%)	9	26	63	97	
					Range (%)	[redacted] (b) (4)				
					%CV	5.7	3.4	2.9	1.1	
			EE 0.75mg	12	Mean (%)	11	29	65	98	
					Range (%)	[redacted] (b) (4)				
					%CV	3.5	3.1	2.7	1.0	

NEETS 14cm² - Norelgestromin

Dosage: NEETS 14 cm² [NGMN 4.86 mg / EE 0.53 mg]
Lot: R6A0014
Test Method: STM-0676
Drug Release Medium: 0.25% Tween® 20 in Water
Volume: 900 mL
Temperature: 32 °C ± 0.5 °C

	Quantity Of Norelgestromin Released, % of Claim			
Sample Number	(b) (4)			
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean, % of claim	9	22	54	97
RSD, %	3.4	4.8	2.6	0.8
Range, % of claim	(b) (4)			

NEETS 14cm² – Ethinyl Estradiol

	Quantity Of Ethinyl Estradiol Released, % of Claim			
Sample Number	(b) (4)			
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean, % of claim	11	27	60	97
RSD, %	2.9	3.5	2.7	0.8
Range, % of claim	(b) (4)			

Ortho Evra® - Norelgestromin

Dosage: Ortho Evra® (6.00 mg NGMN / 0.75 mg EE)
Lot: 8HM6015P1
Test Method: STM-0676
Drug Release Medium: 0.25% Tween® 20 in Water
Volume: 900 mL
Temperature: 32 °C ± 0.5 °C

	Quantity Of Norelgestromin Released, % of Claim			
Sample Number	(b) (4)			
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean, % of claim	9	26	63	97
RSD, %	5.7	3.4	2.9	1.1
Range, % of claim	(b) (4)			

Ortho Evra® – Ethinyl Estradiol

	Quantity Of Ethinyl Estradiol Released, % of Claim			
Sample Number	(b) (4)			
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean, % of claim	11	29	65	98
RSD, %	3.5	3.1	2.7	1.0
Range, % of claim	(b) (4)			

Drug Release Conditions	**Apparatus:**	5 (paddle over disk – transdermal sandwich)
	Speed of Rotation:	50 rpm
	Medium:	USP Buffer, pH 4.5 with 0.25% Tween® 20
	Volume:	900 mL
	Temperature:	32 °C ± 0.5 °C
Firm's Proposed Specifications	N/A	
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
									(b) (4)	
N/A	Nov. 2009	Norelgestromin / Ethinyl Estradiol Transdermal System 14cm² Lot R6A0014 DOM – May 2009	NGMN 4.86mg	12	Mean (%)	6	18	46	90	3.2.P.5.4 Batch Analysis
					Range (%)				(b) (4)	
					%CV	7.5	3.6	4.2	1.6	
			EE 0.53mg	12	Mean (%)	8	22	52	94	
					Range (%)				(b) (4)	
					%CV	4.9	3.0	3.5	3.3	
N/A	Nov. 2009	Ortho Evra® 20cm² Lot 8HM6015P1 Exp. Date July 2010	NGMN 6.00mg	12	Mean (%)	5	16	44	87	
					Range (%)				(b) (4)	
					%CV	0.0	4.2	3.1	1.2	
			EE 0.75mg	12	Mean (%)	7	20	50	94	
					Range (%)				(b) (4)	
					%CV	6.5	2.9	2.7	1.2	

NEETS 14cm² - Norelgestromin

Dosage: NEETS 14 cm² [NGMN 4.86 mg / EE 0.53 mg]
Lot: R6A0014
Test Method: STM-0676
Drug Release Medium: USP Buffer, pH 4.5 with 0.25% Tween® 20
Volume: 900 mL
Temperature: 32 °C ± 0.5 °C

	Quantity Of Norelgestromin Released, % of Claim			
Sample Number	[redacted] (b) (4)			
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean, % of claim	6	18	46	90
RSD, %	7.5	3.6	4.2	1.6
Range, % of claim	[redacted] (b) (4)			

NEETS 14cm² – Ethinyl Estradiol

	Quantity Of Ethinyl Estradiol Released, % of Claim			
Sample Number	[redacted] (b) (4)			
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean, % of claim	8	22	52	94
RSD, %	4.9	3.0	3.5	3.3
Range, % of claim	[redacted] (b) (4)			

Ortho Evra® - Norelgestromin

Table 3: Ortho Evra® - Norelgestromin

Dosage: Ortho Evra® (6.00 mg NGMN / 0.75 mg EE)

Lot: 8HM6015P1

Test Method: STM-0676

Drug Release Medium: USP Buffer, pH 4.5 with 0.25% Tween® 20

Volume: 900 mL

Temperature: 32 °C ± 0.5 °C

	Quantity Of Norelgestromin Released, % of Claim			
Sample Number	(b) (4)			
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean, % of claim	5	16	44	87
RSD, %	0.0	4.2	3.1	1.2
Range, % of claim	(b) (4)			

Ortho Evra® – Ethinyl Estradiol

	Quantity Of Ethinyl Estradiol Released, % of Claim			
Sample Number	(b) (4)			
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean, % of claim	7	20	50	94
RSD, %	6.5	2.9	2.7	1.2
Range, % of claim	(b) (4)			

Drug Release Conditions	**Apparatus:**	5 (paddle over disk – transdermal sandwich)
	Speed of Rotation:	50 rpm
	Medium:	USP Buffer, pH 6.8 with 0.25% Tween® 20
	Volume:	900 mL
	Temperature:	32 °C ± 0.5 °C
Firm's Proposed Specifications	N/A	
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
									(b) (4)	
N/A	Nov. 2009	Norelgestromin / Ethinyl Estradiol Transdermal System 14cm² Lot R6A0014 DOM – May 2009	NGMN 4.86mg	12	Mean (%)	7	18	47	91	3.2.P.5.4 Batch Analysis
					Range (%)				(b) (4)	
					%CV	5.6	5.4	6.6	2.4	
			EE 0.53mg	12	Mean (%)	8	21	53	95	
					Range (%)				(b) (4)	
					%CV	0.0	4.3	5.5	2.2	
N/A	Nov. 2009	Ortho Evra® 20cm² Lot 8HM6015P1 Exp. Date July 2010	NGMN 6.00mg	12	Mean (%)	5	16	40	78	
					Range (%)				(b) (4)	
					%CV	5.8	5.0	6.1	4.0	
			EE 0.75mg	12	Mean (%)	7	19	46	89	
					Range (%)				(b) (4)	
					%CV	6.5	4.2	4.3	3.6	

NEETS 14cm² - Norelgestromin

Dosage: NEETS 14 cm² [NGMN 4.86 mg / EE 0.53 mg]
Lot: R6A0014
Test Method: STM-0676
Drug Release Medium: USP Buffer, pH 6.8 with 0.25% Tween® 20
Volume: 900 mL
Temperature: 32 °C ± 0.5 °C

	Quantity Of Norelgestromin Released, % of Claim			
Sample Number	(b) (4)			
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean, % of claim	7	18	47	91
RSD, %	5.6	5.4	6.6	2.4
Range, % of claim	(b) (4)			

NEETS 14cm² – Ethinyl Estradiol

	Quantity Of Ethinyl Estradiol Released, % of Claim			
Sample Number	(b) (4)			
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean, % of claim	8	21	53	95
RSD, %	0.0	4.3	5.5	2.2
Range, % of claim	(b) (4)			

Ortho Evra® - Norelgestromin

Dosage: Ortho Evra® (6.00 mg NGMN / 0.75 mg EE)
Lot: 8HM6015P1
Test Method: STM-0676
Drug Release Medium: USP Buffer, pH 6.8 with 0.25% Tween® 20
Volume: 900 mL
Temperature: 32 °C ± 0.5 °C

	Quantity Of Norelgestromin Released, % of Claim			
Sample Number	(b) (4)			
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean, % of claim	5	16	40	78
RSD, %	5.8	5.0	6.1	4.0
Range, % of claim	(b) (4)			

Ortho Evra® – Ethinyl Estradiol

	Quantity Of Ethinyl Estradiol Released, % of Claim			
Sample Number	(b) (4)			
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean, % of claim	7	19	46	89
RSD, %	6.5	4.2	4.3	3.6
Range, % of claim	(b) (4)			

II. DEFICIENCY COMMENTS:

1. The firm should generate dissolution profiles on 12 dosage units each of test and reference products generated in pH 1.2 dissolution medium.

2. Long Term Storage Stability data is not sufficient to cover the storage period of the study samples for the bioequivalence studies. The firm should provide Long Term Storage Stability data for at least 96 days for Norelgestromin and 60 days for Ethinyl Estradiol.

III. RECOMMENDATIONS:

The dissolution testing conducted by Mylan Technologies Inc. on its Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 hour and 0.02 mg/24 hour is incomplete due to above deficiency comment #1.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 200910

APPLICANT: Mylan Technologies Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 hour and 0.02 mg/24 hour

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The DBE will review the bioequivalence, adhesion and skin irritation and sensitization studies at a later date. The following deficiencies have been identified:

1. Please provide dissolution profiles on 12 dosage units each of test and reference products generated in pH 1.2 dissolution media.

2. The Long Term Stability (LTS) data in frozen plasma samples you provided is not sufficient to cover the entire storage period of actual samples of the bioequivalence study. Please provide LTS data for at least 96 days for Norelgestromin and 60 days for Ethinyl Estradiol to cover the entire length of the maximum storage duration of the bioequivalence (BE) study samples (i.e., from the time when the first blood sample was drawn until the time when the last plasma sample was analyzed).

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

IV. OUTCOME

ANDA: 200910

V. *Completed Assignment for 200910 ID: 11669*

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
11669	12/31/2009	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Dissolution Review	1
Grand Total	**1**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200910	ORIG-1	MYLAN TECHNOLOGIES	ETHINYL ESTRADIOL;NORELGESTROMIN

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

/s/

SVETLANA A CHERSTNIAKOVA
07/29/2010

MOHEB H MAKARY
07/29/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
07/30/2010

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA#: 200910 **FIRM NAME: Mylan Technologies Inc.**

DRUG NAME: Ethinyl Estradiol and Norelgestromin

DOSAGE FORM: Film, extended release, 0.02 mg / 24 hour and 0.15 mg / 24 hour

SUBJ: Request for examination of Bioequivalence studies.

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: N/A
N/A	**Waiver meets statutory requirements**
N/A	**Waiver does NOT meet statutory requirements**
	Reason: N/A

RECOMMENDATION: ☒ **ADEQUATE** ☐ **INADEQUATE**

Reviewed by:

_____ Date: _____
Wayne DeHaven
Reviewer

_____ Date: _____
Vijay Nerurkar
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐	3	3	1. A BE study with PK endpoints. 2. Adhesion study 3. Skin irritation and sensitization study See CTD section 5.3.1.2
Assay Methodology	☒	☐			
Procedure SOPs	☒	☐			
Methods Validation	☒	☐			
Study Results Ln/Lin	☒	☐			
Adverse Events	☒	☐			
IRB Approval	☒	☐			
Dissolution Data	☒	☐			See reviewers comments below
Pre-screening of Patients	☒	☐			See clinical reports for each study in module 5
Chromatograms	☒	☐			For ORTH-0942, representative chromatography is submitted in Module 5, Attachment 3A-3F
Consent Forms	☒	☐			
Composition	☒	☐			Module 2, 2.3.P, Quality Overall Summary, and 2.7 Clinical Summary, Table 6 Formulation Data
Summary of Study	☒	☐			All 3 studies have a synopsis of study in module 5
Individual Data & Graphs, Linear & Ln	☒	☐			
PK/PD Data Disk Submitted	☒	☐			.XPT files were submitted
Randomization Schedule	☒	☐			
Protocol Deviations	☒	☐			
Clinical Site	☒	☐			Cetero Research 625 Demers Avenue

					East Grand Forks, MN 56721
Analytical Site	☒	☐			Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Rd Morgantown, WV 26505
Study Investigators	☒	☐			Names and CVs submitted with the study reports
Medical Records	☒	☐			
Clinical Raw Data	☒	☐			
Test Article Inventory	☒	☐			
BIO Batch Size	☒	☐			2.7 Table 11 for PK study: 80,100 Production Batch size = 352,750
Assay of Active Content Drug	☒	☐			3.2.P and 2.7 Table 11 TEST POTENCY: Norelgestromin – 100.6% and Ethinyl Estradiol – 99.8% REFERENCE POTENCY: Norelgestromin – 97.7% and Ethinyl Estradiol – 98.1%
Content Uniformity	☒	☐			TEST: Norelgestromin – 99.0% (0.7%) and Ethinyl Estradiol – 98.2% (0.2%) REFERENCE: Norelgestromin – 97.7% (0.9%) and Ethinyl Estradiol – 98.1% (1.7%) See also 3.2.P
Date of Manufacture	☒	☐			Test product manufacture date 05/19/2009 for R6A0014
Exp. Date of RLD	☒	☐			TEST: “To be determined” REFERENCE: 10/2009
BioStudy Lot Numbers	☒	☐			TEST: R6A0014 REFERENCE: 7LM5212 Note: The BE study, Adhesion study and the irritation study were carried out using the above Lots of test and reference products. However, the dissolution studies were carried out with the same lot No. of test product (R6A0014) while using a different lot for reference (8HM6015P)

Statistics	☒	☐			Statistical Reports are provided for each study in module 5 of the eCTD
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			see comments below for all three submitted studies
Waiver requests for other strengths / supporting data	☐	☒	N/A	N/A	No waiver request

Additional Comments regarding the ANDA:

- This is an eCTD formatted submission. The Orange Book (Online Version 2009) lists the RLD as Ortho Evra® (NDA No 021180) manufactured by Ortho Mcneil Janssen. Ortho Evra® has an approval date of November 20, 2001.[1] Ortho Evra® is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.[2]

- There is a draft guidance recommendation for ethinyl estradiol and norelgestromin film, extended release / transdermal, on the FDA external website for individual product guidance page (see APPENDIX I).[3] Briefly, the DBE recommends the following studies:
  1. A **BE study** with PK endpoints
  2. An **adhesion study**
  3. A **skin irritation and sensitization study**

- The firm conducted and submitted the following:
  1. A **BE study** with PK endpoints
     - This was an open-label, single dose, randomized, two-period, two-treatment crossover study investigating the BE of Norelgestromin/Ethinyl Estradiol transdermal patches manufactured by Mylan Technologies Inc. to Ortho Evra® manufactured by Ortho Mcneil Janssen following a single application (Study No. ORTH-0942, CTD section 5.3.1.2). In addition to the PK data, Mylan also submitted adhesion and irritation data collected during the study, which are useful supporting data for the separate adhesion and irritation studies listed below.

     - The Reviewer notes that the firm gives long-term storage stability (LTSS) of only 11 days for norelgestromin. The firm will need to provide evidence of long term storage stability which at least covers the extent of the storage in the BE study submitted.

     - The 90% Confidence Intervals for the PK parameters in the BE study **passed** the 80-125% BE criterion.

  2. An **adhesion study**
     - An Adhesion evaluation study comparing Norelgestromin and Ethinyl Estradiol Transdermal System (NEETS) Patch (0.15 mg/0.02 mg per day; Mylan) to Ortho Evra® Patch (0.15 mg/0.02 mg per day; Ortho McNeil Janssen) in normal healthy

1 http://www.accessdata fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021180&TABLE1=OB_Rx
2 http://dailymed.nlm nih.gov/dailymed/search.cfm?startswith=ortho+evra
3 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM162407.pdf

female volunteers was submitted (Study No. ORTH-09198, CTD section 5.3.1.2).

- The adhesion study was designed as an open-labeled, randomized, single-dose, two treatment, two period study. The rating scale for the adhesion scale was as follows:

95: >90% to <100%
85: >80% to 90%
75: >70% to 80%
65: >60% to 70%
55: >50% to 60%
45: >40% to 50%
35: >30% to 40%
25: >20% to 30%
15: >10% to 20%
5: =0 to 10% Fall-off.

This scoring 10 point scale paradigm differs only slightly from that recommended in the draft guidance. Based on a one sided hypothesis test, it was determined that the adhesion score of Mylan's test product was **non-inferior** to the Ortho Evra® reference product. As supporting data, Mylan also submitted the skin irritation data for study No. ORTH-09198.

3. A **skin irritation and sensitization study**
   - A comparative evaluation of the cumulative irritation and contact sensitization potential of Norelgestromin and Ethinyl Estradiol Transdermal System (NEETS) (0.15 mg/0.02 mg/day: Mylan) to Ortho Evra® (0.15 mg/0.02 mg/day: Ortho) in healthy female volunteers was conducted and the results submitted in Study No. ORTH-0943, CTD 5.3.1.2. Per the draft guidance, greater than 200 subjects were included in the study population.

   - The study was designed as an open label, multiple dose, two treatment, randomized application site, three phase, one period study in order to determine the human dermal safety of the test product compared to the reference product, Ortho Evra®.

   - The reviewer notes that the firm used ½ of the test and reference patches, worn once weekly for 3 applications (21 days) at the same skin application site. This was followed by a 14-day rest phase and subsequent 48-hour challenge phase, followed by a 3-day observation and irritation evaluation. Acute dermal irritation was assessed 30 minutes following each patch removal. The firm also did submit the adhesion data recommended per guidance when using ½ patches. The sizes of the cut patches were not equal, i.e. the test patch is 14 cm2, while the reference patch is 20 cm2.

   - For the assessment of irritation, one 8-point scale for Dermal Response and one 6-point scale for Other Effects were used, similar to the DBE's draft guidance recommendations. In the Dermal Response scale, a score of '0' indicated either no irritation or no effect observed, while a score of '7' indicated a strong reaction spreading beyond the application site. In the Other Effects scale, a score of 'A' indicated a slightly glazed appearance, while a score of 'H' indicated small petechial erosions and/or scabs. The adhesion data was included for informational purposes and

was not statistically analyzed.

- Based on the firm's statistical analysis report, Mylan concluded that the irritation and sensitization potential of Mylan's test product is non-inferior to the Ortho Evra® reference product.

- There is an FDA recommended dissolution testing method for Ethinyl Estradiol and Norelgestromin Film, transdermal patches. The FDA recommends:

Dosage Form: Film, Transdermal

Medium: 0.1% Hydroxypropyl-beta-cyclodextrin at 32° C

Apparatus: Modified USP Type V (Paddle-over-disk)

Speed/RPMs: 50

Modify Date:

Sampling Times: 0.25, 0.5, 1, 2, 4, 8, 12, 16, 20 and 24 hours

Volume: 900

Notes: Added by NT on 7/16/09 Source: N 21180,AR 2009)

Specification: EE (100%=0.75 mg/unit): (b) (4) (b) (4)

- The firm submitted dissolution testing data using the following methods and specifications:

Drug Release Conditions	**Apparatus:**	5 (paddle over disk – transdermal sandwich)
	Speed of Rotation:	50 rpm
	Medium:	**0.25% Tween® 20 in Water** **0.1% Hydroxypropyl β-Cyclodextrin in Water** **USP Buffer, pH 4.5 with 0.25% Tween® 20** **USP Buffer, pH 6.8 with 0.25% Tween® 20**
	Volume:	900 mL
	Temperature:	32 °C ± 0.5 °C
Firm's Proposed Specifications	Ethinyl Estradiol: (b) (4)	(b) (4)
	Norelgestromin: (b) (4)	(b) (4)

APPENDIX I:

Draft Guidance on Ethinyl Estradiol; Norelgestromin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredients: Ethinyl Estradiol; Norelgestromin

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: 0.02 mg/24 hr; 0.15 mg/24 hr
   Subjects: Healthy nonpregnant females, general population, who are candidates for hormonal contraception.
   Additional comments: Specific recommendations are provided below.

---

2. Type of study: Skin Irritation and Sensitization Study
   Design: Randomized, evaluator-blinded, in vivo within-subject repeat test
   Strength: 0.02 mg/24 hr; 0.15 mg/24 hr (Dose: One-half of a 0.02 mg/24 hr; 0.15 mg/24 hr patch)
   Subjects: Healthy nonpregnant females, general population, who are candidates for hormonal contraception.
   Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Ethinyl Estradiol and Norelgestromin in plasma (PK study only)

Bioequivalence based on (90% CI): Ethinyl Estradiol and Norelgestromin (PK study only)

Waiver request of in vivo testing: Not Applicable.

Dissolution test method and sampling times: Please note that a **Dissolution Method Database** is available to the public at the Office of Generic Drugs (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 modified release products, dissolution profiles on 12 dosage units each of test and reference products generated in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Multipoint dissolution profiles should be

obtained using a discriminating agitation speed. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 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 PK bioequivalence and adhesion study:

1. Females should not be pregnant. Due to an increased myocardial risk primarily in smokers, non-smoking subjects who have previously used hormonal contraceptives without complications should be enrolled. Also, females weighing less than 90 kg and not exceeding 35 years of age should be considered since older women may be at a higher risk of drug-related adverse events (AEs). Blood pressure (BP) within 140/80 mm Hg limit should be an inclusion criterion.

2. Criteria should also be developed to discontinue subjects that reach a pre-defined maximum BP throughout the study.

3. The patch should be applied to the abdomen in all subjects.

4. Adhesion performance of the intact test product and RLD patches must be formally evaluated and compared in the PK bioequivalence study or in a separate parallel or crossover adhesion study of single 7-day patch applications of the active test product versus the RLD. No patch reinforcement is allowed when the study is being used to establish adequate adhesion performance to support product approval. Adhesion scoring is to be performed at least daily. 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.

5. 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)

6. The Per-Protocol (PP) Population evaluation of the adhesion parameter should be defined per patch instead of per subject 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 7-day application.

7. The cumulative adhesion score and the time from application until patch detachment (i.e., duration of patch wear) should be calculated for the test product and RLD, and a

statistical analysis of the comparative results should be performed. In addition, the following adhesion data should be provided for the test product and RLD:

a. frequency table showing the number of patches with each adhesion score at each evaluation time point
b. number of patches that are completely detached at each evaluation time

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 cumulative adhesion score for the test product minus 1.25 times the mean cumulative adhesion score for the RLD must be less than or equal to 0. For the adhesion evaluation, the Office of Generic Drugs (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 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 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 cumulative adhesion scores and also show no meaningful difference with regard to degree of detachment.

8. For the Adhesion Analysis, please provide a separate line listing for each individual test article per subject, per each visit (if data exist), using the following headings, if applicable:

a. Subject identifier
b. Treatment: test article (i.e., test product, RLD)
c. Period (i.e., patch was applied during Period 1 or Period 2)
d. Application Number: number of particular test article application (i.e., 1=first, 2=second)
e. Location of Dose Administration: individual test article application site
f. Number of days since baseline visit
g. Application date and time
h. Date and time of removal or complete detachment
i. Duration of Treatment: time (hours) from individual test article application to removal or complete detachment
j. Included in PP population for adhesion analysis (yes/no)
k. Reason for exclusion from PP population for adhesion analysis
l. Scoring date
m. Adhesion scores
n. Identity of the evaluator
o. Was the patch reinforced with tape or overlay (yes/no)

p. If patch was reinforced, time from patch application to reinforcement

Additional comments regarding the skin irritation and sensitization study:

1. The OGD recommends evaluating skin irritation and sensitization in a single study. To support approval, the test product must be no more irritating than the RLD and be no more sensitizing than 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. Safety concerns preclude the use of two whole, active, 0.02 mg/24 hr, 0.15 mg/24 hr ethinyl estradiol/norelgestromin patches on the same healthy subject during the 21-day skin irritation and sensitization study. The optimum design of this study will depend on the design of the test product patch. Since the RLD has a matrix design that can be safely cut in half, one half of the patch can be used for these studies. If the test product patch also has a design that can be cut to a smaller size, it should also be cut in half and one half of the test product patch applied simultaneously with one half of a RLD patch (to separate skin sites). It would not be acceptable to manufacture a separate batch of product in order to use a smaller patch in this study.

3. Cutting patches will change the shape and size of the patch and may alter the adhesive performance. Therefore, if partial patches are used for the skin irritation and sensitization study, the OGD recommends collecting adhesion data in the PK bioequivalence study to demonstrate that the test product adheres at least as well as the RLD for the 7 day duration of wear. To do so, no reinforcement may be applied to patches in the PK study. Alternatively, a separate single-application parallel or crossover design adhesion study may be conducted for the 7 day duration of wear, comparing the un-altered to be marketed test product and RLD.

4. If the test product patch has a reservoir design that cannot be cut in half, then, in order to avoid an unacceptable risk of serious adverse events, the study should be conducted using a parallel design with healthy subjects randomized to receive either the test product or RLD. The study should be powered to show that the test is no more irritating, no more sensitizing, and adheres at least as well as the RLD.

5. 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 when using one half patches, all test articles (i.e., one half of the 0.02 mg/24 hr; 0.15 mg/24 hr test product[1], one half of the 0.02 mg/24 hr; 0.15 mg/24

[1] The test product evaluated should be the actual patches to be marketed. If the test product has a design that can be cut to a smaller size, the OGD recommends cutting them in half.

hr RLD, optional vehicle patch[2] and optional negative control[3]) are to be applied simultaneously to each subject to clean, dry, intact healthy skin at different sites on the buttock, abdomen, upper outer arm or torso, with sequential patch applications to the same skin sites weekly (i.e., every 7 days; the intended duration of wear) for a total of 21 consecutive days. Thus, it is recommended to apply the patches on Days 1, 8, and 15 to the same sites and to have each of them remain in place for 7 days (a total of 21 days altogether). The Day 15 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 when using one half patches consists of a single 48-hour application of one half of the 0.02 mg/24 hr; 0.15 mg/24 hr test product, one half of the 0.02 mg/24 hr; 0.15 mg/24 hr RLD, 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.

Adhesion should be evaluated prior to patch removal throughout the entire study period to ensure adequate skin contact for maximal induction of irritation and sensitization.

6. When evaluating the one half patches, an adequate number of subjects should be enrolled to ensure that at least 200 evaluable subjects are included in the PP population.

7. 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.

8. 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.

9. 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.

---

[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 ethinyl estradiol and norelgestromin.

[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.

10. 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 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.

11. Inclusion Criteria (the sponsor may add additional criteria):
    a. Healthy female subjects 18-35 years of age (inclusive) who are candidates for hormonal contraception.
    b. Subjects who have previously used hormonal contraceptives without complications are the optimal candidates for this study.
    c. Subject willing to stop using any current hormonal contraceptive method.
    d. Subject had a tubal ligation OR throughout the study and for 7 days after completion of the study or premature discontinuation, agrees to abstain from sexual intercourse or use a reliable non-hormonal method of contraception (e.g., diaphragm with spermicide or condom with spermicide).
    e. Negative pregnancy test on first dosing day, prior to application of patch.

