CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 210830

Name: EluRyng (Etonogestrel and Ethinyl Estradiol Vaginal Ring), 0.120mg/0.015mg per day

Sponsor: Amneal Pharmaceuticals

Approval Date: December 11, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210830

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210830

APPROVAL LETTER

ANDA 210830

ANDA APPROVAL

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 25, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for EluRyng (Etonogestrel and Ethinyl Estradiol Vaginal Ring), 0.120 mg/0.015 mg per day.

Reference is also made to the complete response letter issued by this office on April 12, 2019, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your EluRyng (Etonogestrel and Ethinyl Estradiol Vaginal Ring), 0.120 mg/0.015 mg per day, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), NuvaRing Vaginal Ring, of Organon USA, Inc.

Under section 506A of the FD&C 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 and 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 FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and

proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] 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 1st 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.

CONTENT OF LABELING

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 https://www.fda.gov/media/71211/download. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
CAPT, USPHS
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Sarah Kurtz

Digitally signed by Sarah Kurtz
Date: 12/11/2019 02:36:59PM
GUID: 54078879000a1b9e15dd31ed6f0343ca

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210830

OTHER ACTION LETTERS

ANDA 210830

COMPLETE RESPONSE

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) received for review on August 25, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We acknowledge receipt of the October 19, 2018, submission, which constituted a complete response to our June 22, 2018, action letter, and to any amendments thereafter.

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.

PHARMACEUTICAL QUALITY

Drug Product

1. (b) (4)

Drug Product – CDRH Device Evaluation

The Pharmaceutical Quality deficiencies have been classified as MAJOR because of insufficient data to support drug/device compatibility and sustainability for the proposed product as noted in Appendix A, Section A(2)(n) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This information is required

to ensure proper patient in-use of the product. The review of the response will require, in FDA's judgement, a substantial expenditure of FDA resources.

2. You have provided the 90-days study test reports (# 17-00131-G12 and 17-00891-G1) in your amendment received on October 19, 2018. Per the test reports, the test ring (Amneal) and Amneal's placebo ring (Sponsor Control) were dipped (b) (4) prior to being implanted in the animals. We are concerned that this process might remove potentially harmful extractive leachable substances and affect the overall leachable profile of the test article extract, which could result in false negative results. Since your subject device [test ring (Amneal)] is provided as non-sterile, finished product, biocompatibility testing should be done on the representative test article without (b) (4) Please provide justification as to how the test article dipped (b) (4) prior to testing, represents your final, device that is intended to be inserted vaginally without such treatment.

Biopharmaceutics

3. Per our current thinking and understanding for vaginal rings, we recommend the following in-vitro release (IVR) acceptance criteria for the proposed drug product:

   (b) (4)

   We request that you acknowledge your acceptance of the recommended IVR acceptance criteria for your drug product and update the drug product specifications accordingly.

   Your amendment received on October 19, 2018, showed that you have stability data for Day 14 for all exhibit batches. Please submit all available individual unit stability data for Day 5 and Day 14 to the Agency for assessment. In addition, please be advised that all exhibit batches in your stability program are expected to meet the revised IVR acceptance criteria through your proposed expiry period.

DRUG SUBSTANCE / PROCESS / MICROBIOLOGY/ FACILITY INSPECTION / BIOEQUIVALENCE / LABELING

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are using the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence, as required by FDA regulations (21 CFR320.24(a)), please

continue to monitor for the availability of new and revised product specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

We remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling. It is also your responsibility to ensure that your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR** AMENDMENT, given that the deficiencies have been classified as **MAJOR**.

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

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG PRODUCT / BIOPHARMACEUTICS

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). 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 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] 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 or active pharmaceutical ingredients 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 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 Adil Merchant, Regulatory Project Manager, Division of Project Management, at (240) 402 - 3505.

Sincerely yours,

{See appended electronic signature page}

Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Denise
Toyer McKan

Digitally signed by Denise Toyer McKan
Date: 4/12/2019 12:49:53PM
GUID: 5277df670008860f7e1231f730a8684c

ANDA 210830

COMPLETE RESPONSE

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) received for review on August 25, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

Reference is also made to any amendments submitted prior to the issuance of this letter.

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

PHARMACEUTICAL QUALITY

Drug Substance – Ethinyl Estradiol

1. (b) (4)

Drug Substance – Etonogestrel

2. (b) (4)

3.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

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

BIOEQUIVALENCE

As per your study protocol, samples from each subject for all time periods were to be assayed at the same time. Because the analytical method for quantification of ethinyl estradiol and etonogestrel was about 12.5 minutes, multiple periods of each subject were not run together. However, multiple subjects of the same period were analyzed at one time (e.g. period I of subjects (b) (6) were run in a single batch). Please be advised for future studies to analyze all study samples from a subject in a single run in accordance with recommendations in the Guidance for Industry: Bioanalytical Method Validation (Sept. 2013).

LABELING

GENERAL COMMENT

We note that you have submitted a proprietary name for this product. It was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Safety and Epidemiology and found conditionally acceptable on February 13, 2018. If you intend to market with the proprietary name, please submit all labeling pieces with the proprietary name for our review. Please note that your labeling pieces containing the established name, etonogestrel and ethinyl estradiol vaginal ring, are found acceptable.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

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. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

MICROBIOLOGY / BIOEQUIVALENCE

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

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RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT/PROCESS/BIOPHARMACEUTICS/FACILITY INSPECTION/LABELING

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). 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 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

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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.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, call Adil Merchant, Regulatory Project Manager, Division of Project Management, at (240) 402-3505.

Sincerely yours,

{See appended electronic signature page}

Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Denise
Toyer McKan