12. Exclusion Criteria (the sponsor may add additional criteria):
    a. Subject is pregnant or lactating.
    b. Subject is a current smoker.
    c. Subject weighs 90 kg or more.
    d. Systolic blood pressure >140 mmHg at screening measured in supine position after 5 minutes rest; diastolic blood pressure >80 mmHg at screening measured in supine position after 5 minutes rest.
    e. Subject was previous user of RLD.
    f. Subject who is currently using any long-acting hormonal method of contraception (e.g., contraceptive rod implant such as Implanon™, hormonal IUD such as Mirena®, hormone injections such as Depo-Provera or depo-subQ Provera 104) or has used them within past 3 months.
    g. Subject who currently has any of the following conditions:
        1. Thrombophlebitis, thromboembolic disorders
        2. A past history of deep vein thrombophlebitis or thromboembolic disorders
        3. Cerebrovascular or coronary artery disease (current or past history)
        4. Valvular heart disease with complications
        5. Severe hypertension
        6. Diabetes with vascular involvement
        7. Headaches with focal neurological symptoms
        8. Major surgery with prolonged immobilization
        9. Known or suspected carcinoma of the breast or personal history of breast cancer
        10. Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
        11. Undiagnosed abnormal genital bleeding

12. Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use
13. Acute or chronic hepatocellular disease with abnormal liver function
14. Hepatic adenomas or carcinomas
15. 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 investigative site.
j. 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).
k. Within 72 hours prior to dosing, use of antihistamines or use of topical drugs at patch site.
l. 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.
m. Presence of open sores at the application site.

13. Criteria should also be developed to discontinue subjects that reach a pre-defined maximum BP throughout the study.

14. Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
    a. 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, adrenocortical steroids such as prednisone, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG), monoclonal antibodies, radiation therapy).
    b. Hormonal contraception other than test product and RLD (e.g., oral contraceptive pills, contraceptive vaginal ring such as NuvaRing®, contraceptive rod implant such as Implanon™, hormonal IUD such as Mirena®, hormone injections such as Depo-Provera or depo-subQ Provera 104).

15. Subjects should be informed that wearing patches cut in half will not protect them from pregnancy and they are especially at risk for pregnancy during the first week of the Induction Phase, after Day 7 of the rest period and during the entire Challenge Phase.

16. Subjects should receive the first patch within seven days after the first day of a menstrual period. Subjects currently taking hormonal contraceptives should switch to study drug on the day they are scheduled to start a new contraceptive cycle. This will minimize disruption of the menstrual cycle.

17. Subjects should be advised to expect menstrual bleeding after each patch is removed.

18. Following the Challenge Phase, if a subject wishes to use the contraceptive patch or resume oral contraceptives, she may apply a new (RLD) patch to a different site immediately or start a new pill cycle, but she must also continue using non-hormonal contraception for 7 days after starting the new hormonal contraceptive cycle. Subjects who do not wish to use a hormonal contraceptive may experience vaginal bleeding or spotting after removal of the challenge patch.

19. During the induction phase, subjects should return for weekly visits on Days 8 and 15 for adhesion scoring, patch removal, irritation scoring, and patch replacement and on Day 22 for adhesion scoring, patch removal and irritation scoring. 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 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.

20. 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.

21. 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)

22. During both the Induction Phase and Challenge Phase, the skin reactions are to be evaluated and scored according to the following two scales[4]:

[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.

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).

23. 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 the first patch site should be carried forward for all remaining observations in the irritation analysis.

24. 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 completed 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. Whereas this study using partial patches can not be used for a definitive assessment of adhesion performance of the active product, criteria may be established for using tape or an overlay to reinforce any patches that are lifting during the irritation and

sensitization study. 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.

Safety Data and Analyses

25. 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.

26. 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

27. 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 8; Test Product											
Day 8; RLD											
Day 8; Vehicle Patch (optional)											
Day 8; Negative Control (optional)											
Day 15; Test Product											
Day 15; RLD											
etc.											

28. 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).

29. 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.

30. 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.

31. 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

32. Please provide a frequency table showing the number of applications of each test article during the Challenge Phase with a specific combined "Dermal Response" numerical score and "Other Effect" letter score by each evaluation time point.

33. 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.

34. 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 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.

35. For each test article, individually evaluate each Per Protocol 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.

36. The sponsor should provide descriptive statistics comparing the proportion of subjects sensitized or potentially sensitized to each test article.

Adhesion Data Table

37. To ensure adequate skin contact for maximal induction of irritation and sensitization, please provide a frequency table showing the adhesion score for each vehicle patch per study visit. For patches that fall off, provide information about the duration of patch wear before the patch falls off.

Data Submission

38. Study data should be submitted to the OGD in electronic format.

    a. A list of file names included in the CD or diskette(s), 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.

39. 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. Per Protocol (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. Test article moved (yes/no)
q. Number of times test article moved
r. Test article discontinued (yes/no)
s. Reason for test article discontinuation
t. 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	ppsen	ppsen_rs	mv	mv_n	dis	dis_rs	AErpt
101	1	01	54	YEARS	M	1	A	RUA	21	2	Yes		Yes		Yes	1	No		No
101	1	01	54	YEARS	M	1	B	LUA	21	2	Yes		Yes		Yes	1	No		No
101	2	01	45	YEARS	M	2	A	RUA	21	2	Yes		No	B	No		No		No
101	2	01	45	YEARS	M	2	B	LUA	21	2	Yes		No	B	No		No		No

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 Draft dated 7/25/07.

STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study
SITEID: Study Site Identifier
AGE: Age
AGEU: Age units (years)
SEX: Sex, e.g., M, F, U for Male, Female, Unknown
RACE: Race, e.g. 1, 2, 3, 4, 5 (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., RUA=right upper arm, LUA=left upper arm
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: Per Protocol (PP) population for irritation analysis, e.g., Y, N (Yes or 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, N (Yes or 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.
mv: Test article moved, e.g., Y, N (Yes or 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, N (Yes or 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, N (Yes or No)

40. 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. Induction "Dermal Response" numeric score for each site
    o. Induction "Other Effects" letter score for each site
    p. Challenge "Dermal Response" numeric score for each site
    q. Challenge "Other Effects" letter score for each site
    r. Potentially sensitized (yes/no)
    s. Identity of the evaluator
    t. Individual test article moved (yes/no)
    u. Number of times individual test article moved
    v. Date of each move of individual test article
    w. Individual test article discontinued (yes/no)
    x. Reason for discontinuation
    y. Date individual test article discontinued
    z. 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	ind_n1	ind_c1
1	A	1	RUA	1	2004-07-01	1	Monday							

ind_n2	ind_c2	ind_n3	ind_c3	ch_n1	ch_c1	potsens	EVAL	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 Draft dated 7/25/07.

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., RUA=right upper arm, LUA=left upper arm
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
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
mv:	Individual test article moved, e.g., Y, N (Yes or 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, N (Yes or 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, N (Yes or No)

41. 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.

42. Sponsors may submit the protocol for review and comment prior to conducting the study.

Enter Review Productivity and Generate Report:

Reviewer:	DeHaven, Wayne	**Date Completed:**	
Verifier:		**Date Verified:**	
Division:	Division of Bioequivalence		
Description:	Ethinyl Estradiol and Norelgestromin Film, extended release, 0.02 mg / 24 hour and 0.15 mg / 24 hour		

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
10531	12/31/2009	Paragraph 4	Paragraph 4 Checklist	1	1
				Bean Total:	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200910	ORIG-1	MYLAN TECHNOLOGIES	ETHINYL ESTRADIOL;NORELGESTROMIN

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

/s/

WAYNE I DEHAVEN
03/09/2010

SHRINIWAS G NERURKAR
03/09/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
03/10/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200910

OTHER REVIEWS

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

DATE: May 1, 2012

TO: John Peters, M.D.
Director, Division of Clinical Review (DCR)
Office of Generic Drugs (OGD)

FROM: Gopa Biswas, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., RPh
Chief, Bioequivalence Investigations Branch,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D., DABT
Director (Acting)
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering ANDA 200-910, Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24h and 0.02 mg/24h sponsored by Mylan Technologies Inc.

At the request of OGD, DBGC conducted an inspection of the clinical portion of the following bioequivalence study:

Study Number: ORTHO-09198
Study Title: "Adhesion Evaluation Study of Norelgestromin/ Ethinyl Estradiol Transdermal System (NEETS) Patch(0.15 mg/0.02 mg/day; Mylan) and Active Wear of Ortho Evra® Patch (0.15 mg/0.02 mg/day; Ortho-McNeil-Janssen) in Normal Healthy Female Volunteers"

Inspection of the clinical portion of this study was conducted at Cetero Research, Miami from 7/18-21/2011. Form FDA-483 containing an inspectional observation was issued at the end of the inspection (**Attachment 1**).

A written response to the inspectional observation dated 8/1/2011 was received from Cetero Research, Miami by DBGC (**Attachment 2**). This review provides evaluation of the inspectional observation and response as follows:

1) **The investigation was not conducted in accordance with the investigational plan. Specifically, per protocol, the clinic staff involved in adhesion and irritation scoring were to be blinded to the randomization scheme at the time of evaluation. Per further clarification provided by the sponsor, the irritation evaluator also was to be blinded during the evaluations and scoring. The documentation on file disclosed that in several instances during Period 2, the irritation evaluator also conducted the last adhesion assessment at the 168 hour interval post patch application. Irritation evaluations were to be conducted at 30 and 60 minutes time points post patch removal after completion of the 168 hour adhesion period. The physical appearance of both study test articles is clearly distinctive. Therefore, blinding of the evaluator could have been compromised (Period 2, 32 from a total of 40 participating subjects).**

In the written response, Cetero acknowledged the deficiency listed on Form FDA-483. Cetero stated they will use different evaluators for assessing adhesion and irritation for similar future studies.

Although the firm did not adhere to the study protocol, the DBGC reviewer is of the opinion that maintaining blinding during the patch adhesion assessment was not possible. Lack of blinding during irritation evaluation is not likely to have significant impact on the study outcomes, because the results of irritation scoring for Test and Reference drug patches did not differ significantly. However, DBGC reviewer recommends that OGD reviewer should further evaluate the impact of lack of blinding on the study outcome.

Conclusions:

Following evaluation of the inspectional observation for the clinical portion of study ORTHO-09198, the DBGC reviewer recommends that the observation is not likely to have significant impact on study outcomes but recommends that the OGD reviewer should also assess the impact of this observation. The study data can be accepted for Agency review.

Gopa Biswas, Ph.D.
Bioequivalence Branch, DBGC, OSI

Final Classification:

VAI- Cetero Research, Miami, FL
FEI 3008432144

cc:
OSI/Ball/Moreno
OSI/DBGC/Taylor/Dejernett
OSI/DBGC/BB/Haidar/Skelly/Biswas
OPS/OGD/Peters/Patel
SE-FO/FLA-DO/FIB/Torres/
Draft: GB 4/24/2012
Edit: MFS 5/1/2012, SHH 5/4/2012
DSI: 6105; O:\BE\eircover\200910myl.nor.eth.doc
FACTS: 1200604

EMAIL:
CDER DSI PM TRACK

Following this page, 5 Pages Withheld in Full as (b)(4)

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

/s/

GOPA BISWAS
05/06/2012

SAM H HAIDAR
05/11/2012

WILLIAM H TAYLOR
05/18/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200910

PROPRIETARY NAME REVIEWS

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name, Label, Labeling and Packaging Review--ANDA

Date:	April 16, 2013
Reviewer:	Alison Park, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader:	Zachary Oleszczuk, Pharm.D., Team Leader Division of Medication Error Prevention and Analysis
Deputy Director:	Kellie Taylor, Pharm.D., MPH, Deputy Director Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh, Division Director Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Xulane (Norelgestromin and Ethinyl Estradiol Transdermal System) 4.86 mg/0.53 mg per patch (0.15/0.02 mg per 24 hours)
Application Type/Number:	ANDA 200910
Applicant:	Mylan Technologies, Inc.
OSE RCM #:	2012-2503 and 2012-2504

*** This document contains proprietary and confidential information that should not be released to the public.***

CONTENTS

1 INTRODUCTION

This review evaluates the proposed proprietary name, Xulane, from a safety and promotional perspective and the proposed label and labeling for areas of vulnerability that can lead to medication errors. The sources and methods used to evaluate the proposed name and labels are outlined in the reference section and Appendix A, respectively.

1.1 REGULATORY HISTORY

The proposed proprietary name, Xulane, was previously found conditionally acceptable in OSE Review # 2010-1752, dated December 2, 2011, (b) (4) Mylan holds a pending trademark application for the proposed proprietary name, Xulane. The Applicant, Mylan Technologies, submitted a request for proprietary name review for Xulane on October 18, 2012 for ANDA 200910.

The Reference Listed Drug for ANDA 200910 is Ortho Evra (Norelgestromin and Ethinyl Estradiol Transdermal System) 6 mg/0.75 mg per patch (0.15 mg/0.02 mg/24 hours), NDA 021180, Jannsen Pharmaceuticals, approved on November 20, 2001. This is the second proprietary name submitted for this ANDA. The first name, (b) (4) was found unacceptable in OSE Review #2011-2416, dated June 21, 2012 due to orthographic similarity and overlapping product characteristics to (b) (4)

1.2 PRODUCT INFORMATION

The following product information is provided in the October 18, 2012 proprietary name submission.

- Active Ingredient: Norelgestromin and Ethinyl Estradiol
- Indication of Use: Prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception
- Route of Administration: Transdermal
- Dosage Form: Patch
- Strength:4.86 mg/0.53 mg per patch (0.15 mg/0.02 mg/24 hours)
- Dose and Frequency: Apply 1 patch on the upper outer arm, abdomen, buttock or back every week for 3 weeks. Week 4 is patch-free.
- How Supplied: Peach colored patch contains 4.86 mg norelgestromin and 0.53 mg ethinyl estradiol. Each patch printed with "xulane (norelgestrom and ethinyl estradiol)" in brown ink. Each patch packaged in a protective pouch. Three patches contained in one carton.
- Storage: Store patches at 20-25 °C (68-77 °F) in their protective pouches.

- Container and Closure System: A thin, matrix-type transdermal contraceptive patch consisting of three layers. The backing layer is composed of a peach flexible film consisting of a pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutene adhesive, crospovidone, mineral oil, non-woven polyester fabric, oleyl alcohol, and dipropylene glycol as inactive components. The active components in this layer are the hormones, norelgestromin and ethinyl estradiol. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyester film with a fluoropolymer coating on the side that is in contact with the middle adhesive layer. Patches are packaged with additional pieces of protective film above and below the system within each pouch. These pieces of protective film are removed and discarded at the time of use. Xulane is available in folding cartons of 1 cycle each; each cycle contains 3 patches.

2 RESULTS

The following sections provide the information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT OF PROPOSED PROPRIETARY NAME

The Office of Prescription Drug Promotion (OPDP) determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Reproductive and Urologic Products (DRUP) and Office of Generic Drugs (OGD) concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT OF PROPOSED PROPRIETARY NAME

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) SEARCH

The February 28, 2013 search of the United States Adopted Name (USAN) stems did not identify that a USAN stem is present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

The Applicant indicated in their submission that the proposed name, Xulane, has no derivation or inherent meaning. The intended pronunciation provided by the Applicant is "zhoo' lane." This proprietary name is comprised of a single word that does not contain any components (i.e., a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 Medication Error Data Selection of Cases

DMEPA searched FAERS database for medication errors involving the reference listed drug, Ortho Evra, which would be relevant for this review.

The March 18, 2013 search of the FDA Adverse Event Reporting System (FAERS) database used the following search terms: Tradename "ORTHO EVRA" as well as MedDra Terms "Medication Errors" (HLGT), "Product Label Issues" (HLT), "Product Name Confusion" (PT), and "Product Quality Issue" (PT). The date was limited to April 9, 2012 which was the date of the last search conducted for OSE Review #2011-2416, dated June 21, 2012, for the previous proprietary name submission, (b) (4)

Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

After individual review, eleven reports were excluded from further analysis for the following reasons:

- Product Quality issue not due to labels and labeling (e.g., Patch fell off in shower or due to sweating, leaves residue on skin). Note that some of these reports indicate a secondary medication error, such as Dose Omission, Wrong Dose/Under dose, Wrong Technique errors, as a result of the product quality issue (e.g., Patient used medical tape or bandage to keep patch on, patch fell off and patient did not apply new patch)
- Foreign Cases not due to labels and labeling (e.g., dose omission errors, inappropriate schedule of administration errors)

Following exclusions, the search yielded three relevant cases. The first case (Case #8632096 v.1) described an inappropriate schedule of administration in which a patient did not apply the first patch on the first day of her menstrual cycle or on a Sunday after discontinuing medroxyprogesterone intramuscular injection. The patient experienced "sharp pain deep in right buttock." The current insert labeling for Ortho Evra states three different options of how to start the patch (i.e., First Day Start, Sunday Start, or When Switching From the Pill or Vaginal Contraceptive Ring to the Patch) under **Dosage and Administration**. The second case (Case #8519629 v.1) described a monitoring error in which a 50 year old smoker with a history of oophorectomy was placed on Ortho Evra for birth control. Reported outcomes include unintentional weight gain, swollen legs, "bad headache", and lack of a period. The current labeling for Ortho Evra includes a black boxed **Warning** that "hormonal contraceptives, including Ortho Evra, should not be used by women who are over 35 years of age and smoke." The last case (Case #9160142 v.1) described a wrong duration error in which a patient hospitalized for one night due to surgery for a "bone issue" had the same patch on for 2 weeks. The patient experienced a light period. The current labeling for Ortho Evra under **Dosage and Administration**/*When to Change the Ortho Evra Patch* states "The patch works for seven days (one week). The woman applies a new patch on the same day each week (her Patch Change Day) for 3 weeks in a row. She must make sure she has removed her old patch prior to applying the new patch."

2.2.4 FDA Name Simulation Studies

Eighty-nine practitioners participated in DMEPA's prescription studies. The interpretations did not overlap with any currently marketed products. However, three

responses, "Xolare" (n=1) and "Xulaire" (n=2), in the written study are spelled similar and sound similar to the currently marketed product, Xolair (Omalizumab) Powder for Injection. Additionally, one response from the verbal study, "Zolane", sounds similar to the currently marketed product, Zolene HC (Chloroxylenol/Hydrocortisone/Promoxine HCl) Otic Solution. These names have been included in our analysis of the proposed proprietary name. Forty (74%) out of the 54 practitioners in the written study interpreted the name correctly as Xulane. The most common misinterpretation included the letter 'i' or letter string '-ir-' instead of 'u' in the 2nd position (n=5) and the letter string '-ir-' instead of the letter 'n' in the 5th position (n=2). In the verbal study, none of the 35 practitioners interpreted the name correctly as Xulane. The most common misinterpretation included the letter 'Z' instead of 'X' as the beginning letter of the name (n=35) with the majority interpreting the remaining letters correctly (i.e. "Zulane", n=27). All of these variations were considered in our evaluation of the proposed proprietary name. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.5 Comments from Other Review Disciplines

In response to the OSE November 2, 2012 e-mail, the Division of Reproductive and Urologic Products (DRUP) and Office of Generic Drugs (OGD) did not forward any comments or concerns relating to the proposed name at the initial phase of the name review.

2.2.6 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Xulane. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Xulane, identified by the primary reviewer, the Expert Panel Discussion (EPD), other review disciplines. Table 1 also includes the names identified from the FDA Prescription Simulation not previously identified by DMEPA but require further evaluation.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, Independent Name Evaluation)

Look Similar					
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Calan	FDA	Colace	FDA	Dolene	FDA
Forane	FDA	Kadian	FDA	Kariva	FDA
Kerlone	FDA	Kutrase	FDA	Kuvan	FDA
L-Valine	FDA	Matulane	FDA	Melanex	FDA
Navane	FDA	Nubain	FDA	Nulev	FDA
Oxylone	FDA	Perlane	FDA	Rolene	FDA
Tetanus	FDA	Talwin	FDA	Tilade	FDA

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, Independent Name Evaluation)					
Look Similar					
Tulax	FDA	Ultane	FDA	Uni-Lan	FDA
Valine	FDA	Valium	FDA	Vantin	FDA
Veltane	FDA	Vidaza	FDA	Voluven	FDA
Xailin***	FDA	Xalatan	FDA	Xalcom***	FDA
Xalkori	FDA	Xedec	FDA	Xeloda	FDA
Xelox	FDA	Xenical	FDA	Xerclear***	FDA
Xerese	FDA	Xibrom	FDA	Xinlay	FDA
Xolegel	FDA	Xolox	FDA	Xopenex	FDA
(b) (4)	FDA	Xylene	FDA	Zitamin	FDA
Zolene HC	FDA	(b) (4)	FDA	Zurase	FDA
Zydone	FDA				
Sound Similar					
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Suprane	FDA				
Look and Sound Similar					
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Xolair	FDA	Xulane***	FDA	Xylose	FDA
Normal Saline	FDA				

Our analysis of the 57 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined the 57 names will not pose a risk for confusion as described in Appendices D and E.

2.2.7 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated these findings to the Office of Generic Drugs via e-mail on March 29, 2013. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Office of Generic Drugs on March 29, 2013, they stated no additional concerns with the proposed proprietary name, Xulane.

2.3 SAFETY ASSESSMENT OF PROPOSED LABELS, LABELING AND PACKAGING

DMEPA identified the following deficiencies with the proposed labels and labeling.

- The proprietary name on both the carton labeling and pouch label is in all lower case letters.
- The carton labeling and pouch label do not state the total amount of drug that is delivered per unit of time (i.e., per hour, day, or per week).
- The carton labeling and pouch label do not state to never cut, damage, or alter the patch in any way.
- The expiration date is not present on the pouch label.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective.

DMEPA identified deficiencies with the proposed labels and labeling that require revision prior to approval. Our recommendations are provided in section 3.1 below.

If you have further questions or need clarifications, please contact Shawnetta Jackson, OSE project manager, at 301-796-4952.

3.1 DMEPA PROPRIETARY NAME LETTER COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Xulane, and have concluded that this name is acceptable. This proprietary name will be re-evaluated 90 days prior to the approval of the application. The conclusions upon re-review are subject to change.

If any of the proposed product characteristics as stated in your October 18, 2012 submission are altered, the name must be resubmitted for review.

3.2 CONTAINER LABEL AND CARTON LABELING COMMENTS TO THE APPLICANT

1. Pouch Label and Carton Labeling
    a. Revise the presentation of the proprietary name on all labels and labeling to appear in title case lettering (i.e., Xulane).
    b. Revise the principle display panel of all labels and labeling to include the total amount of drug delivered per unit of time (i.e., hour, day, or week) to appear directly under the established name.
    c. Add directions to never cut, damage, or alter the patch on all labels and labeling.
    d. Add an expiration date and lot number to the pouch label.

4 REFERENCES

1. ***Cotter, S., OSE Review #2010-1752 and 2010-1753, Proprietary Name, Label, Labeling and Packaging Review for Xulane, December 2, 2011.***

2. ***Brody, S., OSE Review #2011-2416 and 2011-2417, Proprietary Name, Label, Labeling and Packaging Review for*** (b) (4) ***June 21, 2012.***

3. ***Micromedex Integrated Index (http://csi.micromedex.com)***

   Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

4. ***Phonetic and Orthographic Computer Analysis (POCA)***

   POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

5. ***Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)***

   Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.

6. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

   DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

7. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

   This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

8. ***Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)***

   Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

9. ***U.S. Patent and Trademark Office (http://www.uspto.gov)***

USPTO provides information regarding patent and trademarks.

10. ***Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)***

    Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

11. ***Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at (www.thomson-thomson.com)***

    The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. ***Natural Medicines Comprehensive Databases (www.naturaldatabase.com)***

    Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

13. ***Access Medicine (www.accessmedicine.com)***

    Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

14. ***USAN Stems (http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml)***

    USAN Stems List contains all the recognized USAN stems.

15. ***Red Book (www.thomsonhc.com/home/dispatch)***

    Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

16. ***Lexi-Comp (www.lexi.com)***

    Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

17. ***Medical Abbreviations (www.medilexicon.com)***

    Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

18. ***CVS/Pharmacy (www.CVS.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

19. Walgreens (www.walgreens.com)

This database contains commonly used over the counter products not usually identified in other databases.

20. Rx List (www.rxlist.com)

RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

21. Dogpile (www.dogpile.com)

Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

22. Natural Standard (http://www.naturalstandard.com)

Natural Standard is a resource that aggregates and synthesizes data on complementary and alternative medicine.

23. FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

---

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[2]

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	**Considerations when Searching the Databases**		
	Potential Causes of Drug Name Similarity	*Attributes Examined to Identify Similar Drug Names*	*Potential Effects*
	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Look-alike		Overlapping product characteristics	electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if

any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers gather CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary

Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[3] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section 1.2 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And are there any components of the name that may function as a source of error beyond sound/look-alike?"***

[3] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

6. **Safety Evaluator Risk Assessment of the Proposed Product and associated labels and labeling**

DMEPA searches the FAERS database for any medication error reports associated with the reference listed drug that may be relevant to this product. We also evaluate labels and package insert labeling submitted by the Applicant using the principals of Human Factors and Failure Mode and Effects Analysis,[4] along with post marketing medication error data.

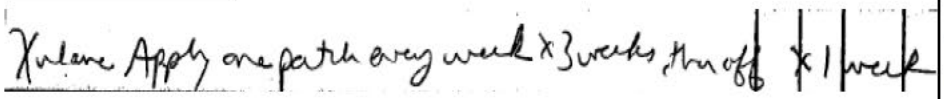
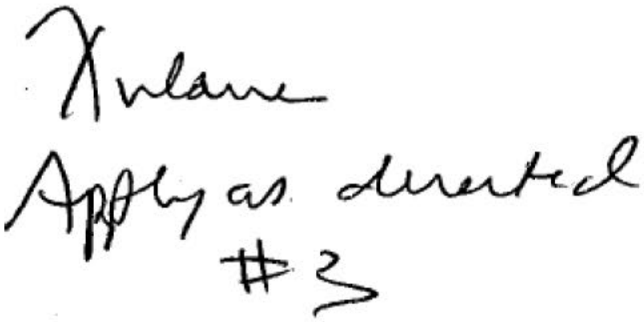
Appendix B: Letters and Letter Strings with Possible Orthographic or Phonetic Misinterpretation

Letters in proposed name, Xulane	**Scripted may appear as:**	**Spoken may be interpreted as:**
Capital 'X'	F, N, K, V, T, Y, U	S, T, Z, KS, KZ
Lower case 'x'	a, r, skinny f, k, n, t, v, y, d, p	ks, kz, s, z, zh
Lower case 'u'	a, e, i, o, n, y, v, w, -er-, -ir-, -el-, -il-	oo, ew
Lower case 'l'	b, e, s, i	
Lower case 'a'	e, i, o, u, el, ci, cl, d	ay, e, i
Lower case 'n'	m, r, v, u, x, h, s, -ir-, -ss-	m, dn, gn, kn, mn, pn
Lower case 'e'	a, u, i, l, o, p, c	a, i
Letter strings		
Letter string 'Xu-'	Xa, Xer, Xi, Xir, Xo, Xv, Xy Za, Zer, Zi, Zir, Zo, Zu, Zy Va, Ver, Vi, Vir, Vo, Vu, Vy Ka, Ker, Ki, Kir, Ko, Ku, Ky	Zo, Zoo, Zu
Letter string '-ane'	-onc ,-one, -ore, -ose, -ove, -are, -ase, -ave, -ene, -ere, -asse -ese, -eve, -une, -ure, -use, -uve	-ain, -aine

[4] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Appendix C: Prescription Simulation Samples and Results

Figure 1. Xulane Study (Conducted on November 6, 2012)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: 	Xulane Apply as directed #3
Outpatient Prescription: 	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

Study Name: Xulane

As of Date 3/12/2013

194 People Received Study

89 People Responded

Study Name: Xulane

Total	26	35	28	
INTERPRETATION	**INPATIENT**	**VOICE**	**OUTPATIENT**	**TOTAL**
XILANE	2	0	1	3
XILARNE	0	0	1	1
XIRLANE	0	0	1	1
XOLARE	1	0	0	1
XRLANE	0	0	1	1
XULAIRE	0	0	2	2
XULANE	21	0	19	40
XULASE	1	0	0	1
XULAVE	0	0	1	1
XULENE	1	0	0	1
XVLANE	0	0	1	1
XYLASSE	0	0	1	1
ZOLAIN	0	1	0	1
ZOLANE	0	1	0	1
ZOOLANE	0	1	0	1
ZOOLANE (ZULAINE??)	0	1	0	1
ZULAIN	0	3	0	3
ZULAINE	0	1	0	1
ZULANE	0	27	0	27

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Proprietary Name	Active Ingredient	Similarity to Xulane	Failure preventions
1.	Calan	Verapamil	Look alike	The pair have sufficient orthographic and/or phonetic differences.
2.	Colace	Docusate Sodium	Look alike	The pair have sufficient orthographic and/or phonetic differences.
3.	Kadian	Morphine Sulfate	Look alike	The pair have sufficient orthographic and/or phonetic differences.
4.	Kuvan	Sapropterin Dihydrochloride	Look alike	The pair have sufficient orthographic and/or phonetic differences.
5.	Matulane	Procarbazine	Look alike	The pair have sufficient orthographic and/or phonetic differences.
6.	Melanex	Hydroquinone	Look alike	The pair have sufficient orthographic and/or phonetic differences.
7.	Oxylone	Flurometholone	Look alike	The pair have sufficient orthographic and/or phonetic differences.
8.	Suprane	Desflurane	Sound alike	The pair have sufficient orthographic and/or phonetic differences.
9.	Tilade	Nedocromil Sodium	Look alike	The pair have sufficient orthographic and/or phonetic differences.
10.	Tulax	Not available	Look alike	Identified in Micromedex according to OSE Review #2010-1752, dated December 2, 2011. However, cannot find in usual databases at this time.
11.	Uni-Lan	Aluminum Hydroxide/Magnesium Hydroxide/Simethicone	Look alike	The pair have sufficient orthographic and/or phonetic differences.
12.	Vantin	Cefpodoxime Proxetil	Look alike	The pair have sufficient orthographic and/or phonetic differences.
13.	Xalkori	Crizotinib	Look alike	The pair have sufficient orthographic and/or phonetic differences.
14.	Kariva	Desogestrel and Ethinyl Estradiol	Look alike	The pair have sufficient orthographic and/or phonetic differences.
15.	Tetanus	Tetanus Immune Globulin	Look alike	The pair have sufficient orthographic and/or phonetic differences.
16.	Voluven	Hetastarch (Hydroxyethyl Starch; HES)	Look alike	The pair have sufficient orthographic and/or phonetic differences.

No.	Proprietary Name	Active Ingredient	Similarity to Xulane	Failure preventions
17.	Xailin***	Naproxcinod	Look alike	(b) (4)
18.	Xalcom***	Latanoprost/Timolol Maleate	Look alike	(b) (4)
19.	Xenical	Orlistat	Look alike	The pair have sufficient orthographic and/or phonetic differences.
20.	Xerese	Acyclovir/Hydrocortisone	Look alike	The pair have sufficient orthographic and/or phonetic differences.
21.	Xolegel	Ketoconazole	Look alike	The pair have sufficient orthographic and/or phonetic differences.
22.	(b) (4)	Methylnaltrexone Bromide	Look alike	IND 064583. This was the alternate name to Relistor (b) (4) The Applicant submitted this IND under NDA 021964 and the Application was approved on 4/24/08 with the name, Relistor.
23.	Zitamin	Prenatal vitamins	Look alike	The pair have sufficient orthographic and/or phonetic differences.
24.	Dolene	Propoxyphene	Look alike	The Agency withdrew approval of Propoxyphene in November 2010 due to risk of cardiac toxicity.
25.	Forane	Isoflurane	Look alike	The pair have sufficient orthographic and/or phonetic differences.
26.	L-Valine	Valine	Look alike	Valine is a branched chain amino acid dietary supplement and not a drug.
27.	Valine	Valine	Look alike	Valine is a branched chain amino acid dietary supplement and not a drug.
28.	Normal Saline	Sodium Chloride	Look and Sound alike	The pair have sufficient orthographic and/or phonetic differences.

No.	Proprietary Name	Active Ingredient	Similarity to Xulane	Failure preventions
29.	Xopenex	Levalbuterol	Look alike	The pair have sufficient orthographic and/or phonetic differences.
30.	(b) (4)	(b) (4)	Look alike	(b) (4)
31.	Xulane	Norelgestromin and Ethinyl Estradiol	Look and Sound alike	Subject of this review. Name found previous Acceptable in OSE Review #2010-1754 (b) (4) dated December 2, 2011.
32.	Xylene	Xylene	Look alike	Pharmaceutical reagent and exipient that is not likely to be ordered on a prescription.
33.	Zurase	Polyethylene Glycol-Modified Uricase	Look alike	The pair have sufficient orthographic and/or phonetic differences. Name identified in orphan drug list. No open commercial IND or pending NDAs within the agency.
34.	Xylose	D-xylose	Look and Sound alike	Name not likely to be written on a prescription. Substance used for a test to investigate absorption from the gastrointestinal tract.
35.	Nulev	Hyoscyamine Sulfate	Look alike	The pair have sufficient orthographic and/or phonetic differences.
36.	Rolene	Betamethasone	Look alike	Identified in Lexicomp. This is a Canadian brand name for betamethasone.
37.	XELOX	Not applicable	Look alike	A chemotherapy regimen consisting of Capecitabine and Oxaliplatin for colorectal or pancreatic cancer and not a specific drug.

No.	Proprietary Name	Active Ingredient	Similarity to Xulane	Failure preventions
38.	Xerclear***	Acyclovir/Hydrocortisone	Look alike	(b) (4)

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**		**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
1.	Kerlone (Betaxolol Hydrochloride) Tablets 10 mg, 20 mg <u>Usual Dosage:</u> 10 mg to 40 mg orally once daily	<u>Orthographic</u> Both names contain similar number of letters (7 vs. 6), contain 2 upstrokes in similar positions, and end in the letter string '-ne.' Additionally, the beginning letter string 'Ker-' and the letter 'o' in Kerlone may appear similar to the letter string 'Xu-' and the letter 'a' in Xulane, respectively, when scripted. <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as a single route of administration <u>Usual Dose</u> One	<u>Product Strength</u> Single strength vs. multiple strengths which must be specified <u>Frequency of Administration</u> Q Weekly or UAD vs. QD

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**	**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion	**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
2. Kutrase (Pancreatin: Lipase, Protease, Amylase) Capsules 2,400 units/30,000 units/ 30,000 units <u>Usual Dosage:</u> One capsule with each meal or snack	<u>Orthographic</u> Both names consist of similar number of letters (7 vs.6), contain 2 upstrokes in the same position, and end in the letter 'e'. Additionally, the beginning letter string 'Ku-' and the ending letter string '-ase' in Kutrase may appear similar to the letter strings 'Xu-' and '-ane' in Xulane, respectively, when scripted. <u>Product Strength</u> Both available in a single strength <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as a single route of administration <u>Usual Dose</u> One	<u>Orthographic</u> The extra letter 'r' after the upstroke in Kutrase makes the infix of both names appear distinct when scripted. <u>Frequency of Administration</u> Q Weekly or UAD vs. TID or with meals

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**		**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
3.	Navane (Thiothixene) Capsules 2 mg, 10 mg, 20 mg <u>Usual Dosage:</u> 2 mg – 20 mg by mouth two to three times a day	<u>Orthographic</u> Both names contain 6 letters and end in the letter string '-ane'. Additionally, the letter string 'Na-' in Navane may appear similar to the letter string 'Xu-' in Xulane when scripted. <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as a single route of administration <u>Usual Dose</u> One	<u>Orthographic</u> The name Xulane contains an upstroke in the 3rd position vs. no upstroke in a similar position in Navane which gives both names a different shape when scripted. <u>Product Strength</u> Single strength vs. multiple strengths which must be specified <u>Frequency of Administration</u> Q Weekly or UAD vs. BID or TID
4.	Nubain (Nalbuphine) Injection solution 10 mg/mL 20 mg/mL <u>Usual Dosage:</u> 10 mg to 20 mg intravenously, intramuscularly, or subcutaneously every three to six hours as needed; 0.3 mg/kg to 3 mg/kg intravenously over 10 to 15 minutes.	<u>Orthographic</u> Both names contain 6 letters and contain 2 upstrokes in the same positions. Additionally, the beginning letter string 'Nub-' in Nubain may appear similar to the letter string 'Xul-' in Xulane when scripted. <u>Dosage Form</u> Both available as a single dosage form	<u>Orthographic</u> The ending letter 'n' in Nubain looks distinct from the ending letter 'e' in Xulane when scripted. <u>Product Strength</u> Single strength vs. multiple strengths which must be specified <u>Route of Administration</u> Apply topically only vs. IV, IM, or SubQ <u>Frequency of Administration</u> Q Weekly or UAD vs. Q 3 to 6 hours

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**		**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
5.	Perlane (Hyaluronate and Derivatives) Intradermal Gel for Injection 20 mg/mL <u>Usual Dosage:</u> Inject as required into deep dermis/superficial subcutis for cosmetic result; typical treatment regimen requires 1.9-4.6 mL; maximum: 6 mL per treatment	<u>Orthographic</u> Both names consist of similar number of letters (7 vs. 6), contain 2 upstrokes, and contain the letter string '-lane'. Additionally, the letter string '-er-' in Perlane may appear similar to the letter 'u' in Xulane when scripted. <u>Product Strength</u> Both available in a single strength <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as single route of administration	<u>Frequency of Administration</u> Q Weekly or UAD vs. One time <u>Usual Dose</u> One patch vs. XX mL
6.	Talwin (Pentazocine) Injection, solution 30 mg/mL <u>Usual Dosage:</u> I.M., SubQ: 30-60 mg every 3-4 hours as needed I.V.: 30 mg every 3-4 hours as needed	<u>Orthographic</u> Both names contain 6 letters and contain 2 upstrokes in the same position. Additionally, the letter string 'tal-' in Talwin may appear similar to the letter string 'Xul-' in Xulane when scripted. <u>Product Strength</u> Both available in a single strength <u>Dosage Form</u> Both available as a single dosage form	<u>Orthographic</u> The ending letter 'n' in Talwin looks distinct from the ending letter 'e' in Xulane when scripted. <u>Route of Administration</u> Apply topically only vs. IV, IM, or SubQ <u>Frequency of Administration</u> Q Weekly or UAD vs. Q 3 to 4 hours prn <u>Usual Dose</u> One patch vs. XX mg or XX mL

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**		**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
7.	Ultane (Sevoflurane) Inhalation Liquid 100% <u>Usual Dosage:</u> Dose individualized and is based on patient's response; Usual dose is 0.5% to 3% with or without nitrous oxide and is administered via a vaporizer by an anesthesiologist	<u>Orthographic</u> Both names contain 6 letters and end in the letter string '-ane'. Additionally, the beginning letter string 'Ul-' in Ultane may appear similar to the letter string 'Xu-' in Xulane if the 'l' is scripted low and skinny. <u>Product Strength</u> Both available in a single strength <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as single route of administration	<u>Frequency of Administration</u> Q Weekly or UAD vs. individualized but unlikely to be Q Weekly <u>Usual Dose</u> One patch vs. 0.5% to 3% <u>Setting of Use</u> Outpatient or inpatient vs. administered by an anesthesiologist
8.	Vidaza (Azacitidine) Reconstituted Suspension for Injection 100 mg <u>Usual Dosage:</u> 75 mg/m^2 to 100 mg/m^2 subcutaneously or IV daily for 7 days. Cycles should be repeated every 4 weeks for a minimum 4 to 6 cycles.	<u>Orthographic</u> Both names consist of similar number of letters and contain 2 upstrokes in the same position. Additionally, the letter string 'Vida-' in Vidaza may appear similar to the letter string 'Xula-' in Xulane when scripted. <u>Product Strength</u> Both available in a single strength <u>Dosage Form</u> Both available as a single dosage form	<u>Route of Administration</u> Apply topically only vs. IV or SubQ <u>Frequency of Administration</u> Q Weekly or UAD vs. daily for 7 days <u>Usual Dose</u> One patch vs. XX mg/m^2 or XX mg

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**	**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion	**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
9. Valium (Diazepam) Tablets 2 mg, 5 mg, 10 mg; Oral solution 5 mg/5 mL, 5 mg/mL; Solution for injection 5 mg/mL <u>Usual Dosage:</u> 2 mg to 10 mg orally two to three times per day. *Parenteral dose:* 2 mg to 10 mg intramuscularly or intravenously for anxiety. May repeat in 3 to 4 hours; 5 mg to 10 mg times one dose preoperatively for anxiety. *Pediatric patients (> 2 years old):* 0.5 mg per pound, up to ½ of the recommended adult dose.	<u>Orthographic</u> Both names contain 6 letters and contain 2 upstrokes in the same position. Additionally, the letter string 'Val-' in Valium may appear similar to the letter string 'Xul-' in Xulane when scripted. <u>Usual Dose</u> One	<u>Orthographic</u> The ending letter 'm' in Valium looks distinct from the ending letter 'e' in Xulane when scripted. <u>Product Strength</u> Single strength vs. multiple strengths which must be specified if tablets (e.g., 2 mg, 5 mg, 10 mg) <u>Dosage Form</u> Single dosage form vs. multiple dosage forms which must be specified (e.g., solution or injection. If tablets, strength must be specified.) <u>Route of Administration</u> Apply topically only vs. oral or IM or IV <u>Frequency of Administration</u> Q Weekly or UAD vs. BID, TID, Q3-4 hours, or one time dose

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**	**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion	**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
10. Veltane (Brompheniramine Maleate) Tablet 4 mg <u>Usual Dosage:</u> 4 mg four times daily or 12 mg to 24 mg every 12 hours	<u>Orthographic</u> Both names consist of similar number of letters (7 vs. 6) and end in the letter string '-ane'. Additionally, the beginning letter string 'Vel-' in Veltane may appear similar to the letter string 'Xu-' in Xulane if the 'l' is scripted skinny and low. <u>Product Strength</u> Both available in a single strength <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as single route of administration <u>Usual Dose</u> One	<u>Frequency of Administration</u> Q Weekly or UAD vs. QID or BID

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**		**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
11.	Xalatan (Latanoprost) Ophthalmic Solution 0.005% <u>Usual Dosage:</u> One drop to affected area once daily	<u>Orthographic</u> Both names consist of similar number of letters (7 vs. 6), begin with the letter 'X', and contain the upstroke 'l' in the 3rd position. <u>Product Strength</u> Both available in a single strength <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as single route of administration <u>Usual Dose</u> One	<u>Orthographic</u> The name Xalatan contains an extra upstroke in the 5th position vs. no extra upstroke in Xulane which gives both names a different shape when scripted. <u>Frequency of Administration</u> Q Weekly or UAD vs. QD

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**		**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
12.	Xedec (Guaifenesin and Phenylephrine) Tablets 800 mg/20 mg <u>Usual Dosage:</u> One-half to one tablet orally every 8 hours	<u>Orthographic</u> Both names consist of similar number of letters (5 vs. 6), begin with the letter 'X', and contain 2 upstrokes in the same position. <u>Product Strength</u> Both available in a single strength <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as single route of administration <u>Usual Dose</u> One	<u>Orthographic</u> The ending letter string '-ec' in Xedec appears shorter then the letter string '-ane' in Xulane when scripted. <u>Frequency of Administration</u> Q Weekly or UAD vs. TID or Q8h
13.	Xeloda (Capecitabine) Tablets 150 mg , 500 mg <u>Usual Dosage:</u> 650 mg/m^2 - 1250 mg/m^2 by mouth twice daily for 2 weeks following a cycle	<u>Orthographic</u> Both names contain 6 letters, begin with the letter 'X' and contain an upstroke 'l' in the 3rd position. <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as single route of administration	<u>Orthographic</u> The name Xeloda contains an extra upstroke in the 5th position vs. no extra upstroke in Xulane which gives both names a different shape when scripted. <u>Product Strength</u> Single strength vs. multiple strengths which must be specified <u>Frequency of Administration</u> Q Weekly or UAD vs. BID <u>Usual Dose</u> One patch vs. XX mg

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**		**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
14.	Xibrom (Bromfenac Sodium) Ophthalmic Solution 0.09% <u>Usual Dosage:</u> Instill one drop into affected eye(s) twice daily beginning 24 hours after cataract surgery and continuing for 14 days.	<u>Orthographic</u> Both names contain 6 letters, begin with the letter 'X', and contain 2 upstrokes in the same position. <u>Product Strength</u> Both available in a single strength <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as single route of administration <u>Usual Dose</u> One	<u>Orthographic</u> The ending letter string '-brom' in Xibrom looks distinct from the ending letter string '-lane' in Xulane when scripted due to the rounded letter 'o' and the wider letter 'm' in Xibrom.. <u>Frequency of Administration</u> Q Weekly or UAD vs. BID

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**	**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion	**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
15. Xinlay (Atrasentan HCl) Capsules 10 mg <u>Usual Dosage:</u> 10 mg once daily	<u>Orthographic</u> Both names contain 6 letters, begin with the letter 'X', and contain an upstroke 'l' in similar positions. <u>Product Strength</u> Both available in a single strength <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as single route of administration <u>Usual Dose</u> One	<u>Orthographic</u> The name Xinlay contains a down stroke 'y' in the last position vs. no down stroke in Xulane giving both names a different shape when scripted. <u>Frequency of Administration</u> Q Weekly or UAD vs. QD

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**		**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
16.	Xolair (Omalizumab) Powder for Injection 150 mg <u>Usual Dosage:</u> 150 mg to 375 mg subcutaneously every two or every four weeks.	<u>Orthographic</u> Both names contain 6 letters, begin with the letter 'X', and contain an upstroke 'l' in the 3rd position. Additionally, the letter string 'Xola-' in Xolair may appear similar to the letter string 'Xula-' in Xulane when scripted. <u>Phonetic</u> Both names contain 2 syllables and begin with the 'Xo' or 'Xu' sound. Additionally, the beginning of the 2nd syllable may sound similar when spoken ('la-'). <u>Product Strength</u> Both available in a single strength <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as single route of administration <u>Frequency of Administration Overlap</u> Q Weekly vs. Q 2Weeks or Q 4 Weeks <u>Usual Dose</u> One	<u>Orthographic</u> While the letter string '-ir' in Xolair may appear similar to the letter 'n' in Xulane, the name Xulane contains the ending letter 'e' which makes the name Xulane appear longer after the upstroke 'l'. <u>Phonetic</u> The ending of the 2nd syllable sound distinct due to the nasal alveolar consonant 'n' in Xulane when spoken ('lair' vs. 'lane') .

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**		**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
17.	Xolox (Oxycodone Hydrochloride and Acetaminophen) Tablets 10 mg/500 mg <u>Usual Dosage:</u> 1 tablet every four to six hours as needed for pain	<u>Orthographic</u> Both names consist of similar number of letters (5 vs. 6), begin with the letter 'X', and contain an upstroke 'l' in the 3rd position. Additionally, the letter string 'Xolo-' in Xolox may appear similar to the letter string 'Xula-' in Xulane when scripted. <u>Product Strength</u> Both available in a single strength <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as single route of administration <u>Usual Dose</u> One	<u>Orthographic</u> The name Xolox ends in a cross-stroke 'x' vs. the letter string '-ne' in Xulane which makes the name appear longer when scripted. <u>Frequency of Administration</u> Q Weekly or UAD vs. QID or Q 4-6 hours prn

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**		**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
18.	Zolene HC (Chloroxylenol, Hydrocortisone, and Pramoxine HCl) Otic Solution 0.1%/1%/1% <u>Usual Dosage:</u> Instill three or five drops into the affected ear(s) three or four times a day	<u>Orthographic</u> Both root names contain 6 letters, contain an upstroke 'l' in the 3rd position, and ends in the letter string '-ne'. Additionally, the beginning letter string 'Zol-' and the ending letter string '-ene' in Zolene may appear similar to 'Xul-' and '-ane' in Xulane, respectively, when scripted. <u>Phonetic</u> Both root names contain 2 syllables. Additionally, the beginning syllable 'Zoh-' and the ending syllable '-lene' in Zolene may sound similar to 'Zhoo-' and '-lane' in Xulane when spoken. <u>Product Strength</u> Both available in a single strength <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as single route of administration	<u>Frequency of Administration</u> Q Weekly or UAD vs. TID or QID <u>Usual Dose</u> One patch vs. 3 to 5 drops

PROPOSED NAME: **Xulane** **(Norelgestromin and Ethinyl Estradiol)**		**STRENGTH:** **0.15 mg /0.02 mg/day**	**USUAL DOSE:** **Apply one patch every week for 3 weeks and then off for week 4** **or** **Apply as directed**
FAILURE MODE: Name Confusion		**CAUSES:** (Potential reasons for name confusion that could lead to medication error)	**PREVENTION OF FAILURE MODE** (Reasons why the risk of medication error is minimized)
19.	Zydone (Hydrocodone and Acetaminophen) Tablets 10 mg/400 mg, 5 mg/400 mg, 7.5 mg/400 mg <u>Usual Dosage:</u> 1 or 2 tablets every four to six hours as needed for pain	<u>Orthographic</u> Both names contain 6 letters, contain 2 upstrokes in the same positions, and end in the letter string '-ne'. Additionally, the beginning letter 'Z' in Zydone may appear similar to the 'X' in Xulane when scripted. <u>Dosage Form</u> Both available as a single dosage form <u>Route of Administration</u> Both available as single route of administration <u>Usual Dose</u> One	<u>Orthographic</u> The name Zydone contains a down stroke 'y' in the 2nd position vs. no down stroke in Xulane. Additionally, the rounded part of the upstroke 'd' in Zydone elongates the beginning part of the name which further gives both names a different shape when scripted. <u>Product Strength</u> Single strength vs. multiple strengths which must be specified. <u>Frequency of Administration</u> Q Weekly or UAD vs. QID or Q 4-6 hours prn

Following this page, 3 Pages of Draft Labeling have been Withheld in Full as (b)(4)

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

/s/

ALISON J PARK
04/16/2013

KELLIE A TAYLOR
04/18/2013

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST
04/19/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name, Label, Labeling and Packaging Review--ANDA

Date:	June 21, 2012
Reviewer(s):	Sarah Brody, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader	Zachary Oleszczuk, Pharm.D., Team Leader Division of Medication Error Prevention and Analysis
Deputy Director	Kellie Taylor, Pharm.D., MPH, Deputy Director Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh, Division Director Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength(s):	(b) (4) (Norelgestromin and Ethinyl Estradiol Transdermal System) 4.86 mg/0.53 mg per patch (0.15 mg/0.02 mg/24 hours)
Application Type/Number:	ANDA 200910
Applicant:	Mylan Technologies
OSE RCM #:	2011-2416 and 2011-2417

*** This document contains proprietary and confidential information that should not be released to the public.***

Following this page, 76 Pages Withheld in Full as (b)(4)

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

/s/

SARAH J BRODY
06/21/2012

ZACHARY A OLESZCZUK
06/21/2012

KELLIE A TAYLOR
06/22/2012

CAROL A HOLQUIST
06/22/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200910

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ **APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **CGMP**

Division: I	**Team: 12**	**PM: Select**

Electronic ANDA: Yes ☒ No ☐

ANDA #:200910
Firm Name:Mylan Technologies Inc.
ANDA Name:Norelgestromin and Ethinyl Estradiol Transdermal System
RLD Name:Ortho Evra/N21180/Janssen Pharmaceuticals, Inc.

Electronic AP Routing Summary Located:
V:\Chemistry Division I\Team 12\Electronic AP Summary\200910.APsummary.doc

AP/TA Letter Located:
V:\Chemistry Division I\Team 12\Approval Letters\200910.APletter.doc

Project Manager Evaluation: **Date: 1/17/14 Initials:** SKB

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec′d date 12/31/09	Date of Application 12/31/09	Date Acceptable for Filing 12/31/09
Patent Certification (type) PIV ('746,'377)	Date Patent/Excl. expires 11/20/15('746); 6/7/15 ('377)	Citizens' Petition/Legal Case? Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒ **DMF#:** (b) (4) (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

GDUFA User Fee Obligation Status: ☒ Met ☐ Unmet**:** ☐ Facility Fee not paid, ☐ Backlog fee not paid
EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable: 11/26/13(until 7/12/14)* ☐ Warning Letter Issued; Date:

Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 12/19/13 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 2/5/14 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location:)
Date of Acceptable Labeling _____ Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) _____

Methods Val. Samples Pending: Yes ☐ No ☒**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:

☐ Labeling Endorsement, Date emailed: _____ REMS Required: Yes ☐ No ☐ REMS Acceptable: Yes ☐ No ☐

☐ Regulatory Support

☐ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☐ Division

☐ Bob West / Peter Rickman

☐ Kathleen Uhl

☐Filed AP Routing Summary in DARRTs	☐Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS″ distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 4/15/14**

Chief, Reg. Support Branch **Initials:** KAA for MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD =ORTHO EVRA NDA#N021180 Date Checked 4/15/14 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 11/12/13	

Any filing status changes requiring addition Labeling Review Yes ☒ No ☐☐ **An email was sent to MYLAN on 4/14/14 notifying them of the recently approved labeling for the RLD. In the email, MYLAN was advised to update the carton, pouch and patch labels to include the expression of strength, "150/35 mcg per day" after the established name in a similar size font. A memo containing a copy of the email was checked into DARRTS and signed by Danielle Russell (Labeling Project Manager).**

Type of Letter:
☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:

Comments:ANDA rec'd on 12/31/2009, BOS=Ortho Evra (NDA 021-180). ANDA ack for filing with PIV certifications to both Patent no. 5'972'377 exp on Jun 7, 2015 and Patent no. 5'876'746 exp on Nov 20, 2015. ACK letter signed and mailed out on 4/19/2010. Patent Amendment rec'd on 9/23/2010 containing (b) (4) delivery receipts for PIV notices sent by MYLAN - to the General Counsel for Johnson & Johnson, New Brunswick, NJ, Johnson & Johnson Pharma R&D in Raritan, NJ and Ortho-McNeil-Janssen Pharma. The PIV notices sent to the aforementioned offices were delivered on 5/7/2010. MYLAN also sent a notice to Janssen Pharmaceutica Pharma NV, Beerse, Belgium and that notice was delivered on 5/10/2010. The patent amendment rec'd on 9/23/2010 also indicated that no civil action was initiated against MYLAN by the notified entities within the statutory 45 day period.
This ANDA was NOT the first generic application received with PIV patent certs for this drug product (b) (4) Consequently, there are no barriers to approval and this ANDA is eligible for full approval.

2. ***Labeling Endorsement***

Reviewer, Malik Imam:
Date4/15/14

Labeling Team Leader, Lilli Golson:
Date4/15/14

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☐n/a

Comments:
From: Golson, Lillie D
Sent: Tuesday, April 15, 2014 5:10 PM
To: Basi, Surjit; Golson, Lillie D
Subject: FW: AP Package: ANDA 200910/Norelgestromin/Ethinyl Estradiol (Xulane)/Mylan

Hello Surjit,

Please endorse the AP routing form on behalf of Malik and me.

Thanks

From: Basi, Surjit
Sent: Tuesday, April 15, 2014 4:48 PM
To: Imam, Malik; Golson, Lillie D
Subject: AP Package: ANDA 200910/Norelgestromin/Ethinyl Estradiol (Xulane)/Mylan
Hello Malik and Lillie,

Please provide concurrence on AP package for ANDA 200910

V:\Chemistry Division I\Team 12\Approval Letters

V:\Chemistry Division I\Team 12\Electronic AP Summary

Thank you,
Surjit

3. ***Paragraph IV Evaluation*** **PIV's Only**

David Read **Date 15Apr2014**
OGD Regulatory Counsel **InitialsDTR**

Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes to AP letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 04/14/2014**

Chemistry Div. **V** **InitialsBR**

Comments:CMC is adequate for approval./Bhagwant Rege, Ph.D., Acting Deputy Director, Division of Chelistry I.

OGD Office Management Evaluation

5. Peter Rickman **Date 4/16/14**
Director, DLPS **Initials rlw/for**

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 ☐
Date PETS checked for first generic drug _____

Comments: Bioequivalence studies (fasting) found acceptable. In-vitro dissolution testing also found acceptable Bio study sites have acceptable OSI inspection histories. Office-level bio (pK) endorsed 9/6/13 and 2/5/14.

Clinical Bio (Adhesion, Dermal Irritation and Contact Sensitization studies) found acceptable 2/21/14.

Final-printed labeling (FPL) found acceptable for approval 4/15/14. No REMS is required. Product is labeled 150 mcg/35 mcg/day). Proprietary name, Xulane, found acceptable by DMETS.

CMC found acceptable for approval (Chemistry Review #5) 12/19/13.

OR

6. Robert L. West **Date 4/16/14**
Deputy Director, OGD **Initials 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 ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 11/26/13 (Verified 4/16/14). No "OAI" Alerts noted.

Mylan provided paragraph IV certifications to the '746 and '377 patents, but was not sued within the 45-day period. Approval of this ANDA is not blocked by any other applicant's eligibility for 180-day generic drug exclusivity for this drug product. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

This first-generic ANDA is recommended for approval.

7. ***OGD Director Evaluation***
Kathleen Uhl

Comments: RLWest for Kathleen Uhl, M.D., Acting Director, Office of Generic Drugs 4/16/14.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐
Press Release Acceptable ☐

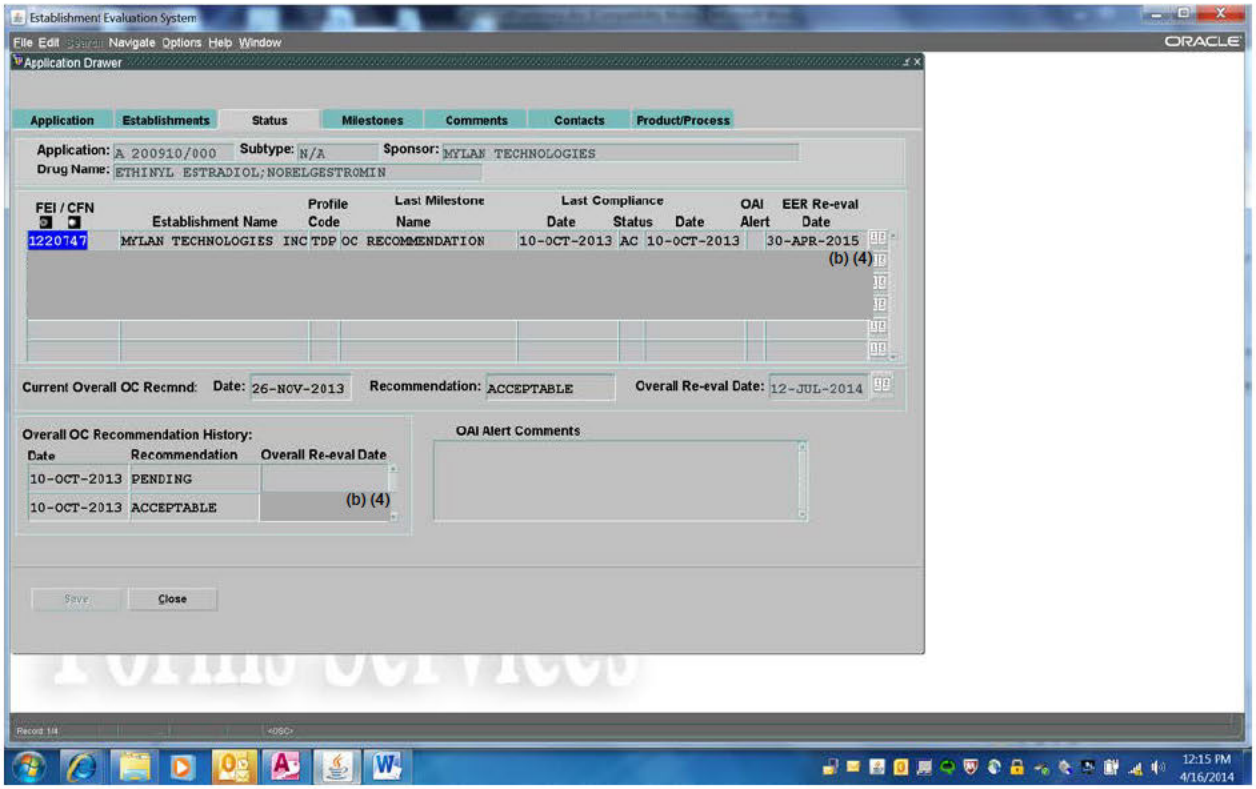
Comments:

8. Project Manager **Date 4/16/14**
Initials SKB

Comments:

Check Communication and Routing Summary into DARRTS

EES DATA:


Establishment Evaluation System
File Edit Search Navigate Options Help Window
ORACLE
Application Drawer
Application
Establishments
Status
Milestones
Comments
Contacts
Product/Process
Application: A 200910/000
Subtype: N/A
Sponsor: MYLAN TECHNOLOGIES
Drug Name: ETHINYL ESTRADIOL;NORELGESTROMIN
FEI / CFN
Establishment Name
Profile Code
Last Milestone Name
Last Compliance Date
Status
Date
OAI Alert
EER Re-eval Date
1220747
MYLAN TECHNOLOGIES INC
TDP
OC RECOMMENDATION
10-OCT-2013
AC
10-OCT-2013
30-APR-2015
(b) (4)
Current Overall OC Recmnd:
Date: 26-NOV-2013
Recommendation: ACCEPTABLE
Overall Re-eval Date: 12-JUL-2014
Overall OC Recommendation History:
Date
Recommendation
Overall Re-eval Date
10-OCT-2013
PENDING
10-OCT-2013
ACCEPTABLE
(b) (4)
OAI Alert Comments
Save
Close
12:15 PM
4/16/2014

Orange Book Report:

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 021180 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021180	001	5876746	Nov 20, 2015		Y	U - 514	
N021180	001	5972377	Jun 7, 2015			U - 514	

Exclusivity Data

There is no unexpired exclusivity for this product.

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

/s/

SURJIT K BASI
04/16/2014

Email was sent to the firm before approval. Includes OGD's comment to the statement made in Mylan's labeling amendment.

From: West, Robert L
Sent: Wednesday, April 16, 2014 12:51 PM
To: Wayne.Talton@mylanlabs.com
Cc: Basi, Surjit
Subject: Re: ANDA 200910 for Xulane (Norelgestromin and Ethinyl Estradiol Transdermal System

Dear Mr. Talton:

It has been brought to my attention that the cover letter to your April 15 amendment contains the following statements (emphasis added):

As agreed with the Office of Generic Drugs, Mylan is providing our revised labeling in draft form. Mylan commits to provide final printed prescribing information, pouch, carton, and patch labeling that are identical to the submitted draft labeling, as soon as they are available but no more than 30 days after they are printed, similar to the treatment accorded the RLD.

As the Agency is aware, Mylan has made significant investment in launch preparedness activities to ensure that sufficient quantities of this important first generic product are available to patients immediately upon FDA approval. Thus, given the late-breaking nature of this RLD labeling change and the considerations noted below, Mylan intends to implement the revised labeling as provided herein at the first printing following approval of our application, and to distribute the initial launch quantities of this product utilizing the labeling previously submitted that we understand was otherwise acceptable to FDA. That course of action parallels the Agency's treatment of the RLD, which remains on the market with the previously approved labeling and which has not been subjected to recall or withdrawal despite the recent approval of revised labeling that the RLD holder intends to implement on a prospective basis.

As one or more individuals from OGD have told you on prior occasions, the agency cannot endorse such a plan. We remind you that under the Federal Food, Drug and Cosmetic Act, your product may be legally marketed only with the labeling that FDA has approved.

Robert L. West
Deputy Director
Office of Generic Drugs

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

/s/

SURJIT K BASI
04/16/2014

The email change below captures some of the events leading to and following the NDA's (Ortho Evra) labeling change to include rate of delivery.

From: Min, Jeen
Sent: Monday, April 14, 2014 3:49 PM
To: CDER-Orange Book Staff
Cc: Toufanian, Maryll; West, Robert L; Lee, Koung U; Holquist, Carol A; Imam, Malik; Uhl, Kathleen (CDER); Read, David T; Flanagan, Keith; Shimer, Martin; Rickman, William P
Subject: NDA 021180/S-046 Ortho Evra Strength Change to

Derrick/Iris,

Supplement 021180/S-046 Ortho Evra Patch was approved on 4/11/2014 for a strength change from 0.75MG;6MG to 0.035MG/24HR;0.15MG/24HR.

Please update the strength for the March update.

	Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength
Old	N021180		Yes	ETHINYL ESTRADIOL; NORELGESTROMIN	FILM, EXTENDED RELEASE;TRANSDERMAL	0.75MG;6MG
New	N021180		Yes	ETHINYL ESTRADIOL; NORELGESTROMIN	FILM, EXTENDED RELEASE;TRANSDERMAL	0.035MG/24HR;0.15MG/24HR

New Labeling:

----------DOSAGE FORMS AND STRENGTHS----------
Transdermal system: 150 mcg/day norelgestromin and 35 mcg/day ethinyl estradiol. (3)

Thanks,

Jeen

From: Basi, Surjit
Sent: Monday, April 14, 2014 2:57 PM
To: McKan, Denise; Toufanian, Maryll; West, Robert L
Cc: Lee, Koung U; Holquist, Carol A; Imam, Malik; Uhl, Kathleen (CDER); Read, David T; Flanagan, Keith; Stewart, Kendra; Min, Jeen; Shimer, Martin; Rickman, William P
Subject: RE: SUMMARY OF CENTER DIRECTOR BRIEFING ON ORTHO EVRA

Dear All,

Drugs@FDA has been updated with the approved labeling revisions for the supplement and Mylan has been notified. I have not been given a timeframe for their response, but will let the group know if there are any updates.

Regards,

Surjit

From: McKan, Denise
Sent: Friday, April 11, 2014 5:27 PM
To: Toufanian, Maryll; West, Robert L
Cc: Lee, Koung U; Holquist, Carol A; Imam, Malik; Uhl, Kathleen (CDER); Read, David T; Flanagan, Keith; Stewart, Kendra; Basi, Surjit; Min, Jeen; Shimer, Martin; Rickman, William P
Subject: RE: SUMMARY OF CENTER DIRECTOR BRIEFING ON ORTHO EVRA

Dear All,

From OND's perspective it goes electronically. However, I believe that Peter was going to reach out to Paul Stauffer who works directly in posting to see if it could be expedited. I'll let Peter comment further.

With regards to the pouch, carton, etc. Koung and Imam, finalized labels were not available, so you will have to look in DARRTS at the submissions dated April 8 and 11, to see the submitted and agreed upon pieces respectively.

Denise

From: Toufanian, Maryll
Sent: Friday, April 11, 2014 5:07 PM
To: McKan, Denise; West, Robert L
Cc: Lee, Koung U; Holquist, Carol A; Imam, Malik; Uhl, Kathleen (CDER); Read, David T; Flanagan, Keith; Stewart, Kendra; Basi, Surjit; Min, Jeen; Shimer, Martin; Rickman, William P
Subject: Re: SUMMARY OF CENTER DIRECTOR BRIEFING ON ORTHO EVRA

All,

This is great news! OCC indicated that we should notify Mylan per our normal course, which I understand would be to direct the company to drugs@fda for the supplement and the approved labeling. Is there any way to expedite that posting?

Thanks,
Maryll

From: McKan, Denise
Sent: Friday, April 11, 2014 04:59 PM
To: West, Robert L
Cc: Lee, Koung U; Holquist, Carol A; Imam, Malik; Uhl, Kathleen (CDER); Read, David T; Toufanian, Maryll; Flanagan, Keith; Stewart, Kendra; Basi, Surjit; Min, Jeen; Shimer, Martin
Subject: RE: SUMMARY OF CENTER DIRECTOR BRIEFING ON ORTHO EVRA

Please see the attached approval letter for Ortho Evra. I'm checking on labels and labeling and will forward information when I have it.

Denise

From: West, Robert L
Sent: Wednesday, April 09, 2014 2:48 PM
To: McKan, Denise
Cc: Lee, Koung U; Holquist, Carol A; Imam, Malik; Uhl, Kathleen (CDER); Read, David T; Toufanian, Maryll; Flanagan, Keith; Stewart, Kendra; Basi, Surjit; Min, Jeen; Shimer, Martin
Subject: RE: SUMMARY OF CENTER DIRECTOR BRIEFING ON ORTHO EVRA

Denise:

Thank you! As soon as we can get our hands on a copy of the signed letter, please inform Koung and Malik so that the appropriate OGD letter can be prepared.

Bob

From: McKan, Denise
Sent: Wednesday, April 09, 2014 2:41 PM
To: West, Robert L; Toufanian, Maryll
Cc: Flanagan, Keith; Stewart, Kendra; Min, Jeen; Basi, Surjit; Imam, Malik; Lee, Koung U; Raney, Sameersingh; Read, David T; Shimer, Martin; Peters, John (CDER); Uhl, Kathleen (CDER); Lionberger, Robert
Subject: RE: SUMMARY OF CENTER DIRECTOR BRIEFING ON ORTHO EVRA

Charlene Williamson is the PM. I will ask her to keep me in loop with regards to the approval.

From: West, Robert L
Sent: Wednesday, April 09, 2014 1:52 PM
To: Toufanian, Maryll
Cc: Flanagan, Keith; McKan, Denise; Stewart, Kendra; Min, Jeen; Basi, Surjit; Imam, Malik; Lee, Koung U; Raney, Sameersingh; Read, David T; Shimer, Martin; Peters, John (CDER); Uhl, Kathleen (CDER); Lionberger, Robert
Subject: RE: SUMMARY OF CENTER DIRECTOR BRIEFING ON ORTHO EVRA

Maryll:

Thank you for the update. Do we know who the OND project manager for this ANDA is? Seems like we need to establish contact with that person.

Bob

> **From:** Toufanian, Maryll
> **Sent:** Wednesday, April 09, 2014 12:52 PM
> **To:** Peters, John (CDER); Lionberger, Robert; Uhl, Kathleen (CDER); West, Robert L
> **Cc:** Flanagan, Keith; McKan, Denise; Stewart, Kendra; Min, Jeen; Basi, Surjit; Imam, Malik; Lee, Koung U; Raney, Sameersingh; Read, David T; Shimer, Martin
> **Subject:** RE: SUMMARY OF CENTER DIRECTOR BRIEFING ON ORTHO EVRA
>
> An update: I received word that the division reached out to Janssen about the proposed labeling change and Janssen submitted a new supplement yesterday that provides only for inclusion of the rate in the label. The division indicated that it intended to approve before Tuesday. OCC reminded the division that Mylan is expecting action on its ANDA no later than Monday, and that OGD can't disclose the Janssen supplement to Mylan until the supplement is approved. OCC emphasized that approval of the supplement before Monday would be optimal in order to give OGD time to notify Mylan.

From: Peters, John (CDER)
Sent: Tuesday, April 08, 2014 3:01 PM
To: Lionberger, Robert; Uhl, Kathleen (CDER); West, Robert L
Cc: Flanagan, Keith; Toufanian, Maryll; McKan, Denise; Stewart, Kendra; Min, Jeen; Basi, Surjit; Imam, Malik; Lee, Koung U; Raney, Sameersingh
Subject: RE: SUMMARY OF CENTER DIRECTOR BRIEFING ON ORTHO EVRA

When I spoke with Carolyn and Lisa, they said they were using the OGD irritation/sensitization criteria for the new formulation of Ortho Evra (changed adhesive) and were not aware of any active efforts to change the criteria for irritation/sensitization as they now stand. That may be something for the future, but at least for now we have the backing of OND for the criteria we use.

Also—they will be doing their Ortho Evra study with the current Ortho Evra as comparator, so, assuming they pass with the new adhesive, Mylan will not get stuck in the rut of having to do another irritation/sensitization study before approval. We really don't need to have another speed bump for that application.

J

From: Lionberger, Robert
Sent: Tuesday, April 08, 2014 2:36 PM
To: Uhl, Kathleen (CDER); Peters, John (CDER); West, Robert L
Cc: Flanagan, Keith; Toufanian, Maryll; McKan, Denise; Stewart, Kendra; Min, Jeen; Basi, Surjit; Imam, Malik; Lee, Koung U; Raney, Sameersingh
Subject: RE: SUMMARY OF CENTER DIRECTOR BRIEFING ON ORTHO EVRA

For the irritation/sensitization studies I don't think there is agreement yet on how to revise the comparison (like we did for the adhesion studies).

Sam Raney will put this on the agenda for the transdermal working group to start the discussion, but I think the next meeting will focus on the Ortha Evra strength issues.

Rob

From: Uhl, Kathleen (CDER)
Sent: Tuesday, April 08, 2014 1:05 PM
To: Peters, John (CDER); West, Robert L
Cc: Flanagan, Keith; Toufanian, Maryll; McKan, Denise; Lionberger, Robert; Stewart, Kendra; Min, Jeen; Basi, Surjit; Imam, Malik; Lee, Koung U
Subject: RE: SUMMARY OF CENTER DIRECTOR BRIEFING ON ORTHO EVRA

Great. So can we strike while the iron is hot wrt the CDER Topical WG? Rob or John, are you guys on this WG? Is there Center agreement or guidance that needs to be issued about this issue?

From: Peters, John (CDER)
Sent: Monday, April 07, 2014 11:47 AM
To: West, Robert L; Uhl, Kathleen (CDER)
Cc: Flanagan, Keith; Toufanian, Maryll; McKan, Denise; Lionberger, Robert; Stewart, Kendra; Min, Jeen; Basi, Surjit; Imam, Malik; Lee, Koung U
Subject: Re: SUMMARY OF CENTER DIRECTOR BRIEFING ON ORTHO EVRA

That was my take too. One additional point though....based on post meeting discussion w Carolyn...OND will be subjecting Jand J to the same irritation/sensitization protocol and analysis as done by OGD. This will be important re Mylan's other application where they challenge our irritation criteria.

Tx

J

From: West, Robert L
Sent: Monday, April 07, 2014 07:42 AM
To: Uhl, Kathleen (CDER)
Cc: Flanagan, Keith; Toufanian, Maryll; McKan, Denise; Lionberger, Robert; Peters, John (CDER); Stewart, Kendra; Min, Jeen; Basi, Surjit; Imam, Malik; Lee, Koung U
Subject: SUMMARY OF CENTER DIRECTOR BRIEFING ON ORTHO EVRA

Cook:

Here's my take of the main points of the meeting held with Dr. Woodcock (and approximately 25 others) on Friday April 4, 2014.

The agreement reached at the meeting (no objections were voiced) is that the new drug division can separate the labeling issues (delivery rate) from the manufacturing issues (change in formulation) contained in the current supplemental application (S-045) under review. The division is to prepare a

"Supplement Request" letter to be sent to J&J requesting labeling changes containing language stating that Ortho Evra delivers 150 mcg of Norelgestromin and 35 mcg of ethinyl estradiol to the bloodstream in 24 hours. This is a change from the current delivery (no longer stated in the labeling) of 20 mcg of ethinyl estradiol (EE) delivered to the bloodstream in 24 hours. The consensus of the group is that the 20 mcg amount is clearly an understatement, and that based upon current evaluations, the figure is most likely around 35 mcg. Some suggested that it could be greater. J&J will be requested to perform further studies post-approval of the labeling change supplement to confirm the correct amount of EE delivered.

OND representatives (review division) will have a telephone conference with J&J representatives early this week regarding the labeling change. The agency expectation is that J&J will agree to make the labeling change and that the labeling change (separate from the formulation change) can be approved on or before April 14th.

If all goes according to plan, Mylan will be informed of the labeling change upon approval of J&J's labeling change. Mylan can then submit updated labeling and if found acceptable obtain approval (based upon the acceptable BE studies) of their ANDA.

Bob

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

/s/

SURJIT K BASI
04/16/2014

Russell, Danielle

From: Russell, Danielle
Sent: Monday, April 14, 2014 4:40 PM
To: 'joseph.sobecki@mylan.com'
Cc: Golson, Lillie D; Imam, Malik
Subject: ANDA 200910

Dear Mr. Sobecki,

This email is regards to your ANDA application 200910, and we refer you to drugs@fda for the recently approved NDA RLD labeling. In addition please update your carton, pouch and patch labels to include the expression of strength, "150/35 mcg per day" after the established name in similar size font.

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

Danielle E. Russell, PharmD
LCDR, United States Public Health Service
Labeling Project Manager
Food and Drug Administration
CDER, Office of Generic Drugs
7520 Standish Place, Room 2335
Rockville, MD 20857
240.276.9678 Office

"If you compare yourself with others, you may become vain and bitter;
for always there will be greater and lesser persons than yourself."— Max Ehrmann 1927, Desiderata

---

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

/s/

DANIELLE E RUSSELL
04/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 200910

Joseph J. Sobecki
Vice President, Regulatory Affairs
Mylan Technologies, Inc.
781 Chestnut Ridge Rd.
Morgantown, WV 05478

Dear Mr. Sobecki:

We are writing in regard to an issue that has been identified during the review of abbreviated new drug application (ANDA) 200910 for norelgestromin/ethinyl estradiol transdermal system submitted by Mylan Technologies, Inc. (Mylan) on December 31, 2009.

The reference listed drug (RLD) for your proposed product, Ortho Evra® sponsored by Janssen Pharmaceuticals, Inc., was approved in 2001. At that time, the labeling of the product reflected the product strength as a release rate of 150 mcg of Norelgestromin (NGMN) and 20 mcg of Ethinyl Estradiol (EE) per 24 hours.[1] The labeling also included information reflecting the total drug content (TDC) for each patch as 6 mg NGMN and 0.75 mg of EE. On November 10, 2005, the label for the RLD was revised to reflect strength as 6 mg NGMN and 0.75 mg of EE, and no longer reflects the release rate.[2]

Mylan submitted its ANDA in December 2009 with a strength reflected in a statement contained in the ANDA as a release rate of 0.15 mg of NGMN and 0.02 mg EE per 24 hours, and a TDC for each patch of 4.86 mg NGMN and 0.53 mg of EE.

With this information in mind, it appears that Mylan's proposed product does not have the same strength as the RLD as required by section 505(j)(2)(A)(iii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Also, we note that FDA's therapeutic equivalence ratings are determined based on, among other things, the strength of a product. If a product differs in strength, that product cannot receive an "AB" therapeutic equivalence rating to the RLD.[3]

[1] Letter to R. W. Johnson Pharm. Research Institute fr. F. Houn, Office of Drug Evaluation III, FDA re. NDA 21-108 (Nov. 20, 2001).

[2] Letter to Johnson & Johnson Pharm Research and Dev. LLC fr. D. Shames, Div. Reproductive and Urological Products, FDA re. NDA 21-180/S-019 (Nov. 10, 2005).

[3] *Orange Book*, Introduction, Sec. 1.2 Therapeutic Equivalence-Related Terms, at vi-v (2014).

.

In light of the foregoing, we invite you to offer Mylan's position on possible administrative steps the company could take to pursue approval for its proposed drug product, including Mylan's position on whether it would be permissible to convert Mylan's ANDA to a new drug application under section 505(b)(2) of the FD&C Act, or to pursue any alternative course.

We realize this entails some careful considerations on your part, and it is unnecessary to impose any deadline on your reply. We will, however, hold further review of this ANDA in abeyance until we have agreed on a mutually acceptable regulatory path forward.

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/

KATHLEEN UHL
03/10/2014

Meeting Minutes (Adobe Connect)

Date: February 7, 2014

Time: 10:00 am-11:00am

Meeting Location: MPN1, Conference Room 245

Application Number: ANDA 200910

Drug Product: Xulane ™(Norelgestromin and Ethinyl Estradiol Transdermal System)

Firm: Mylan Technologies

FDA Participants: Danielle Russell, Malik Imam, Surjit Basi, Bryan Newman, Robert West, Priyanka Ghosh, Lillie Golson, William Rickman, Martin Shimer, Jeen Min, Dale Conner*, Tu-Van Lambert, Mary Dempsey*, David Read, Micheal Jones, Hoainhon Nguyen*, John Peters*
*Phone-in

Background:
Ortho Evra:
In 2005, Janssen's Ortho Evra changed its labeling from rate of delivery to total drug content, making it the only transdermal patch to be listed this way. Janssen later submitted SLR-045, which proposed for a new adhesive layer. The supplement is currently pending due to a complete response issued and may take more than a year for approval.

Xulane ™
Xulane ™, Mylan's ANDA for Ortho Evra, is also listed as total drug content in its labeling to match Janssen. Although both ANDA and NDA match in rate of delivery, they differ in total drug content. Xulane's proposed labeling would be listed as 0.53mg;4.86mg, whereas Ortho Evra is listed as 0.75mg;6mg. The labeling review was found to be adequate; however, recent concern has been brought forth as to whether the ANDA can be approved with the labeling discrepancy. Division of Bioequivalence opened up a consult regarding the issue, but withdrew it in February 2014 as it was related to labeling only.

Discussion:
Confusion in the marketplace:
Concern that generic may appear to be less potent and not equivalent to the brand if listed in the OB with different strengths. An explanation can be provided in a special section in the OB, however, this would not resolve the confusion for the public when comparing the generic and RLD labeling side by side since the labels themselves do not contain the explanation.

Xulane AB rated to Ortho Evra
The differing strengths are not consistent with listings in the Orange Book and AB rating. Mylan did not address this issue upon initial submission in 2009 since the listing of Ortho Evra in the Orange Book was not changed from total drug content to rate of delivery until 2012.

Changing the labeling of Ortho Evra

There is concern that Janssen has created a situation where no generic will be able to match the labeling of the brand. A citizen's petition was already filed against Janssen for their product, but it was denied. Changing Janssen's current labeling is not an option at this time.

Options moving forward:

1) List the drug as labeled in the Orange book with special explanation.
2) Change to a 505(b)(2) application on basis of differing strengths. AB rating will not be granted until labeling for both drugs match. If SLR-045 gets approval for the proposed changes to labeling, Mylan will also have to reflect these changes in their product. At this time they may have potential for AB rating once Mylan is able to match RLD labeling.

Conclusion:

Malik Imam, Peter Rickman, Marty Shimer, and Dave Read will work to draft a letter to Mylan informing them that due to the current findings, we cannot approve the ANDA as is. The letter will address the fact that an AB rating cannot be permitted at this time, and suggest conversion to a 505(b)(2) application based on the differing strengths.

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

/s/

SURJIT K BASI
02/12/2014

MALIK M IMAM
02/14/2014

FDA FAX

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: MYLAN TECHNOLOGIES INC

TEL: 304-599-2595 x 6551

ATTN: S. Wayne Talton

FAX: 304-285-6407

This facsimile is in reference to your abbreviated new drug application(s), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

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

ADDENDUM TO CONSULT REQUEST TO DIVISION OF RESEARCH AND STANDARDS, OGD	
To:	Robert Lionberger, Ph.D., Acting Director for Regulatory Science, Division of Research and Standards, Office of Generic Drugs
From:	Suman Dandamudi, Reviewer, Team 8, Division of Bioequivalence I, Office of Generic Drugs
Through:	Hoainhon Nguyen, Deputy Director, Division of Bioequivalence I (DBI), Office of Generic Drugs
Re:	**WITHDRAWAL OF CONSULT REQUEST**: For ANDA 200910 (Mylan's Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch) (See the original consult request attached)

Withdrawal of Consult Request:

Since determination of the appropriateness of the current RLD labeling with respect to the therapeutic equivalence rating determination for ANDA 200910 (once approved), is not a bioequivalence issue, but rather a pharmaceutical equivalence and labeling issue, DBI withdraws its pending consult request to the Science Staff (Division of Research and Standards, OGD) (See the content of the consult request attached).

DBI confirms that both the bioequivalence (BE) and dissolution testing portions of the ANDA are **adequate**, and the Division has no further question at this time. The adequacy and completeness of the BE and dissolution portions have been previously documented in the following two reviews:

DARRTS, DANDAMUDI, SUMAN, REV-BIOEQ-21(Primary Review), Submit/Final Date 09/06/2013

DARRTS, DANDAMUDI, SUMAN, REV-BIOEQ-02(Dissolution Review), Submit/Final Date 11/11/2013

ATTACHMENT I: PENDING CONSULT REQUEST	
To:	Robert Lionberger, Ph.D., Acting Director for Regulatory Science, Division of Research and Standards, Office of Generic Drugs
From:	Suman Dandamudi, Reviewer, Team 8, Division of Bioequivalence I, Office of Generic Drugs
Through:	Hoainhon Nguyen, Deputy Director, Division of Bioequivalence I (DBI), Office of Generic Drugs
Re:	Request opinion on the appropriateness of the change in the labeling (from "rate of drug release" to "amount of drug content") of the reference product, Ortho-McNeil's Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch, with respect to determination of the therapeutic equivalence for a generic product, Mylan's Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch (ANDA 200910)

Introduction:

Mylan Technologies submitted ANDA 200910 which contains the results of three studies, (1) a fasting bioequivalence (BE) study with a pharmacokinetic (PK) endpoint, comparing the test product Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch to the corresponding reference product, Ortho-McNeil's Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch; (2) Adhesion study (Orth-Cln-09198); and (3) Sensitization/Irritation study (Orth-Cln-0943). The Division of Bioequivalence reviews the BE study, and the Division of Clinical Review reviews the adhesion and sensitization/irritation studies.

The Division of Bioequivalence found the fasting BE study to be acceptable[1].

Based on the OCP recommendation[2], the potency of Ortho-McNeil's Ortho Evra® should be expressed as the **"amount of drug content"** instead of **"rate of drug release"** in the Orange Book, unlike other transdermal drug products approved to date (Please see the email communication attached). Since generic drug products generally have different drug release mechanism, they may contain different amounts of drug content and still can be bioequivalent to the respective reference products in the rate and extent of absorption. Specifically, Mylan's Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch (ANDA 200910) contains different amounts of drug content, compared with Ortho-McNeil's Ortho Evra® patch, but it is bioequivalent to this reference listed drug (RLD) product. However, with the RLD labeling expressed in the amount of drug content and the "strength" of this RLD product listed in the Orange Book in the drug content amount that is different from Mylan's product, the Division of Bioequivalence is concerned that the therapeutic equivalence rating of Mylan's product, once approved, cannot be made appropriately in the Orange Book. Additional details of the issue related to the labeling recommendation by the OCP are below.

[1] DARRTS for ANDA 200910: DANDAMUDI, SUMAN 06/11/2013 N/A 06/11/2013 REV-BIOEQ-21(Primary Review) Original-1 (Not Applicable) Archive
[2] DARRTS for NDA 021180: WILLIAMSON, ZETA-MAE C 05/17/2006 N/A 05/17/2006 REV-RPM-05(General Review) Supplement-20 (Labeling) Archive

Labeling of the RLD vs. Labeling of Mylan's Product:

- The test product is a 14 cm^2 square patch with round corners that contains 4.86 mg norelgestromin and 0.53 mg ethinyl estradiol. Whereas, the RLD product, Ortho Evra® is a transdermal patch with a contact surface area of 20 cm^2 containing 6 mg norelgestromin and 0.75 mg ethinyl estradiol. Even though there are differences in the amounts of the active ingredients in the patch, both the generic and RLD products are designed to deliver to the systemic circulation, 0.15 mg norelgestromin and 0.02 mg ethinyl estradiol daily.

- Based on the review of the controlled correspondence 07-0512[3], the following are the general considerations for Transdermal Drug Delivery Systems: "*Transdermal products are considered as extended release drug products. The strength of a transdermal product is related to the amount of active ingredient that is delivered into the blood stream over a defined period of time, and not to amount of active ingredient initially in the patch. The amount of active ingredient in the generic product may differ from the amount of active ingredient in the RLD as long as the amount of the active ingredient absorbed into the blood stream in both products is equivalent. The difference in the amount of the active ingredient in the proposed generic compared to the RLD would have to be justified, regardless of equivalent pharmacokinetic and bioequivalence data".*

- Although there are differences in the formulation design and amounts of the active ingredients in the patch between the test and reference products, the fasting BE study (ORTH-0942) revealed that the 90% confidence intervals are with in the acceptance range of 80% and 125% for LnAUC0-t, LnAUCi and LnCmax. Thus the study demonstrated bioequivalence between the test and reference products[1].

- Currently, in the Orange Book, the strength of the RLD product (Ortho Evra®) is listed as 0.75 mg/6 mg (total amount of drug content) rather than 0.02 mg/0.15 mg/24 hrs (rate of drug release)[4].

- The above potency change in the Orange Book was made based on the recommendation by Office of Clinical Pharmacology (See below for email communication with Office of Clinical Pharmacology (OCP)) to reflect the current RLD labeling[5].

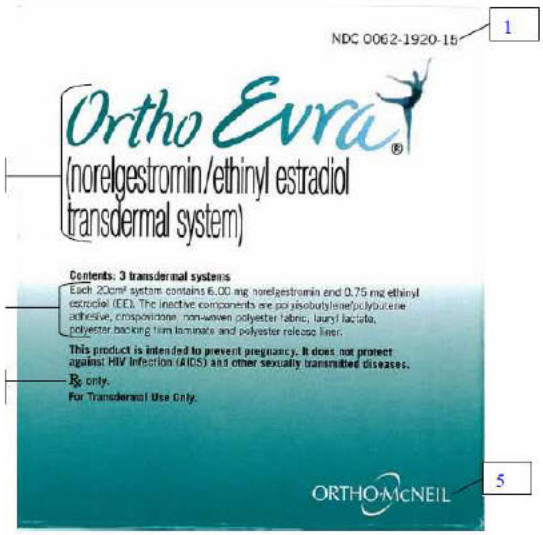
- In 2006, the reference drug product labeling has been revised to omit the "rate of drug release". From both the carton and pouch labeling, the following text has been deleted: **"releases 150 g of norelgestromin and 20 g of ethinyl estradiol to the blood stream for 24 hours"**[2]. The current RLD labeling states the following under Description section: ***"ORTHO EVRA is a combination transdermal contraceptive system with a contact surface area of 20 cm2. It contains 6 mg NGMN and 0.75 mg EE".***

---

[3] V:\firmsam\Mylan\Controls\070512C0407.doc
[4] Online-Orange Book (2013). http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm (Last accessed: 12/19/2013)
[5] http://dailymed nlm nih.gov/dailymed/lookup.cfm?setid=f8e8a69e-a018-469a-af56-e20f61fe4e06 (Last accessed: 12/19/2013)

- Therefore, both the generic and innovator's carton labeling now contains information only on the "total drug content" and not "release rate" (See below).

Comparison of Carton Labeling between the Generic and Innovator Products[6]

Innovator's Carton	Mylan's Draft Carton (b) (4)
Front of Carton 	(b) (4)

- In spite of the same release rate (0.15 mg/0.02 mg/24 hrs), the RLD and Mylan's products are not "equivalent" with respect to their amount-per-patch strengths as stated in the respective labels. The DBI requests the Division of Research and Standards (DRS) opinion on the appropriateness of the RLD labeling, and whether the RLD labeling should be changed to allow accurate therapeutic equivalence (TE) comparison between this innovator product and all generic versions of Norelgestromin and Ethinyl Estradiol Transdermal Patch as well as their subsequent TE rating in the Orange Book.

- Additionally, if DRS agree that the RLD labeling should be revised, please advice on the process by which such revision can take place.

[6] DARRTS for ANDA 200910: Firm's submission: 1 0000 12/31/2009 12/31/2009 New/ANDA Original-1 (Not Applicable) View EDR. Module 1.14.3. Listed Drug Labeling

Current Orange Book Listing of the RLD Product:

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N021180		Yes	ETHINYL ESTRADIOL; NORELGESTROMIN	FILM, EXTENDED RELEASE;TRANSDERMAL	0.75MG;6MG	ORTHO EVRA	JANSSEN PHARMS

Additional Information:

Section I: OGD History of this Drug Product

Currently there are no approved generic products of Norelgestromin and Ethinyl Estradiol Transdermal Film Extended Release listed in the Orange Book[4].

(b) (4)

Section II: Drug Product Information[4,5]

Test Product	Norelgestromin and Ethinyl Estradiol Transdermal Film Extended Release, 4.86 mg/0.53 mg (0.15 mg/0.02 mg/day)
Reference Product	Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal Film Extended Release, 6 mg/0.75 mg (0.15 mg/0.02 mg/day)
RLD Manufacturer	Ortho-McNeil Pharmaceutical, Inc.
NDA No.	021180
RLD Approval Date	November 20, 2001
Indication	Ortho Evra® is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception

PK/PD Information[5]

Bioavailability	Following a single application of the drug product, both Norelgestromin (NGMN) and Ethinyl Estradiol (EE) reach a plateau by approximately 48 hours. Pooled data from the 3 clinical studies have demonstrated that steady state is reached within 2 weeks of application. Absorption of NGMN and EE following application of ORTHO EVRA® to the buttock, upper outer arm, abdomen and upper torso (excluding breast) was examined. While absorption from the abdomen was slightly lower than from other sites, absorption from these anatomic sites was considered to be therapeutically equivalent. The absorption of NGMN and EE following application of ORTHO EVRA® was studied under conditions encountered in a health club (sauna, whirlpool and treadmill) and in a cold water bath. The results indicated that for NGMN there were no significant treatment effects on Css or AUC when compared to normal wear. For EE, increased exposures were observed due to sauna, whirlpool and treadmill. There was no significant effect of cold water on these parameters. Results from a study of consecutive ORTHO EVRA® wear for 7 days and 10 days indicated that serum concentrations of NGMN and EE dropped slightly during the first 6 hours after the patch replacement, and recovered within 12 hours. By Day 10 of patch administration, both NGMN and EE concentrations had decreased by approximately 25% when compared to Day 7 concentrations.
Food Effect	N/A
Tmax	48 hours
Metabolism	Since ORTHO EVRA® is applied transdermally, first-pass metabolism (via the gastrointestinal tract and/or liver) of NGMN and EE that would be expected with oral administration is avoided. Hepatic metabolism of NGMN occurs and metabolites include norgestrel (active) and various hydroxylated and conjugated metabolites. Ethinyl estradiol is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.
Excretion	Ethinyl estradiol is excreted in the urine primarily as glucuronide conjugates. The metabolites of NGMN and EE are eliminated by renal and fecal pathways.
Half-life	Half-lives of NGMN and EE are approximately 28 hours and 17 hours respectively.
Dosage and Administration	This system uses a 28-day (four-week) cycle. A new patch is applied each week for three weeks (21 total days). Week Four is patch-free. Every new patch should be applied on the same day of the week. This day is known as the "Patch Change Day." For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time. The ORTHO EVRA® patch should not be cut, damaged or altered in any way. If the ORTHO EVRA® patch is cut, damaged or altered in size, contraceptive efficacy may be impaired. On the day after Week Four ends a new four-week cycle is started by applying a new patch. Under no circumstances should there be more than a seven-day patch-free interval between dosing cycles.

Maximum Daily Dose	1 patch/week
Drug Specific Issues (if any)	**Black Box Warning:** **Cigarette Smoking and Serious Cardiovascular Risks:** Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, hormonal contraceptives, including ORTHO EVRA®, should not be used by women who are over 35 years of age and smoke. **Risk of Venous Thromboembolism:** The risk of venous thromboembolism (VTE) among women aged 15–44 who used the ORTHO EVRA® patch compared to women who used several different oral contraceptives was assessed in five U.S. epidemiologic studies using electronic healthcare claims data. The relative risk estimates ranged from 1.2 to 2.2; one of the studies found a statistically significant increased relative risk of VTE for current users of ORTHO EVRA®. **Pharmacokinetic Profile of Ethinyl Estradiol:** The pharmacokinetic (PK) profile for the ORTHO EVRA® patch is different from the PK profile for oral contraceptives in that it has higher steady state concentrations and lower peak concentrations. Area under the time-concentration curve (AUC) and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using ORTHO EVRA® compared with women using an oral contraceptive containing 35 mcg of EE. In contrast, peak concentrations for EE are approximately 25% lower in women using ORTHO EVRA®. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using ORTHO EVRA® compared with women using oral contraceptives containing 30–35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including venous thromboembolism.

Attachment:

E-mail Communication Regarding the Ortho Evra® Potency Change in Orange Book

---

From: Nguyen, Hoainhon T
Sent: Thursday, July 05, 2012 12:52 PM
To: Imam, Malik; Parise, Cecelia M; Conner, Dale P; Dandamudi, Suman; Smith, Glen J; Read, Shanaz; Tran, Trang
Cc: Ramson, Teresa; Nguyen, Hoainhon T
Subject: RE: Ortho Evra and Orange Book potency change

Unless I read the proposed labeling for ANDA 200910 incorrectly, this generic product does not contain the same total drug content, i.e., 0.53 mg EE/4.86 mg NGMN, versus 0.75 mg EE/6.00 mg NGMN in the RLD (Ortho Evra) product. With "different" strength(s), ANDA 200910 may have a problem referencing Ortho Evra? For transdermal patch products in general, it is not the total drug content that matters, but it is the rate that the drug is released from the patch. From the email exchange between Mary Ann and OCP below, it is not clear why the OCP recommended the change in the potency expression to the total drug content from the rate (which was originally approved for the NDA labeling).

Thanks,
Hoai

From: Imam, Malik
Sent: Thursday, July 05, 2012 11:35 AM
To: Parise, Cecelia M; Conner, Dale P; Nguyen, Hoainhon T; Dandamudi, Suman; Smith, Glen J; Read, Shanaz; Tran, Trang
Subject: RE: Ortho Evra and Orange Book potency change

For 200910 the rate is not mentioned on the box only the total drug content, so it should not be a problem.

Thanks,
Malik

From: Parise, Cecelia M
Sent: Thursday, July 05, 2012 9:14 AM
To: Conner, Dale P; Nguyen, Hoainhon T; Dandamudi, Suman; Smith, Glen J; Read, Shanaz; Imam, Malik; Tran, Trang
Subject: FW: Ortho Evra and Orange Book potency change

Folks,

Is this going to be a problem for ANDA 200910?

Thanks,

Cecelia

From: Holovac, Mary Ann
Sent: Thursday, July 05, 2012 8:53 AM
To: CDER-Orange Book Staff
Cc: Shimer, Martin; Parise, Cecelia M
Subject: FW: Ortho Evra and Orange Book potency change

For next update please make the following change to the potency display:

NDA 21180 Ortho Evra (EE + Norelgestromin)

FROM 0.02mg/24hr; 0.15mg/24hr TO 0.75mg; 6mg

Please note this is not a new potency but a change in potency display as the rate per hour was dropped from the labeling in 2005. The new potency will reflect the total drug content of the product.
(ANDA issues??)

Mary Ann

From: Yu, Chongwoo
Sent: Thursday, July 05, 2012 7:13 AM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

Mary Ann,

Thanks for your note and sorry for my late reply.
I was out of my office on Tuesday.

This is not for a new potency.
It is a labeling change of an existing product.

It is a long story but in simple terms, any reference of 0.02mg/24hr;0.15mg/24hr was removed from the product label sometime in 2006 and we would like to have the Orange Book reflect that.

I hope this answers your question. Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: Holovac, Mary Ann
Sent: Monday, July 02, 2012 3:38 PM
To: Yu, Chongwoo
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

First I would like to confirm that this is a labeling change of an existing product and not a new potency. Most transdermal products are listed in the orange book as dose per time period so this is an odd type of change that could possibly present challenges for the generics. What prompted this change?
Thanks.

From: Yu, Chongwoo
Sent: Monday, July 02, 2012 3:00 PM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

Yes… but the orange book still has the nominal delivery rate (0.02MG/24HR;0.15MG/24HR) on it which we would also like to correct to the total drug content.

Can you please give us a hand on this and let me know what is involved in this process? Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: Holovac, Mary Ann
Sent: Monday, July 02, 2012 2:48 PM
To: Yu, Chongwoo
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

Hi,
I'm back in the office, was on leave.
Looking at the latest labeling on the drugs@fda website it appears the product is now labeled with total drug content vs a dosage per hour?
Mary Ann

From: Yu, Chongwoo
Sent: Thursday, June 28, 2012 6:16 PM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book
Importance: High

Mary Ann,

Can you please give us a hand on this?
Your help is greatly appreciated. Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719

Email: chongwoo.yu@fda.hhs.gov

From: Yu, Chongwoo
Sent: Friday, June 15, 2012 9:46 AM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

Mary Ann,

I am the current Clinical Pharmacology reviewer of Ortho Evra and just want to follow up with the email below as we have not heard back from you. Your help and input would be greatly appreciated. Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: Kim, Myong-Jin
Sent: Thursday, June 07, 2012 12:15 PM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Yu, Chongwoo; Tran, Doanh
Subject: Ortho Evra and Orange Book

Hi Mary Ann,

I left you a voice message regarding Ortho Evra and Orange Book yesterday afternoon.

Currently, the Orange Book lists Ortho Evra's strength as 0.02mg/24hr;0.15mg/24hr. However, any reference of 0.02mg/24hr;0.15mg/24hr was removed from the product label sometime in 2006 and we would like to have the Orange Book reflect that.

So, my question to you is what is involved to revise the Orange Book and how soon does it get updated? Once the ClinPharm team comes up with our proposed strength for this product and convey this to your group, does the Orange Book get updated soon (daily, weekly, monthly)? Do we work with you directly or someone from your group?

Thanks in advance,

MJ

Clinical Pharmacology Team Leader
Office of Clinical Pharmacology

ATTACHMENT II: DISCUSSION BETWEEN OGD AND OND CONCERNING THE ISSUES RELATED TO THE CURRENT RLD LABELING

From: Nguyen, Hoainhon T
To: Chuh, Esther; West, Robert L
Cc: Patel, Nitin K. (CDER/OGD); Dandamudi, Suman; Conner, Dale P; Basi, Surjit; Parise, Cecelia M; Imam, Malik;
Nguyen, Hoainhon T
Subject: RE: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System) - consult to science team
Date: Friday, January 31, 2014 12:17:00 PM
Attachments: RE Ortho Evra Delivery Rate - Implications on Current Supplement and ANDA 200910.msg

Esther,

Please see the email attached for the update on the latest discussion/decision related to Ortho Evra and the approval of ANDA 200910. Based on the unresolved deficiencies related to the pending supplement of the RLD application (NDA 21180), it is not certain how they would affect the decision of approval of the ANDA.

However, DBI would like to clarify the following:
1. Currently, there is NO bioequivalence issue related to this ANDA. We sent a consult to the Science Staff about the discrepancy between the RLD and ANDA labeling just to make sure the issue is addressed, as it appeared to us, at the time we completed our BE review, that no one from OGD/OND seemed to be concerned with this discrepancy.
2. The issue is actually a pharmaceutical equivalence and labeling issue to be addressed at the Office level by disciplines other than bioequivalence.
3. DBI will withdraw the consult sent to the Science Staff to make it clear that the pending issue is not a bioequivalence issue.

We will provide any technical assistance needed in this matter, but DBI cannot address the pharmaceutical equivalence/labeling issue at hand.

Thanks,
Hoai

From: Chuh, Esther
Sent: Friday, January 31, 2014 11:41 AM
To: Nguyen, Hoainhon T; West, Robert L
Cc: Patel, Nitin K. (CDER/OGD); Dandamudi, Suman; Conner, Dale P; Basi, Surjit; Parise, Cecelia M; Imam, Malik
Subject: RE: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System) - consult to science team
Hello Hoai,
I would like to follow up on the meeting held on Tuesday on the labeling issue.
I am interested in knowing how this will impact the timeline for the approval of the ANDA.
Thank you,
Esther
From: Nguyen, Hoainhon T
Sent: Thursday, January 23, 2014 12:50 PM
To: Chuh, Esther; West, Robert L
Cc: Patel, Nitin K. (CDER/OGD); Lionberger, Robert; Dandamudi, Suman; Conner, Dale P; Basi, Surjit; Nguyen, Hoainhon T; Parise, Cecelia M; Imam, Malik
Subject: RE: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System) - consult to

science team

Esther,

There is a meeting on the labeling issue for this drug product next Tuesday. Please see attached. With respect to the awareness of the labeling group on this issue, please see my email attached, which showed that Malik from the labeling group was in the email conversation. Cecelia first raised the issue in 2012, and Mary Ann from the Orange Book (OB) was aware of the impact on ANDAs as well. However, it is not clear what has been done since that time. Recently DBI was wrapping up its BE/dissolution review and found out that the OB had changed the strength of the RLD to be expressed in amount and not rate, so it consulted the Science Staff to make sure that this issue is being addressed. DBI was not aware of any target approval for this drug product at any time during our review.

Thanks,
Hoai

From: Chuh, Esther
Sent: Thursday, January 23, 2014 11:55 AM
To: Nguyen, Hoainhon T; West, Robert L
Cc: Patel, Nitin K. (CDER/OGD); Lionberger, Robert; Dandamudi, Suman; Conner, Dale P; Basi, Surjit
Subject: RE: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System) - consult to science team

Hi Hoai,

Does this consult have any impact on the bio review that is currently acceptable? I am trying to find out how this newly identified issue will impact the review time line for the approval of the ANDA (currently – we are targeting for approval in Feb).
For my understanding, what is the bio involvement with this labeling issue? Is labeling aware of this? I am thinking revision to labeling may be needed based on the outcome of the consult.
Thank you,
Esther

From: Nguyen, Hoainhon T
Sent: Friday, January 17, 2014 12:36 PM
To: West, Robert L; Chuh, Esther
Cc: Patel, Nitin K. (CDER/OGD); Lionberger, Robert; Dandamudi, Suman; Nguyen, Hoainhon T; Conner, Dale P
Subject: RE: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System) - consult to science team

Bob,
As of yesterday, we understand that Rob's group and a working group in OND are currently working on resolving the labeling issue related to this drug product. Without the labeling issue (related to using rate vs. amount to express product strengths) being clarified, there may be a problem with approval of generic products.
Thanks,
Hoai

From: West, Robert L
Sent: Friday, January 17, 2014 11:32 AM
To: Chuh, Esther
Cc: Patel, Nitin K. (CDER/OGD); Nguyen, Hoainhon T; Lionberger, Robert
Subject: FW: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System) - consult to

science team

Esther/Nitin:
I missed much of the discussion a few weeks ago between OGD and Mylan. Mylan is referring to a meeting held on September 24, 2013 with the agency and to recent telephone conversations that included Cook regarding the alternative statistical analysis issue.
I also see that DBE recently issued a consult to the OGD Science Team.
Can I have an interim update on where we currently are?
Thank you,
Bob

From: Wayne.Talton@mylanlabs.com [mailto:Wayne.Talton@mylanlabs.com]
Sent: Friday, January 17, 2014 8:38 AM
To: West, Robert L
Subject: ANDA 200910 (Norelgestromin and Ethinyl Estradiol Transdermal System)

Hi Bob
As we discussed this morning, I am providing you with some summary background information on a key first generic product, Norelgestromin and Ethinyl Estradiol Transdermal System (ANDA 200910), which has been pending approval at the Agency following 48 months of review. No generic alternative currently exists for this important women's health product and patients pay an average of $80 or more per monthly prescription of Ortho-Evra according to IMS. There are no legal barriers preventing Mylan from launching our product immediately upon ANDA approval.
Product: Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 hours and 0.02 mg/24 hours
ANDA Number: 200910
RLD: Ortho Evra
Original Submission Date: December 31, 2009
Time in Review: 48 months
Regulatory Status: Complete Response Amendment Submitted August 20, 2013; Labeling Amendment Submitted September 18, 2013 (due to RLD Update); Drug Release Amendment Submitted October 11, 2013.
Legal Status: PIV filed with no suit. The first to file applicant withdrew their ANDA per FDA's PIV List so Mylan's product represents a First Generic
FDA Feedback on the Regulatory Status: Application pending review however our request for expedited review has been granted.
Commercial Readiness: Mylan has product readily available in our distribution center for immediate distribution upon the receipt of approval.
Primary Issue Rate Limiting for Approval: Mylan proposed an alternative statistical analysis (to evaluate irritation/adhesion) from that published in the bioequivalence guidance since the model does not work well when both the test and reference product perform wells. We met with the Agency on this matter on September 24, 2013 and they acknowledged the issue.
I look forward to receiving further on the approval status of our application.
Wayne
Mylan
304.554.6551

From: Strasinger, Caroline
Sent: Thursday, January 30, 2014 11:52 AM
To: Joffe, Hylton; Bina, Christine; Soule, Lisa; Duffy, Eric P; Ghosh, Tapash; Kitchens, Kelly; Jennings, Kerri-Ann; Williamson, Charlene; Yu, Chongwoo; Davis, Daniel; Abraham, Ciby
Cc: Ghosh, Priyanka *; Newman, Bryan *; Dandamudi, Suman; Kim, Myong-Jin; Gassman, Audrey; Li, Guohua; Braddy, April; Nguyen, Hoainhon T; Cai, Bing; Rege, Bhagwant; Li, Xihao; Ahn, Hae Young; Bashaw, Edward D; Conner, Dale P; Stier, Ethan; Lionberger, Robert; Huang, Yih Chain
Subject: RE: Ortho Evra Delivery Rate - Implications on Current Supplement and ANDA 200910

Hello,
I believe the meeting was productive in the very least at orientating everyone with all the moving parts between the two applications. At this time our rough plan is as follows:
1) As MJ pointed out, Jansen did not perform an actual irritation/sensitization study and that was one of the CR items in the first CR letter. The company instead attempted to justify the lack of study with adverse events table and a paragraph. We sent a consult to Clin/pharm for their comments on the justification, and I believe this will result in a second CR letter.

a. All other PIB adhesive change products (e.g. Nicoderm) have performed irritation/sensitization studies as part of their BE study, and I believe it is what is required to establish BE of a generic transdermal product, so it isn't an unreasonable claim, despite their argument that very few irritations showed up in the AE.
b. We offered at least once (maybe more) to review their BE protocol, this offer was captured in the Advice Letter (04/23/2013) in Darrts. They obviously never took us up on that offer, had they, we would have advised them to perform an irritation study among other things (we now know they didn't because they had already conducted the studies in 2008). I plan to put a memo in Darrts regarding this bullet point this week.

2) With a CR on lack of irritation/sensitization study, we will also tie in the request for the strength to be presented as a rate and that this rate should be supported with PK data from a new study which should include an IV infusion arm in order to obtain a clearance with the current validated analytical methods. Additionally, residual drug analysis will need to be performed on the used samples to further support the rate.

a. This step still needs work, and will need some collaborative language I am sure, but that is the rough idea.
b. We all agree that the Orange Book/strength will have to change and we all agree that that change should not just revert back to 20/150

3) What to do with Mylan's generic product is still a bit of a gray area, I believe (and OGD correct me if I am not summarizing correctly)

a. The labels don't match, but should it be determined the Mylan product can still be approved (with slightly different labels?), the Orange Book will halt them because there would have to be 2 different listings of strength in the Orange Book, which will cause prescriber confusion and would be precedence setting (in a bad way)

b. With a CR issued to Janssen, I believe a company has 1 year to respond so it could be at least a year before we could get the Orange Book changed, however, this doesn't stop Mylan from wondering why it doesn't just get changed back to 20/150.

Everyone who attended via donut fueled presence or via phone please feel free to adjust, add or comment on the above summary. And thank you again to all who participated and who are continuing to work on this tricky situation.
Caroline

From: Joffe, Hylton
Sent: Thursday, January 30, 2014 7:51 AM
To: Bina, Christine; Strasinger, Caroline; Soule, Lisa; Duffy, Eric P; Ghosh, Tapash; Kitchens, Kelly; Jennings, Kerri-Ann;
Williamson, Charlene; Yu, Chongwoo; Davis, Daniel; Abraham, Ciby
Cc: Ghosh, Priyanka *; Newman, Bryan *; Dandamudi, Suman; Kim, Myong-Jin; Gassman, Audrey; Li, Guohua; Braddy,
April; Nguyen, Hoainhon T; Cai, Bing; Rege, Bhagwant; Li, Xihao; Ahn, Hae Young; Bashaw, Edward D; Conner, Dale P;
Stier, Ethan; Lionberger, Robert; Huang, Yih Chain
Subject: RE: Ortho Evra Delivery Rate - Implications on Current Supplement and ANDA 200910
Sorry I had to leave before the meeting ended. Did we reach alignment on the path forward?
Hylton

From: Bina, Christine
Sent: Wednesday, January 29, 2014 5:23 PM
To: Strasinger, Caroline; Soule, Lisa; Duffy, Eric P; Ghosh, Tapash; Kitchens, Kelly; Jennings, Kerri-Ann; Williamson,
Charlene; Yu, Chongwoo; Davis, Daniel; Abraham, Ciby
Cc: Ghosh, Priyanka *; Newman, Bryan *; Dandamudi, Suman; Kim, Myong-Jin; Gassman, Audrey; Joffe, Hylton; Li,
Guohua; Braddy, April; Nguyen, Hoainhon T; Cai, Bing; Rege, Bhagwant; Li, Xihao; Ahn, Hae Young; Bashaw, Edward D;
Conner, Dale P; Stier, Ethan; Lionberger, Robert; Huang, Yih Chain
Subject: RE: Ortho Evra Delivery Rate - Implications on Current Supplement and ANDA 200910

Just as a follow up to yesterday's meeting the medical necessity determination has been completed and Ortho Evra was found to be not medically necessary noting there are many effective alternative choices for contraception. Additionally, DSS has not yet been notified by the company of a shortage.
Thanks,
Christine

-----Original Appointment-----
From: Strasinger, Caroline
Sent: Friday, January 17, 2014 12:13 PM
To: Strasinger, Caroline; Soule, Lisa; Duffy, Eric P; Ghosh, Tapash; Kitchens, Kelly; Jennings, Kerri-Ann; Williamson, Charlene; Yu, Chongwoo; Davis, Daniel; Abraham, Ciby; Bina, Christine
Cc: Ghosh, Priyanka *; Newman, Bryan *; Dandamudi, Suman; Kim, Myong-Jin; Gassman, Audrey; Joffe, Hylton;
Li, Guohua; Braddy, April; Nguyen, Hoainhon T; Cai, Bing; Rege, Bhagwant; Li, Xihao; Ahn, Hae Young; Bashaw,
Edward D; Conner, Dale P; Stier, Ethan; Lionberger, Robert; Huang, Yih Chain
Subject: Ortho Evra Delivery Rate - Implications on Current Supplement and ANDA 200910
When: Tuesday, January 28, 2014 9:00 AM-10:30 AM (UTC-05:00) Eastern Time (US & Canada).

Where: CDER WO 1537 conf rm Bldg21 - AR
3

Updated with Call-in, Adobe Connect, and Preliminary Information:

Additional information will be presented at the meeting but I wanted to provide this preliminary Slide Deck in
advance:

Call-In Information:
Number: 877-693-8068
Participant Passcode: 22442381
Please use the following link to access slides that will be discussed during the meeting:
https://collaboration.fda.gov/transdermalwg/
<< File: OE.ppt >> << File: OE CR letter.pdf >>

This meeting is being held to discuss the delivery rate of Ortho Evra. Ortho Evra is facing a drug shortage if we do not approve the current supplement for adhesive change. With our original CR the question of delivery rate and strength presentation has resurfaced. Additionally, Mylan is seeking approval for a generic product and a request/consultation to change the orange book back to the original strength presentation is currently in progress from OGD.

With that said, I have information to share regarding the delivery rate of Ortho Evra from the Mylan application which indicates that the J&J in vivo delivery rate of OE of 20/150 ug/day is wrong (most on this email are well aware of that fact), however, now we have some potential PK proof and actual estimates that the delivery rate is more along the lines of (b) (4) ug/day, albeit from a generic application that we can't share with the innovator.

This meeting is being held to strategize our next move on OE and then briefly the implications on the Generic. It appears Mylan has successfully matched OE but at a roughly 3 times the delivery of what J&J says their rate is.

It is confusing, I know. I will provide slides (and call-in information/adobe connect) at a later date that may help with clarity, but at this time I just wanted to get it on the calendar. I have included a large group of OCP, OND, ONDQA, and OGD, however, please forward the invite to those who may also need the information or be part of the discussion.

Thank you,
Caroline

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

/s/

SUMAN DANDAMUDI
02/03/2014

UTPAL M MUNSHI
02/03/2014

HOAINHON N CARAMENICO
02/04/2014

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: [redacted] (b) (4) **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
Mobile: (b) (6)

APPEARS THIS WAY ON ORIGINAL

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

/s/

IAIN MARGAND
02/04/2014

To:	Robert Lionberger, Ph.D., Acting Director for Regulatory Science, Division of Research and Standards, Office of Generic Drugs
From:	Suman Dandamudi, Reviewer, Team 8, Division of Bioequivalence I, Office of Generic Drugs
Through:	Hoainhon Nguyen, Deputy Director, Division of Bioequivalence I (DBI), Office of Generic Drugs
Re:	Request opinion on the appropriateness of the change in the labeling (from "rate of drug release" to "amount of drug content") of the reference product, Ortho-McNeil's Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch, with respect to determination of the therapeutic equivalence for a generic product, Mylan's Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch (ANDA 200910)

Introduction:

Mylan Technologies submitted ANDA 200910 which contains the results of three studies, (1) a fasting bioequivalence (BE) study with a pharmacokinetic (PK) endpoint, comparing the test product Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch to the corresponding reference product, Ortho-McNeil's Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal System, 6 mg/0.75 mg/Patch; (2) Adhesion study (Orth-Cln-09198); and (3) Sensitization/Irritation study (Orth-Cln-0943). The Division of Bioequivalence reviews the BE study, and the Division of Clinical Review reviews the adhesion and sensitization/irritation studies.

The Division of Bioequivalence found the fasting BE study to be acceptable[1].

Based on the OCP recommendation[2], the potency of Ortho-McNeil's Ortho Evra® should be expressed as the **"amount of drug content"** instead of **"rate of drug release"** in the Orange Book, unlike other transdermal drug products approved to date (Please see the email communication attached). Since generic drug products generally have different drug release mechanism, they may contain different amounts of drug content and still can be bioequivalent to the respective reference products in the rate and extent of absorption. Specifically, Mylan's Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch (ANDA 200910) contains different amounts of drug content, compared with Ortho-McNeil's Ortho Evra® patch, but it is bioequivalent to this reference listed drug (RLD) product. However, with the RLD labeling expressed in the amount of drug content and the "strength" of this RLD product listed in the Orange Book in the drug content amount that is different from Mylan's product, the Division of Bioequivalence is concerned that the therapeutic equivalence rating of Mylan's product, once approved, cannot be made appropriately in the Orange Book. Additional details of the issue related to the labeling recommendation by the OCP are below.

[1] DARRTS for ANDA 200910: DANDAMUDI, SUMAN 06/11/2013 N/A 06/11/2013 REV-BIOEQ-21(Primary Review) Original-1 (Not Applicable) Archive
[2] DARRTS for NDA 021180: WILLIAMSON, ZETA-MAE C 05/17/2006 N/A 05/17/2006 REV-RPM-05(General Review) Supplement-20 (Labeling) Archive

Labeling of the RLD vs. Labeling of Mylan's Product:

- The test product is a 14 cm^2 square patch with round corners that contains 4.86 mg norelgestromin and 0.53 mg ethinyl estradiol. Whereas, the RLD product, Ortho Evra® is a transdermal patch with a contact surface area of 20 cm^2 containing 6 mg norelgestromin and 0.75 mg ethinyl estradiol. Even though there are differences in the amounts of the active ingredients in the patch, both the generic and RLD products are designed to deliver to the systemic circulation, 0.15 mg norelgestromin and 0.02 mg ethinyl estradiol daily.

- Based on the review of the controlled correspondence 07-0512[3], the following are the general considerations for Transdermal Drug Delivery Systems: "*Transdermal products are considered as extended release drug products. The strength of a transdermal product is related to the amount of active ingredient that is delivered into the blood stream over a defined period of time, and not to amount of active ingredient initially in the patch. The amount of active ingredient in the generic product may differ from the amount of active ingredient in the RLD as long as the amount of the active ingredient absorbed into the blood stream in both products is equivalent. The difference in the amount of the active ingredient in the proposed generic compared to the RLD would have to be justified, regardless of equivalent pharmacokinetic and bioequivalence data".*

- Although there are differences in the formulation design and amounts of the active ingredients in the patch between the test and reference products, the fasting BE study (ORTH-0942) revealed that the 90% confidence intervals are with in the acceptance range of 80% and 125% for LnAUC0-t, LnAUCi and LnCmax. Thus the study demonstrated bioequivalence between the test and reference products[1].

- Currently, in the Orange Book, the strength of the RLD product (Ortho Evra®) is listed as 0.75 mg/6 mg (total amount of drug content) rather than 0.02 mg/0.15 mg/24 hrs (rate of drug release)[4].

- The above potency change in the Orange Book was made based on the recommendation by Office of Clinical Pharmacology (See below for email communication with Office of Clinical Pharmacology (OCP)) to reflect the current RLD labeling[5].

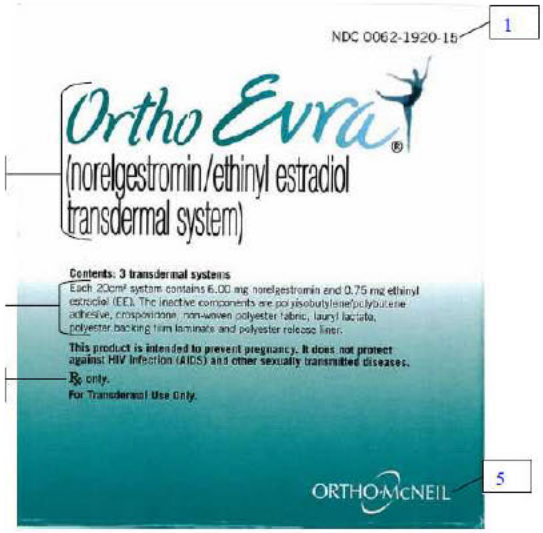
- In 2006, the reference drug product labeling has been revised to omit the "rate of drug release". From both the carton and pouch labeling, the following text has been deleted: **"releases 150 g of norelgestromin and 20 g of ethinyl estradiol to the blood stream for 24 hours"**[2]. The current RLD labeling states the following under Description section: ***"ORTHO EVRA is a combination transdermal contraceptive system with a contact surface area of 20 cm2. It contains 6 mg NGMN and 0.75 mg EE".***

---

[3] V:\firmsam\Mylan\Controls\070512C0407.doc
[4] Online-Orange Book (2013). http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm (Last accessed: 12/19/2013)
[5] http://dailymed nlm nih.gov/dailymed/lookup.cfm?setid=f8e8a69e-a018-469a-af56-e20f61fe4e06 (Last accessed: 12/19/2013)

- Therefore, both the generic and innovator's carton labeling now contains information only on the "total drug content" and not "release rate" (See below).

Comparison of Carton Labeling between the Generic and Innovator Products[6]

Innovator's Carton	Mylan's Draft Carton (b) (4)
Front of Carton 	(b) (4)

- Inspite of the same release rate (0.15 mg/0.02 mg/24 hrs), the RLD and Mylan's products are not "equivalent" with respect to their amount-per-patch strengths as stated in the respective labels. The DBI requests the Division of Research and Standards (DRS) opinion on the appropriateness of the RLD labeling, and whether the RLD labeling should be changed to allow accurate therapeutic equivalence (TE) comparison between this innovator product and all generic versions of Norelgestromin and Ethinyl Estradiol Transdermal Patch as well as their subsequent TE rating in the Orange Book.

- Additionally, if DRS agree that the RLD labeling should be revised, please advice on the process by which such revision can take place.

[6] DARRTS for ANDA 200910: Firm's submission: 1 0000 12/31/2009 12/31/2009 New/ANDA Original-1 (Not Applicable) View EDR. Module 1.14.3. Listed Drug Labeling

Current Orange Book Listing of the RLD Product:

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N021180		Yes	ETHINYL ESTRADIOL; NORELGESTROMIN	FILM, EXTENDED RELEASE;TRANSDERMAL	0.75MG;6MG	ORTHO EVRA	JANSSEN PHARMS

Additional Information:

Section I: OGD History of this Drug Product

Currently there are no approved generic products of Norelgestromin and Ethinyl Estradiol Transdermal Film Extended Release listed in the Orange Book[4].

(b) (4)

Section II: Drug Product Information[4,5]

Test Product	Norelgestromin and Ethinyl Estradiol Transdermal Film Extended Release, 4.86 mg/0.53 mg (0.15 mg/0.02 mg/day)
Reference Product	Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal Film Extended Release, 6 mg/0.75 mg (0.15 mg/0.02 mg/day)
RLD Manufacturer	Ortho-McNeil Pharmaceutical, Inc.
NDA No.	021180
RLD Approval Date	November 20, 2001
Indication	Ortho Evra® is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception

PK/PD Information[5]

Bioavailability	Following a single application of the drug product, both Norelgestromin (NGMN) and Ethinyl Estradiol (EE) reach a plateau by approximately 48 hours. Pooled data from the 3 clinical studies have demonstrated that steady state is reached within 2 weeks of application. Absorption of NGMN and EE following application of ORTHO EVRA® to the buttock, upper outer arm, abdomen and upper torso (excluding breast) was examined. While absorption from the abdomen was slightly lower than from other sites, absorption from these anatomic sites was considered to be therapeutically equivalent. The absorption of NGMN and EE following application of ORTHO EVRA® was studied under conditions encountered in a health club (sauna, whirlpool and treadmill) and in a cold water bath. The results indicated that for NGMN there were no significant treatment effects on Css or AUC when compared to normal wear. For EE, increased exposures were observed due to sauna, whirlpool and treadmill. There was no significant effect of cold water on these parameters. Results from a study of consecutive ORTHO EVRA® wear for 7 days and 10 days indicated that serum concentrations of NGMN and EE dropped slightly during the first 6 hours after the patch replacement, and recovered within 12 hours. By Day 10 of patch administration, both NGMN and EE concentrations had decreased by approximately 25% when compared to Day 7 concentrations.
Food Effect	N/A
Tmax	48 hours
Metabolism	Since ORTHO EVRA® is applied transdermally, first-pass metabolism (via the gastrointestinal tract and/or liver) of NGMN and EE that would be expected with oral administration is avoided. Hepatic metabolism of NGMN occurs and metabolites include norgestrel (active) and various hydroxylated and conjugated metabolites. Ethinyl estradiol is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.
Excretion	Ethinyl estradiol is excreted in the urine primarily as glucuronide conjugates. The metabolites of NGMN and EE are eliminated by renal and fecal pathways.
Half-life	Half-lives of NGMN and EE are approximately 28 hours and 17 hours respectively.
Dosage and Administration	This system uses a 28-day (four-week) cycle. A new patch is applied each week for three weeks (21 total days). Week Four is patch-free. Every new patch should be applied on the same day of the week. This day is known as the "Patch Change Day." For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time. The ORTHO EVRA® patch should not be cut, damaged or altered in any way. If the ORTHO EVRA® patch is cut, damaged or altered in size, contraceptive efficacy may be impaired. On the day after Week Four ends a new four-week cycle is started by applying a new patch. Under no circumstances should there be more than a seven-day patch-free interval between dosing cycles.

Maximum Daily Dose	1 patch/week
Drug Specific Issues (if any)	**Black Box Warning:** **Cigarette Smoking and Serious Cardiovascular Risks:** Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, hormonal contraceptives, including ORTHO EVRA®, should not be used by women who are over 35 years of age and smoke. **Risk of Venous Thromboembolism:** The risk of venous thromboembolism (VTE) among women aged 15–44 who used the ORTHO EVRA® patch compared to women who used several different oral contraceptives was assessed in five U.S. epidemiologic studies using electronic healthcare claims data. The relative risk estimates ranged from 1.2 to 2.2; one of the studies found a statistically significant increased relative risk of VTE for current users of ORTHO EVRA®. **Pharmacokinetic Profile of Ethinyl Estradiol:** The pharmacokinetic (PK) profile for the ORTHO EVRA® patch is different from the PK profile for oral contraceptives in that it has higher steady state concentrations and lower peak concentrations. Area under the time-concentration curve (AUC) and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using ORTHO EVRA® compared with women using an oral contraceptive containing 35 mcg of EE. In contrast, peak concentrations for EE are approximately 25% lower in women using ORTHO EVRA®. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using ORTHO EVRA® compared with women using oral contraceptives containing 30–35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including venous thromboembolism.

Attachment:

E-mail Communication Regarding the Ortho Evra® Potency Change in Orange Book

---

From: Nguyen, Hoainhon T
Sent: Thursday, July 05, 2012 12:52 PM
To: Imam, Malik; Parise, Cecelia M; Conner, Dale P; Dandamudi, Suman; Smith, Glen J; Read, Shanaz; Tran, Trang
Cc: Ramson, Teresa; Nguyen, Hoainhon T
Subject: RE: Ortho Evra and Orange Book potency change

Unless I read the proposed labeling for ANDA 200910 incorrectly, this generic product does not contain the same total drug content, i.e., 0.53 mg EE/4.86 mg NGMN, versus 0.75 mg EE/6.00 mg NGMN in the RLD (Ortho Evra) product. With "different" strength(s), ANDA 200910 may have a problem referencing Ortho Evra? For transdermal patch products in general, it is not the total drug content that matters, but it is the rate that the drug is released from the patch. From the email exchange between Mary Ann and OCP below, it is not clear why the OCP recommended the change in the potency expression to the total drug content from the rate (which was originally approved for the NDA labeling).

Thanks,
Hoai

From: Imam, Malik
Sent: Thursday, July 05, 2012 11:35 AM
To: Parise, Cecelia M; Conner, Dale P; Nguyen, Hoainhon T; Dandamudi, Suman; Smith, Glen J; Read, Shanaz; Tran, Trang
Subject: RE: Ortho Evra and Orange Book potency change

For 200910 the rate is not mentioned on the box only the total drug content, so it should not be a problem.

Thanks,
Malik

From: Parise, Cecelia M
Sent: Thursday, July 05, 2012 9:14 AM
To: Conner, Dale P; Nguyen, Hoainhon T; Dandamudi, Suman; Smith, Glen J; Read, Shanaz; Imam, Malik; Tran, Trang
Subject: FW: Ortho Evra and Orange Book potency change

Folks,

Is this going to be a problem for ANDA 200910?

Thanks,

Cecelia

From: Holovac, Mary Ann
Sent: Thursday, July 05, 2012 8:53 AM
To: CDER-Orange Book Staff
Cc: Shimer, Martin; Parise, Cecelia M
Subject: FW: Ortho Evra and Orange Book potency change

For next update please make the following change to the potency display:

NDA 21180 Ortho Evra (EE + Norelgestromin)

FROM 0.02mg/24hr; 0.15mg/24hr TO 0.75mg; 6mg

Please note this is not a new potency but a change in potency display as the rate per hour was dropped from the labeling in 2005. The new potency will reflect the total drug content of the product.
(ANDA issues??)

Mary Ann

From: Yu, Chongwoo
Sent: Thursday, July 05, 2012 7:13 AM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

Mary Ann,

Thanks for your note and sorry for my late reply.
I was out of my office on Tuesday.

This is not for a new potency.
It is a labeling change of an existing product.

It is a long story but in simple terms, any reference of 0.02mg/24hr;0.15mg/24hr was removed from the product label sometime in 2006 and we would like to have the Orange Book reflect that.

I hope this answers your question. Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: Holovac, Mary Ann
Sent: Monday, July 02, 2012 3:38 PM
To: Yu, Chongwoo
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

First I would like to confirm that this is a labeling change of an existing product and not a new potency. Most transdermal products are listed in the orange book as dose per time period so this is an odd type of change that could possibly present challenges for the generics. What prompted this change?
Thanks.

From: Yu, Chongwoo
Sent: Monday, July 02, 2012 3:00 PM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

Yes… but the orange book still has the nominal delivery rate (0.02MG/24HR;0.15MG/24HR) on it which we would also like to correct to the total drug content.

Can you please give us a hand on this and let me know what is involved in this process? Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: Holovac, Mary Ann
Sent: Monday, July 02, 2012 2:48 PM
To: Yu, Chongwoo
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

Hi,
I'm back in the office, was on leave.
Looking at the latest labeling on the drugs@fda website it appears the product is now labeled with total drug content vs a dosage per hour?
Mary Ann

From: Yu, Chongwoo
Sent: Thursday, June 28, 2012 6:16 PM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book
Importance: High

Mary Ann,

Can you please give us a hand on this?
Your help is greatly appreciated. Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719

Email: chongwoo.yu@fda.hhs.gov

From: Yu, Chongwoo
Sent: Friday, June 15, 2012 9:46 AM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Kim, Myong-Jin; Tran, Doanh
Subject: RE: Ortho Evra and Orange Book

Mary Ann,

I am the current Clinical Pharmacology reviewer of Ortho Evra and just want to follow up with the email below as we have not heard back from you. Your help and input would be greatly appreciated. Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: Kim, Myong-Jin
Sent: Thursday, June 07, 2012 12:15 PM
To: Holovac, Mary Ann
Cc: Williamson, Charlene; Soule, Lisa; Yu, Chongwoo; Tran, Doanh
Subject: Ortho Evra and Orange Book

Hi Mary Ann,

I left you a voice message regarding Ortho Evra and Orange Book yesterday afternoon.

Currently, the Orange Book lists Ortho Evra's strength as 0.02mg/24hr;0.15mg/24hr. However, any reference of 0.02mg/24hr;0.15mg/24hr was removed from the product label sometime in 2006 and we would like to have the Orange Book reflect that.

So, my question to you is what is involved to revise the Orange Book and how soon does it get updated? Once the ClinPharm team comes up with our proposed strength for this product and convey this to your group, does the Orange Book get updated soon (daily, weekly, monthly)? Do we work with you directly or someone from your group?

Thanks in advance,

MJ

Clinical Pharmacology Team Leader
Office of Clinical Pharmacology

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

/s/

SUMAN DANDAMUDI
12/23/2013

APRIL C BRADDY
12/23/2013

HOAINHON N CARAMENICO
12/23/2013

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

APPEARS THIS WAY ON ORIGINAL

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)

Gloria McHenry, MPM, Project Manager, Global Regulatory
Alison Pangilinan, MBA, Program Director, R&D
(b) (4)
Marcie McClintic-Coates, JD, MBA, Global Regulatory Affairs
(b) (4)

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, Dr. Koch, 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

Following this page, 35 Pages Withheld in Full as (b)(4)

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

/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)

Per Jason's recommendation, I have cc'ed Keith, Marty and Dave on this email for their input.

Thank you,
Esther

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

/s/

EUNJUNG E CHUH
12/13/2013

ROBERT L WEST
12/13/2013
Deputy Director, Office of Generic Drugs

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 200910

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, Vice President, RA FAX: (304) 285-6407

FROM: Esther Chuh FDA CONTACT PHONE: 240-276-9663

Dear Sir:

This communication is in reference to your abbreviated new drug application (ANDA) dated December 31, 2009, submitted pursuant to 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.

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, Esther Chuh, at 240-276-9663.

We have completed our review, as amended, and have the following comments:

PRODUCT QUALITY

1. (b) (4)

2.

Sincerely yours,

{See appended electronic signature page}

Andre S. Raw, Ph.D.
Director
Division of Chemistry I
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/

BHAGWANT D REGE
11/26/2013

BIOEQUIVALENCE AMENDMENT

ANDA 200910

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: Joseph J. Sobecki FAX: (304) 285-6407

FROM: Esther Chuh FDA CONTACT PHONE: (240) 276-8530

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on December 31, 2009 pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch.

Reference is also made to your amendments dated October 8, 2010 and August 20, 2013.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ page(s). 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: 200910

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal Patch, 4.86 mg/0.53 mg/Patch

The Division of Bioequivalence I (DBI) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the fasting bioequivalence (BE) study will be conducted later. The following deficiency has been identified:

The dissolution testing using your proposed method in 0.25% Tween 20 in water is acceptable. However, your proposed specifications are not acceptable. Based on the data submitted, the DBI has recommended more appropriate specifications for the test product. Please acknowledge your acceptance of the following method and specifications:

The dissolution testing should be conducted in 900 mL of 0.25% Tween 20 at (b)(4)°C ± 0.5°C, using USP apparatus V (paddle over disk) at 50 rpm. The test product should meet the following specifications:

Norelgestromin: 0.5 hr- NMT (b)(4)%, 2 hrs- (b)(4)%, 8 hrs- (b)(4)%, 20 hrs- NLT (b)(4)%

Ethinyl Estradiol: 0.5 hr- NMT (b)(4)%, 2 hrs- (b)(4)%, 8 hrs- (b)(4)%, 20 hrs- NLT (b)(4)%

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

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

/s/

DALE P CONNER
10/03/2013

COMPLETE RESPONSE

ANDA 200910

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: 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, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

We have completed the review and have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

ANDA 200910

COMPLETE RESPONSE

Mylan Technologies, Inc.
Attention: S. Wayne Talton
Vice President, Regulatory Affairs

110 Lake St.
St. Albans, VT 05478

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) 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 (Xulane ™), 0.15 mg/24 hour and 0.02 mg/24 hour.

We acknowledge receipt of your amendments dated March 17, May 25, June 29, September 24, and October 8, 2010; June 9, June 28, July 29 (two submissions), October 3, and December 22, 2011; March12, March 13, April 5, June 7, July 30, September 19, and October 18,2012.

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

A. The deficiency presented below represents MINOR deficiency.

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". To ensure this, the ANDA applicant should provide information about the formulation performance to ensure that the sensitivity to in-use conditions like heat /hot water exposure 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 release

data to the RLD at normal and "stress" situations: 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 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 (DBI) has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. The comparative dissolution testing conducted using your proposed method is considered inadequate. Your proposed method gave release profiles with more gradual slopes, compared with the FDA method, for both the test and reference products, and therefore, demonstrated superiority. However, the dissolution testing based on your method did not include sufficient sampling time points to characterize adequately the more gradual release profiles. Please conduct additional comparative dissolution testing using your method on a fresh test lot and unexpired reference lot, using the time points of 0.5, 2, 6, 8, 14, 20 and 24 hours. The fresh test lot should be manufactured using the same manufacturing conditions, specifications and formulation as the bio study test lot, and the Chemistry, Manufacturing and Controls records for the fresh test lot should be submitted to the Division of Chemistry for evaluation. The Certificate of Analysis for this fresh test lot should also be submitted to DBI for confirmation.

2. Following the inspection of the analytical site, Mylan Pharmaceuticals, Inc. Bioanalytical Department, 3711 Collins Ferry Rd, Morgantown, WV, between August 18-26, 2010, by the Office of Scientific Investigations (OSI) for bioequivalence (BE) studies from another application, Form FDA- 483 was issued for the site.

   For considering the impact of similar study conduct and site practices by the same analytical facility on the fasting bioequivalence (BE) study of the current ANDA, the DBI reviewed the above OSI inspection report and found that the following objectionable findings by the OSI at the analytical site could potentially compromise the integrity of the study of current ANDA as well:

   - Stability of processed samples was determined with only mid level QCs during pre-study validation for the audited studies. Processed stability was not evaluated with low and high QC concentrations.

   - Failure to document all aspects of the study conduct.

No documentation was maintained for identity of the weighing scales used for quarterly qualification for pipettes during the audited studies.

Please address the above specific findings by the OSI with respect to their impact on the fasting BE study of the current ANDA, providing any necessary supporting documents in your response.

3. During the fasting BE study (ORH-0942), two (2) study samples for norelgestromin were re-assayed for the reason of "Abnormal Internal Standard Response" as per Bioanalytical report (ORTH-0942_NORE), Table 5- Repeat Analysis Results for NORE in Human Plasma. However, in the table of Reanalysis of Study Samples, you have stated the reason for the re-assay as "Documented Sample Processing Error". Please be advised that for the future submissions, you should provide consistent information concerning repeat analyses throughout your submission.

CLINICAL

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

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 adhesion study (**ORTH-09198)**, your product was statistically significantly less adhesive than the reference product .

LABELING

Labeling Deficiencies determined on May 16, 2013 based on your submission dated October 18, 2012:

1. GENERAL
   Revise the presentation of the proprietary name on all labels and labeling to appear in title case lettering (i.e., Xulane).

2. SPL
   Please note that you are required to submit SPL labeling from which we will review the data elements. For additional information, please refer to 21 CFR 314.94(d)(ii), the SPL Implementation Guide for FDA Content of Labeling Submissions at:

   http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Submit your revised labeling electronically in final print format.

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

Prior to the submission of your amendment, please check labeling resources, including 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

06/13/2013

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 200910

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Mylan Technologies, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

ATTENTION: Joseph J. Sobecki
Vice President, Regulatory Affairs

Dear Mr. Sobecki:

Please refer to your Abbreviated New Drug Application (ANDA) dated and received December 31, 2009, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 hour and 0.02 mg/24 hour.

We also refer to your correspondence, dated and received October 18, 2012, requesting review of your proposed proprietary name, Xulane. We have completed our review of the proposed proprietary name, Xulane and have concluded that it is acceptable.

The proposed proprietary name, Xulane, will be re-reviewed 90 days prior to the approval of the ANDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your October 18, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application contact Esther Chuh, Regulatory Project Manager in the Office of Generic Drugs (OGD), at (240) 276-8530.

Sincerely,
{See appended electronic signature page}
Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
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/

CAROL A HOLQUIST
05/06/2013

QUALITY DEFICIENCY - MINOR

ANDA 200910

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Mylan Technologies Inc.

TEL: (304) 599-2595

ATTN: S. Wayne Talton

FAX: (802) 527-8155

FROM: Trang Q. Tran

FDA CONTACT PHONE: (240) 276-8518

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 31, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 h and 0.02 mg/24 h.

Reference is also made to your amendment dated April 5, 2012.

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: 200910 APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 h and 0.02 mg/24 h.

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)

2.

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

We encourage you to apply Quality by Design (QbD) principles to the pharmaceutical development of your future original ANDA product submissions. A risk-based, scientifically sound submission would be expected to include the following:

- Quality target product profile (QTPP)
- Critical quality attributes (CQAs) of the drug product
- Product design and understanding including identification of critical attributes of excipients, drug substance(s), and/or container closure systems
- Process design and understanding including identification of critical process parameters and in-process material attributes
- Control strategy and justification

An example illustrating QbD concepts can be found online at FDA's **Generic Drugs: Information for Industry** webpage: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf

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

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

/s/

BHAGWANT D REGE on behalf of BING CAI
07/19/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

ANDA 200910

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Mylan Technologies, Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Attention: S. Wayne Talton
Vice President, Regulatory Affairs

Dear Mr. Talton:

Please refer to your Abbreviated New Drug Application (ANDA) dated and received December 31, 2009, submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norelgestromin and Ethinyl Estradiol Transdermal Patch, 0.15 mg/24 hour and 0.02 mg/24 hour.

Please also refer to your correspondence dated and received June 28, 2011, requesting review of the proposed proprietary name, (b) (4) We have completed our review of the proposed proprietary name, (b) (4) and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name, (b) (4) is orthographically similar to and shares overlapping product characteristics with the marketed (b) (4)

Following this page, 1 Page Withheld in Full as (b)(4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application contact Trang Tran, Product Quality Regulatory Project Manager in the Office of Generic Drugs (OGD), at (240) 276-8518.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
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/

CAROL A HOLQUIST
06/29/2012

Please send an email to the labeling reviewer (Malik.Imam@fda.hhs.gov) to confirm that you received the labeling comments

Labeling Comments

ANDA 200910

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 Inc.

TEL: 304-599-2595

ATTN: S. Wayne Talton

FAX: 802-527-8155

FROM: Malik Imam
240-276-8964

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:

Norelgestromin and Ethinyl Estradiol Transdermal System.

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	200910
Date of Submission	03/12/2012
Applicant's Name	Mylan Technologies Inc.
Established Name	Norelgestromin and Ethinyl Estradiol Transdermal System
Proprietary Name	(b) (4) Under review

Labeling Deficiencies:

A. Carton Label:

1. Please note that the following statement appears on the side panel of the carton:

   (b) (4)

   As this statement does not appear on the RLD Carton labeling please remove it.

Please submit final printed labeling 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

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

/s/

LILLIE D GOLSON
06/01/2012
for Wm. Peter Rickman

Please send an email to the labeling reviewer (charles.hoppes@fda.hhs.gov) to confirm that you received the labeling comments

Labeling Comments

ANDA 200910

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 X6551

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 Norgestromin and Ethinyl Estradiol Transdermal System.

Pages (including cover and signature page): 4

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: 200910 Date of Submission: 12/22/2011

Applicant's Name: Mylan Technologies

Proprietary Name: (b) (4)

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

---

Labeling Deficiencies:

A. GENERAL COMMENTS:

We acknowledge your comments regarding review submission of certain labeling pieces with respect to the ongoing review of your proposed proprietary name. The name continues to be under review in the Division of Medication Error Prevention and Analysis (DMEPA) of the Office of Safety and Epidemiology. We will inform you of their comments when they become available to us.

B. PATIENT LABELING:

With regard to the request to delete, "[See USP Controlled Room Temperature]", from the storage statement of your patient information:

We acknowledge that you have not consistently applied this terminology to your patient labeling, sometimes omitting reference to "USP" and "Controlled Room Temperature", as you state you use this term on the "majority" (but not all) patient information. (b) (4)

There is a group in the Office of New Drugs (OND) which reviews patient information associated with NDA labeling for patient comprehension. Part of the goal for this Center-level review is to ensure that patient labeling is simple and understandable. The majority of patient labeling (including the RLD labeling of the product for which you are seeking approval) reviewed by OND in the Center does not include reference to "USP" or "Controlled Room Temperature".

For these reasons, we request that you revise your labeling to be the **same as the RLD**, silent to the above mentioned terminology. Alternatively, if you prefer, we can consult the CDER group which reviews labeling for patient comprehension as to whether or not these terms should appear in your labeling.

If you choose the latter approach, please explain how you believe patients will understand the meaning of "USP" or Controlled Room Temperature", or provide any other information to support your request to retain these terms.

You need not submit labeling at this time as your proprietary name is under review.

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

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

/s/

JOHN F GRACE
01/03/2012
for Wm Peter Rickman

QUALITY DEFICIENCY - MINOR

ANDA 200910
OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Mylan Technologies Inc

TEL: 304-599-2595 ext. 6551

ATTN: S. Wayne Talton

FAX: 304-285-6407

FROM: Esther Chuh

FDA CONTACT PHONE: (240) 276-8530

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 31, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 hours and 0.02 mg/24 hours (7-day patch)

Reference is also made to your amendment dated July 29, 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: 200910

APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 h and 0.02 mg/24 h

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

9. Please provide updated stability data for the exhibit batch(es).

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

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

/s/

BING CAI
12/20/2011

Please send an email to the labeling reviewer (charles.hoppes@fda.hhs.gov) to confirm that you received the labeling comments

Labeling Comments

ANDA 200910

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 X6551

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 Norgestromin and Ethinyl Estradiol Transdermal System.

Pages (including cover and signature page): 4

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: 200910 Dates of Submission: 12/31/2009, 6/29/2010, 6/9/2011 6/28/2011, 10/3/2011

Applicant's Name: Mylan Technologies

Proprietary Name: (b) (4)

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

---

Labeling Deficiencies:

A. GENERAL COMMENTS:

We acknowledge that your proposed proprietary name is under review in the Division of Medication Error Prevention and Analysis (DMEPA) of the Office of Safety and Epidemiology. We will inform you of their comments when they become available to us. Additionally we note that there is a mixture of labeling which does and does not reference the proposed proprietary name. For, example if the name (b) (4) is found acceptable by DMEPA, the most recently submitted package insert labeling must be revised to reflect the proprietary name as it refers to labeling pieces, such as the patch print in terms of the established name rather than the proprietary name.

B. PATCH LABEL:

1. See GENERAL COMMENTS above.

2. Include the established name with the proprietary name. We refer you to 21 CFR 201.10(g)(1), for guidance.

C. POUCH LABEL:

1. See GENERAL COMMENTS above.

2. Increase the contrast of print which appears beneath the principal display panel by lightening the background.

D. CARTON LABELING (3 Systems and Outer Carton Labeling):

See GENERAL COMMENTS and comments for POUCH LABEL above.

E. PACKAGE INSERT:

See GENERAL COMMENTS above.

F. DETAILED PATIENT LABELING:

1. We note that the patch application direction you propose differ from the RLD. Have similar application directions/pictorials for your transdermal system been approved in a different application? If so, which?

2. OTHER INFORMATION – Revise to delete "[See USP Controlled Room Temperature]".

Alternatively explain how you believe patients will understand the meaning of “USP” or Controlled Room Temperature”.

G. PATCH CHANGE REMINDER STICKERS:

Please submit this labeling piece for our review and approval.

Submit final printed labeling 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

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

/s/

JOHN F GRACE
11/15/2011
for Wm Peter Rickman

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2011-0571	
TO *(Division/Office)* DRUP - HFD-580 Thru: Jennifer Mercier , ODEIII HFD-103			FROM: Shahnaz Read	
DATE: 10/28/2011	IND NO.	ANDA NO. 200910	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 7/29/2011,
NAME OF DRUG Norelgestromin and Ethinyl Estradiol Transdermal System		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG Contraceptive	DESIRED COMPLETION DATE 12/27/2011

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

The firm has set a specification for (b) (4) in the adhesive (b) (4) at (b) (4) ppm. This would result in a maximum of (b) (4) in the final transdermal patch. Thus the maximum potential exposure of patient to (b) (4) would be (b) (4) in 24 h. Is this amount acceptable based on the Safety Assessment that has been attched from the firm?Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) on the review when it is being checked into DFS. 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

Following this page, 26 Pages Withheld in Full as (b)(4)

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

/s/

SHAHNAZ T READ
10/31/2011

TRANG Q TRAN
10/31/2011

QUALITY DEFICIENCY - MINOR

ANDA 200910

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Mylan Techonologies, Inc. TEL: 304-599-2595 ext. 6551

ATTN: S. Wayne Talton, VP, Regulatory Affairs FAX: 304-285-6407

FROM: Esther Chuh FDA CONTACT PHONE: (240) 276-8530

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 31, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 hours and 0.02 mg/24 hours.

Reference is also made to your amendments dated March 17, and September 24, 2010.

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: 200910

APPLICANT: Mylan Techonologies, Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 h and 0.02 mg/24 h.

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.
9.
10.

(b) (4)

11.

12.

13.

14.

15.

16.

17.

18.

19.

20.

21.

22.

23.

24. [redacted] (b) (4)

25.

26.

27.

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

1. The labeling and bioequivalence portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate cover.

2. Please provide updated stability data for the exhibit batches.

3. [redacted] (b) (4)

Sincerely yours,

{See appended electronic signature page}

Paul Schwartz, Ph.D
Acting Director
Division of Chemistry I
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/

BING CAI
05/27/2011
For Paul Schwartz

From: Shimer, Martin
To: "Wayne.Talton@mylanlabs.com";
cc: Shimer, Martin;
Subject: RE: Request to Use (b) (4) in Lieu of the US Postal Service for Sending PIV Notice for ANDA 200910
Date: Tuesday, April 20, 2010 6:07:25 AM

Wayne,

It is permissible to use (b) (4) in lieu of the US Postal service for the purpose of providing notice to the NDA holder and any patent assignees associated with PIV certifications contained within ANDA 200910.

Regards,

Marty

From: Wayne.Talton@mylanlabs.com [mailto:Wayne.Talton@mylanlabs.com]
Sent: Monday, April 19, 2010 6:15 PM
To: Shimer, Martin
Subject: Request to Use (b) (4) in Lieu of the US Postal Service for Sending PIV Notice for ANDA 200910

Hi Marty

Mylan recently received our Acceptance for Filing letter for our ANDA for Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 hour and 0.02 mg/24 hour (ANDA 200910). Since this ANDA contained PIV patent certifications, we would like to request permission to use (b) (4) in lieu of the US Postal service for sending our PIV notice to the NDA and/or patent owners and to document the receipt of notice. Thanks for your assistance.

Wayne
Mylan
304.554.6551

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

/s/

MARTIN H Shimer
01/18/2011

BIOEQUIVALENCE AMENDMENT

ANDA 200910

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Mylan Technologies Inc. TEL: (304) 599-2595

ATTN: S. Wayne Talton FAX: (802) 527-8155

FROM: Teresa Ramson FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on December 31, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norelgestromin and Ethinyl Estradiol 0.15 mg/24 hour and 0.02 mg/24 hour Transdermal System.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **1** page. 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
Long Term Stability

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 will be:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010.** 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: 200910

APPLICANT: Mylan Technologies Inc.

DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 hour and 0.02 mg/24 hour

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The DBE will review the bioequivalence, adhesion and skin irritation and sensitization studies at a later date. The following deficiencies have been identified:

1. Please provide dissolution profiles on 12 dosage units each of test and reference products generated in pH 1.2 dissolution media.

2. The Long Term Stability (LTS) data in frozen plasma samples you provided is not sufficient to cover the entire storage period of actual samples of the bioequivalence study. Please provide LTS data for at least 96 days for Norelgestromin and 60 days for Ethinyl Estradiol to cover the entire length of the maximum storage duration of the bioequivalence (BE) study samples (i.e., from the time when the first blood sample was drawn until the time when the last plasma sample was analyzed).

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200910	ORIG-1	MYLAN TECHNOLOGIES	ETHINYL ESTRADIOL;NORELGESTROMIN

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

/s/

DALE P CONNER
07/30/2010

MEMORANDUM
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 29, 2010

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#	200910
Product	Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 hour and 0.02 mg/24 hour
Sponsor: full address	Mylan Technologies Inc. 781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Phone	304-599-2595
Fax	403-285-6407
Sponsor Contact	S. Wayne Talton, Vice President, Regulatory Affairs
Phone	304-599-2595
Fax	403-285-6407
Submission Date	December 31, 2009

PRIORITY: C

A (highest) = ready for approval in the office
B = ready for approval, clinical study under review
C = pending clinical review

DUE DATE: October 29, 2010

REASON FOR REQUEST:

	Not inspected in the last three years
	For Cause/Violative History
X	New Sites
	Other

Clinical Endpoint Study

TITLE:	Adhesion Evaluation Study of Norelgestromin/Ethinyl Estradiol Transdermal System (NEETS) Patch (0.15 mg/0.02 mg/day; Mylan) and Active Wear of Ortho Evra® Patch (0.15 mg/0.02 mg/day; Ortho-McNeil-Jannsen) in Normal Healthy Female Volunteers
STUDY #:	ORTH-09198
NUMBER OF STUDY SITES:	1
CROs/SMO:	Not provided with submission

SITE TO BE INSPECTED	
Site	Cetero Research – Miami
Address	1405 NW 167th Street Miami Gardens, FL 33169
Phone	Tel: 305-624-9191 Cell: 786-316-1806
Investigator (Name/Contact Info)	Lawrence A. Galitz, MD
# of subjects	37

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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200910	ORIG-1	MYLAN TECHNOLOGIES	ETHINYL ESTRADIOL;NORELGESTROMIN

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

/s/

NITIN K PATEL
07/29/2010

DENA R HIXON
07/29/2010

From: Middleton, Saundra T

Sent: Monday, May 17, 2010 11:12 AM

To: 'Wayne.Talton@mylanlabs.com'

Subject: RE: ANDA 200910 NORELGESTROMIN AND ETHINYL ESTRADIOL TRANSDERMAL SYSTEM

Hi Wayne,

The e-mail is fine. I will save this under your ANDA.

Regards,

Saundra

From: Wayne.Talton@mylanlabs.com [mailto:Wayne.Talton@mylanlabs.com]

Sent: Monday, May 17, 2010 10:49 AM

To: Middleton, Saundra T

Subject: Re: ANDA 200910 NORELGESTROMIN AND ETHINYL ESTRADIOL TRANSDERMAL SYSTEM

Hi Saundra

Here is the information you requested. Do we need to submit this as a formal am endment to the ANDA or is the email correspondence acceptable?

The name and address of (b) (4) :

(b) (4)

(b) (4)

The name and address of (b) (4)

(b) (4)

(b) (4)

Wayne Talton

Mylan

"Middleton, Saundra T" <Saundra.Middleton@fda.hhs.gov>

05/17/2010 09:55 AM

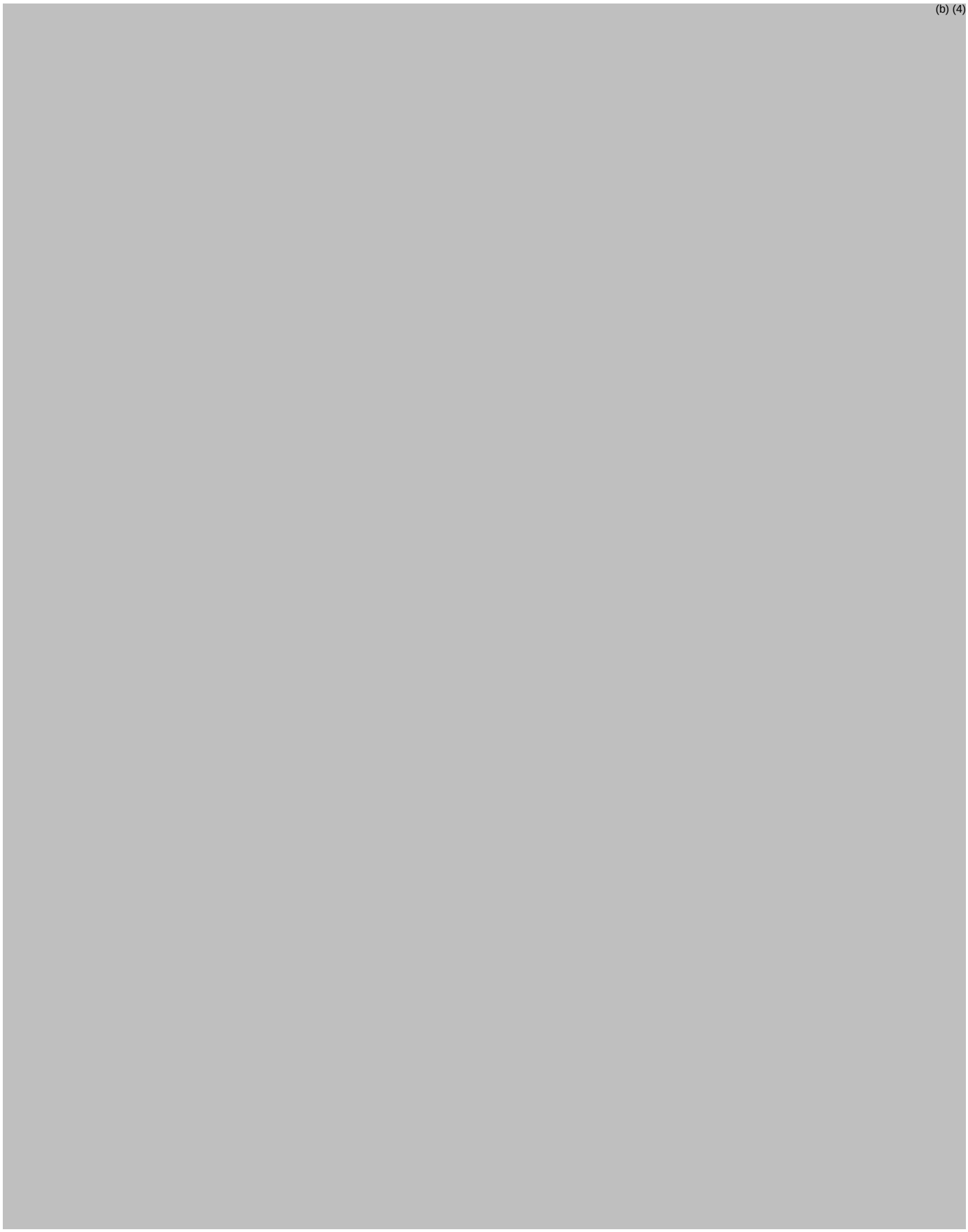
To Wayne.Talton@mylanlabs.com

cc

Subject ANDA 200910 NORELGESTROMIN AND ETHINYL ESTRADIOL TRANSDERMAL SYSTEM

Hi Wayne,

Could you provide me with the fax numbers for the following U.S. Agent below. T he fax numbers are required to submit an inspection request.


(b) (4)

Thanks,

Saundra

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200910	ORIG-1	MYLAN TECHNOLOGIES	ETHINYL ESTRADIOL;NORELGESTROMIN

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

/s/

SAUNDRA T MIDDLETON
05/17/2010
EES contact fax numbers

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 200910

Mylan Technologies Inc.
Attention: S. Wayne Talton
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This letter is in reference to your Abbreviated New Drug Application (ANDA) dated December 31, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 hour and 0.02 mg/24 hour.

In addition to the acknowledgement letter sent to you on April 19, 2010, the following information should be submitted to your ANDA for review in the interim:

1. A frequency table for dermal response, "other effects" and combined scores (dermal response score plus other effects score) for test and reference product for each patch application day (e.g., day 8, 15, 22) during induction phase and for Day 38, 39, 30 and 41 during challenge phase is requested for the review.

2. The dataset "orth0943irr.xpt" included a column of "other effects" (i.e., IND_C1) but no scores were reported. You are required to explain the reason for the missing data.

3. Provide dermal response score, "other effects" score, combination of dermal response and other effects scores in the primary dataset (SAS .xpt file).

4. Submit adhesion data in SAS .xpt file. The dataset should include at least the following variables: subject, treatment, period, evaluator, included in the adhesion analysis (yes/no), reason for discontinuation or exclusion, adhesion scores at each adhesion assessment time points.

5. Provide a list of concomitant medications used during the study and adverse events in SAS .xpt file.

6. In general, the data submission should include the following details in the primary dataset:

1) 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. 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. 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.

2) 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 or RLD)
   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. Per Protocol (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)

Refer to Table 1 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 1: 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	RUA	21	2	Y	
101	1	01	54	YEARS	M	1	B	LUA	21	2	Y	
101	2	01	45	YEARS	M	2	A	RUA	21	2	Y	
101	2	01	45	YEARS	M	2	B	LUA	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 Draft dated July 25, 2007.

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, E=test overlay, F=reference overlay

EXLOC: Location of Dose Administration (exposure): specific anatomical site of patch application, e.g., RUA=right upper arm, LUA=left upper arm

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: Per Protocol (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: Per Protocol (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 8 adhesion scoring due to AE that was not intolerable irritation, B=failed to complete Day 8 adhesion scoring due to lost to follow-up, C=failed to complete Day 8 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

3) For the Irritation, Sensitization and Adhesion Analyses, you should 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, RLD)
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 scores (e.g., Hours 0-7 days)
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 each site
r. Challenge "Other Effects" letter score for each 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)

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 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	RUA	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 Draft dated July 25, 2007.

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, E=test overlay, F=reference overlay
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., RUA=right upper arm, LUA=left upper arm
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. to Day 8)
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

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240)276-8419.

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

Should you have questions concerning this application, contact:

Sarah Nguyen
Project Manager
(240) 276-8467

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-200910	ORIG-1	MYLAN TECHNOLOGIES	ETHINYL ESTRADIOL;NORELGESTROMIN

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

/s/

MARTIN H Shimer
05/11/2010
Signing for Wm Peter Rickman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 200910

Mylan Technologies Inc.
Attention: S. Wayne Talton
781 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 telephone conversation dated March 17, 2010 and your correspondence dated March 17, 2010.

NAME OF DRUG: Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/24 hour and 0.02 mg/24 hour

DATE OF APPLICATION: December 31, 2009

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 31, 2009

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 the 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.

Your skin irritation/sensitization study (orth-0943) and adhesion study (orth-09198) are acceptable for receiving your ANDA.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240)276-8419.

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:

Sarah Nguyen
Project Manager
(240) 276-8467

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-200910	ORIG-1	MYLAN TECHNOLOGIES	ETHINYL ESTRADIOL;NORELGESTROMIN

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

/s/

MARTIN H Shimer
04/19/2010
Signing for Wm Peter Rickman

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 #: 200910 **FIRM NAME**: MYLAN TECHNOLOGIES INC.

PIV: YES **Electronic or Paper Submission:** GATEWAY (ELECTRONIC DATA)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: NORELGESTROMIN AND ETHINYL ESTRADIOL
DOSAGE FORM: TRANSDERMAL SYSTEM, 0.15MG/0.02MG (24 HOURS) FILM

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC3 Team 4 ☒***Activity***	***Bio Team 8: Shriniwas Nerurkar*** ☒***Activity***
ANDA/Quality RPM: Sarah Nguyen ☒ ***FYI***	Bio PM: Steven Mazzella/Teresa Vu ☐ ***FYI***
Quality Team Leader: Liu, Shing Hou No assignment needed in DARRTS	***Clinical Endpoint Team Assignment: Random Clinical Team*** ☒***Activity***
Labeling Reviewer: Burhan Nour ☒***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: DECEMBER 31, 2009 **Received Date**: DECEMBER 31, 2009

Comments: EC- 2 YES **On Cards:** YES
Therapeutic Code: 3010600 CONTRACEPTIVES (TRANSDERMAL)

Archival copy: GATEWAY (ELECTRONIC DATA) **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 Saundra T. Middleton **Date 4/13/2010**	**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:

March 16 and 17, 2010 – Mylan was requested to provide additional information on Polyisobutene Adhesive [redacted (b) (4)] Specifically they were asked to provide information on the component of [redacted (b) (4)] and to clarify the amount of [redacted (b) (4)]

This above request was adequately addressed on 3/17/2010 (see explanation below).

In the interim, Mylan will be advised of the following comments from the Clinical Team (this will be sent in a separate memo to the firm):

Your skin irritation/sensitization study (orth-0943) and adhesion study (orth-09198) are acceptable for receiving your ANDA.

In the interim, the following additional information should be submitted for review:

1. A frequency table for dermal response, "other effects" and combined scores (dermal response score plus other effects score) for test and reference product for each patch application day (e.g., day 8, 15, 22) during induction phase and for Day 38, 39, 30 and 41 during challenge phase is requested for the review.

2. The dataset "orth0943irr.xpt" included a column of "other effects" (i.e., IND_C1) but no scores were reported. You are required to explain the reason for the missing data.

3. Provide dermal response score, "other effects" score, combination of dermal response and other effects scores in the primary dataset (SAS .xpt file).

4. Submit adhesion data in SAS .xpt file. The dataset should include at least the following variables: subject,

treatment, period, evaluator, included in the adhesion analysis (yes/no), reason for discontinuation or exclusion, adhesion scores at each adhesion assessment time points.

5. Provide a list of concomitant medications used during the study and adverse events in SAS .xpt file.

6. In general, the data submission should include the following details in the primary dataset:

1) 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. 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. 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.

2) 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 or RLD)
   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. Per Protocol (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)

Refer to Table 1 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 1: 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	RUA	21	2	Y	
101	1	01	54	YEARS	M	1	B	LUA	21	2	Y	
101	2	01	45	YEARS	M	2	A	RUA	21	2	Y	
101	2	01	45	YEARS	M	2	B	LUA	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 Draft dated July 25, 2007.

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, E=test overlay, F=reference overlay
EXLOC: Location of Dose Administration (exposure): specific anatomical site of patch application, e.g., RUA=right upper arm, LUA=left upper arm
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: Per Protocol (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: Per Protocol (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 8 adhesion scoring due to AE that was not intolerable irritation, B=failed to complete Day 8 adhesion scoring due to lost to follow-up, C=failed to complete Day 8 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

3) For the Irritation, Sensitization and Adhesion Analyses, you should 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, RLD)
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 scores (e.g., Hours 0-7 days)
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 each site
r. Challenge "Other Effects" letter score for each 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)

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 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	RUA	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 Draft dated July 25, 2007.

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, E=test overlay, F=reference overlay

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., RUA=right upper arm, LUA=left upper arm

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. to Day 8)

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

Following this page, 1 Page Withheld in Full as (b)(4)

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: DECEMBER 31, 2009	☒
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 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES 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 to '746 and '377
2. Paragraph: (Check all certifications that apply)
   MOU ☐ PI ☐ PII ☐ PIII ☐
   PIV ☒ (Statement of Notification) ☐
3. Expiration of Patent(s): 11/20/2015
   a. Pediatric exclusivity submitted?
   b. Expiration of Pediatric Exclusivity?
4. Exclusivity Statement: YES

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 021180 Product 001 in the OB_Rx list.

<>

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021180	001	5876746	Nov 20, 2015		Y	U - 514	
N021180	001	5972377	Jun 7, 2015			U - 514	

There is no unexpired exclusivity for this product.

This page defines the patent use codes.

Code	Definition
U - 514	PREVENTION OF OVULATION IN A WOMAN

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) NORELGESTROMIN AND
      # (b) (4) ETHINYL ESTRADIOL
   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

NDA# : 21-180
Ref Listed Drug: ORTHO EVRA
Firm: ORTHO MCNEIL JANSSEN
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 **YES** 2. Active ingredients **YES** 3. Inactive ingredients **YES** 4. Route of administration **YES** 5. Dosage Form **YES** 6. Strength **YES**	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☐
1.14.1	**Draft Labeling** **(Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) E- SUBMISSION **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.) **HOW SUPPLIED:** Each peach Norelgestromin and Ethinyl Estradiol Transdermal System patch contains 4.86 mg norelgestromin and 0.53 mg ethinyl estradiol, USP.	☒
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**	☒

MODULE 2
SUMMARIES ACCEPTABLE

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** **Word Processed e.g., MS Word** **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary Table 4. Bioanalytical Method Validation Table 6. Formulation Data **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies Table 3. Statistical Summary of the Comparative BA Data **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) **YES** 2. Function or Responsibility **YES** 3. Type II DMF number for API **YES #** (b) (4) NORELGESTROMIN AND # (b) (4) ETHINYL ESTRADIOL 4. CFN or FEI numbers **YES**	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) **YES** **3.2.S.4.2 Analytical Procedures YES** **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples **YES** 2. Samples-Statement of Availability and Identification of: a. Drug Substance **YES** b. Same lot number(s) **YES** **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) **YES** 2. Applicant certificate of analysis **YES** **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems – IN DMF**	☒
3.2.S.7	**Stability – IN DMF**	☒

MODULE 3
3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition **YES** 2. Inactive ingredients and amounts are appropriate per IIG **YES –** see notes above on Polyisobutene Adhesive (b) (4)	☒
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) **YES** 2. CGMP Certification: YES 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) 3. If sterile product: Aseptic fill / Terminal sterilization 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 2. Filter validation (if aseptic fill)	☒
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	☒

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 **YES** **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 **YES** 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 **YES – 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 **YES** 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 NO** 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 – SEE BELOW** **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)	☒

(b) (4)

[redacted]

(b) (4)

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) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **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) 2. Summary Bioequivalence tables: Table 10. Study Information Table 12. Dropout Information Table 13. Protocol Deviations **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information Table 16. Composition of Meal Used in Fed Bioequivalence Study **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples **5.3.7** **Case Report Forms and Individual Patient Listing**	☐
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution:	☐
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/BIO TEAM HIXON

☒

Found adequate by DBE on 3/10/2010 see review in DARRTS.

Found adequate by the Clinical Team on 4/12/2010 see review in DARRTS and comments above.

1. In-Vivo PK Study BE with Pharmacokinetic and PK Endpoints and Adhesion Study
   1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) YES
   2. In-Vitro Dissolution YES
   3. EDR Email: Data Files Submitted GATEWAY (ELECTRONIC DATA)
2. Adhesion Study YES
3. Skin Irritation/Sensitization Study YES

MYLAN

2.7.1.3 STATISTICAL SUMMARY OF THE COMPARATIVE BIOAVAILABILITY DATA (BIOEQUIVALENCE SUMMARY TABLE 3)

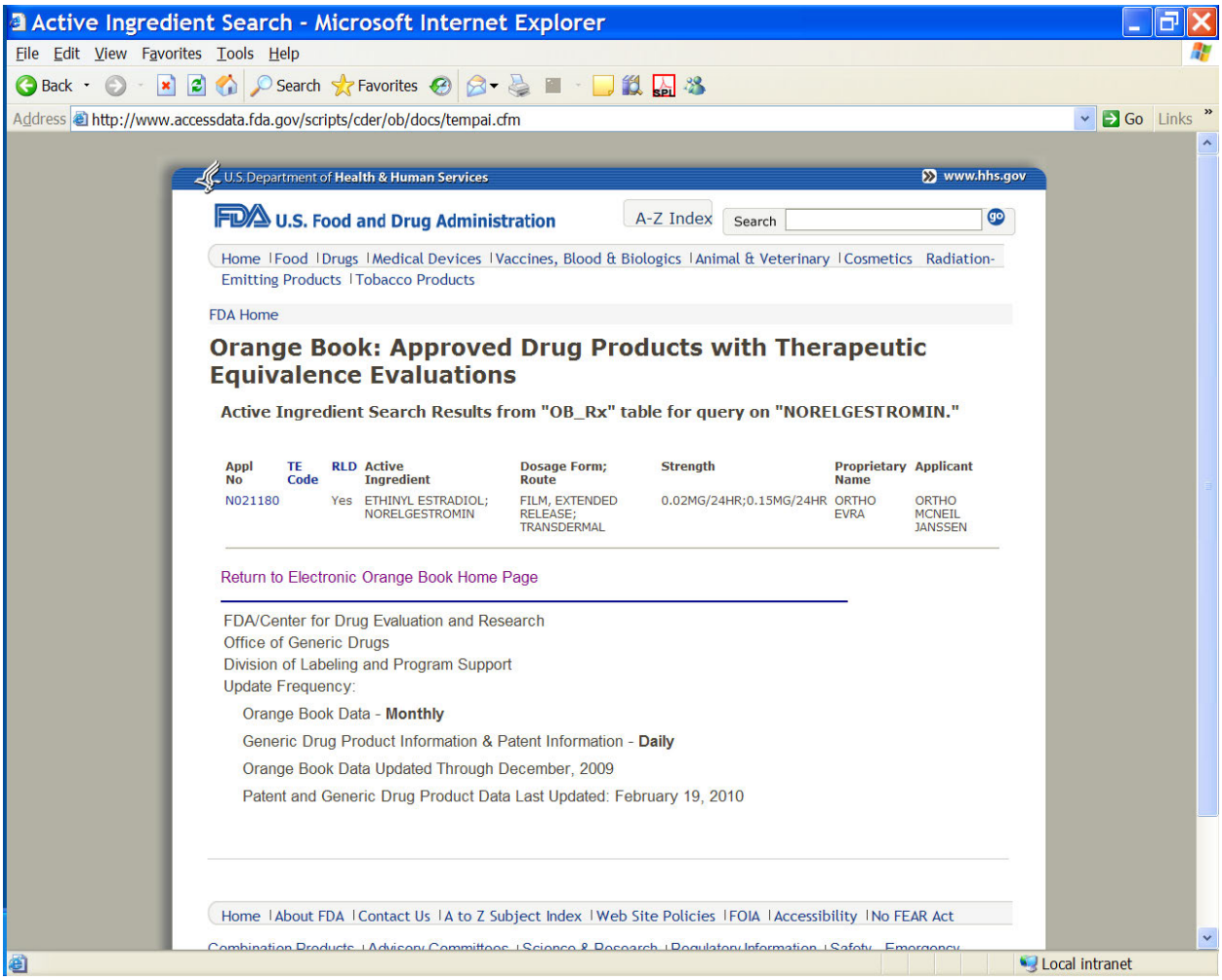
NORELGESTROMIN AND ETHINYL ESTRADIOL TRANSDERMAL SYSTEM

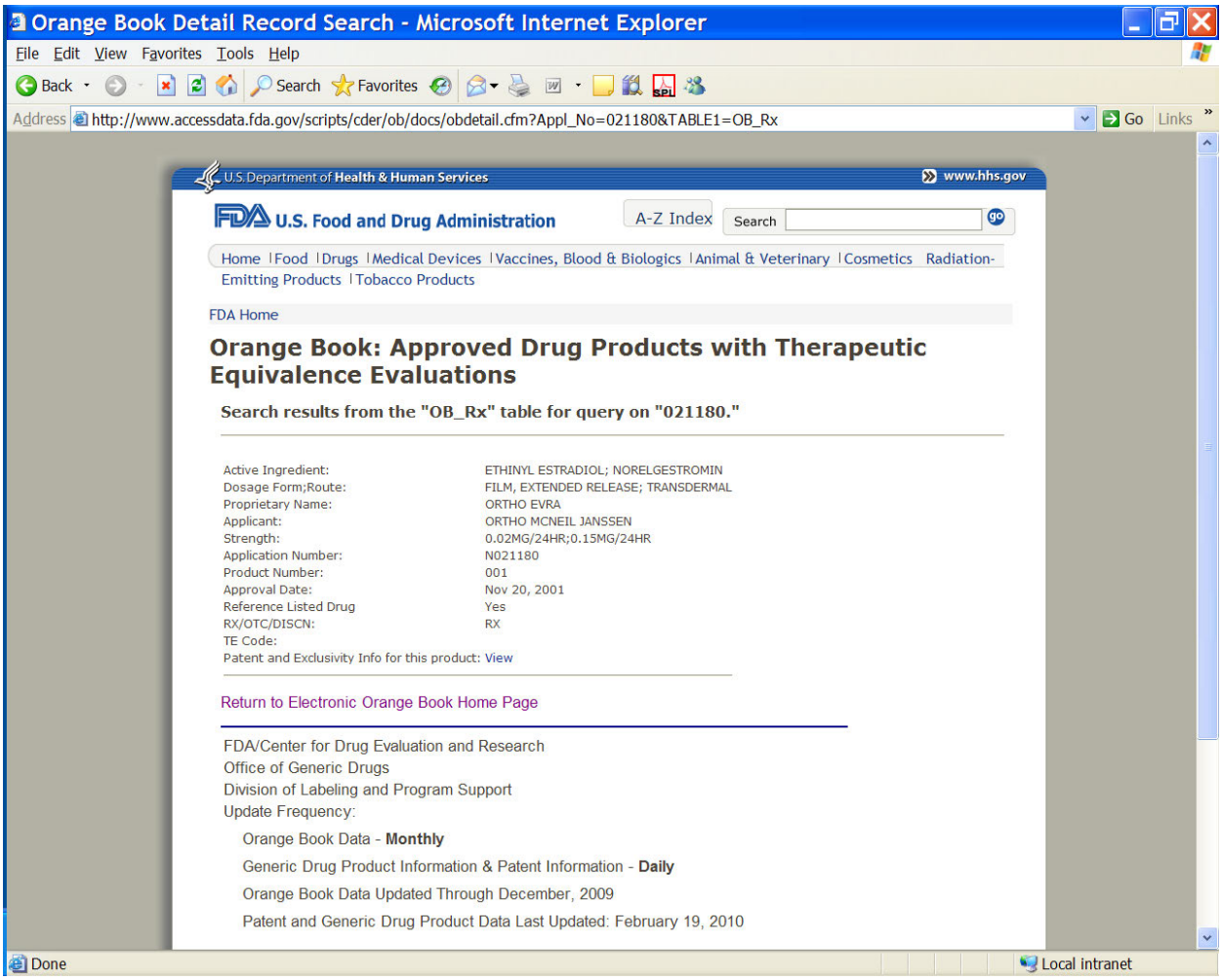
NORELGESTROMIN/ETHINYL ESTRADIOL TRANSDERMAL SYSTEM, 0.15 MG/0.02 MG/DAY Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
ORTH-0942 Norelgestromin				
Parameter	Test (n = 21)	Reference (n = 21)	Ratio*	90% C.I.**
AUC0-t (ng × hr/mL)	185.4	199.7	0.93	86.5%-99.7%
AUC∞ (ng × hr/mL)	189.9	204.8	0.93	86.5%-99.4%
C_{max} (ng/mL)	1.316	1.347	0.98	90.1%-105.9%
ORTH-0942 Ethinyl Estradiol				
Parameter	Test (n = 21)	Reference (n = 21)	Ratio*	90% C.I.**
AUC0-t (pg × hr/mL)	12529.4	14486.1	0.86	81.2%-92.2%
AUC∞ (pg × hr/mL)	12671.3	14650.0	0.86	81.2%-92.2%
C_{max} (pg/mL)	95.16	105.5	0.90	82.5%-98.6%

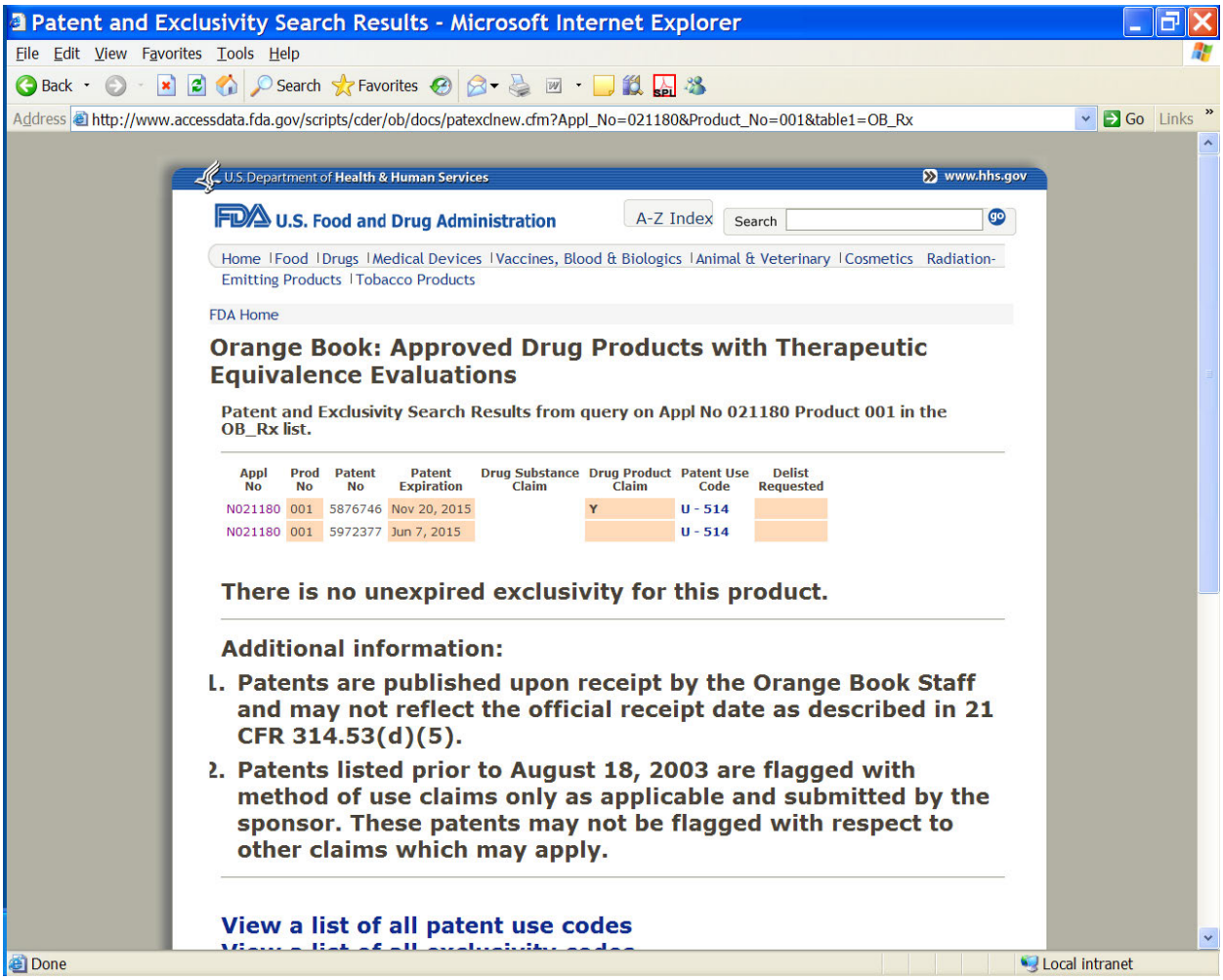
*Ratio (A/B) = $e^{[LSMEAN\ of\ LNA\ -\ LSMEAN\ of\ LNB]}$

**Used Natural Log Transformed Parameter

Updated 10/19/2009


Active Ingredient Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
Go Links
U.S. Department of Health & Human Services
www.hhs.gov
U.S. Food and Drug Administration
A-Z Index
Search
go
Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products
FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Active Ingredient Search Results from "OB_Rx" table for query on "NORELGESTROMIN."
Appl No
TE Code
RLD
Active Ingredient
Dosage Form; Route
Strength
Proprietary Name
Applicant
N021180
Yes
ETHINYL ESTRADIOL; NORELGESTROMIN
FILM, EXTENDED RELEASE; TRANSDERMAL
0.02MG/24HR;0.15MG/24HR
ORTHO EVRA
ORTHO MCNEIL JANSSEN
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 December, 2009
Patent and Generic Drug Product Data Last Updated: February 19, 2010
Home | About FDA | Contact Us | A to Z Subject Index | Web Site Policies | FOIA | Accessibility | No FEAR Act
Combination Products | Advisory Committees | Science & Research | Regulatory Information | Safety | Emergency
Local intranet


Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021180&TABLE1=OB_Rx
Go Links
U.S. Department of Health & Human Services
www.hhs.gov
U.S. Food and Drug Administration
A-Z Index
Search
go
Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products
FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Search results from the "OB_Rx" table for query on "021180."
Active Ingredient: ETHINYL ESTRADIOL; NORELGESTROMIN
Dosage Form;Route: FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name: ORTHO EVRA
Applicant: ORTHO MCNEIL JANSSEN
Strength: 0.02MG/24HR;0.15MG/24HR
Application Number: N021180
Product Number: 001
Approval Date: Nov 20, 2001
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
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 December, 2009
Patent and Generic Drug Product Data Last Updated: February 19, 2010
Done
Local intranet



Following this page, 5 Pages Withheld in Full as (b)(4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-200910	ORIG-1	MYLAN TECHNOLOGIES	ETHINYL ESTRADIOL;NORELGESTROMIN

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

/s/

SAUNDRA T MIDDLETON
04/19/2010

MARTIN H Shimer
04/19/2010

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 20, 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 200910 for Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15mg/0.02mg (24 hours) Film 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 200910 for Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15mg/0.02mg (24 hours) Film. 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 December 31, 2009 for its Norelgestromin and Ethinyl 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-200910	ORIG-1	MYLAN TECHNOLOGIES	ETHINYL ESTRADIOL;NORELGESTROMIN

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

/s/

EDA E HOWARD
02/22/2010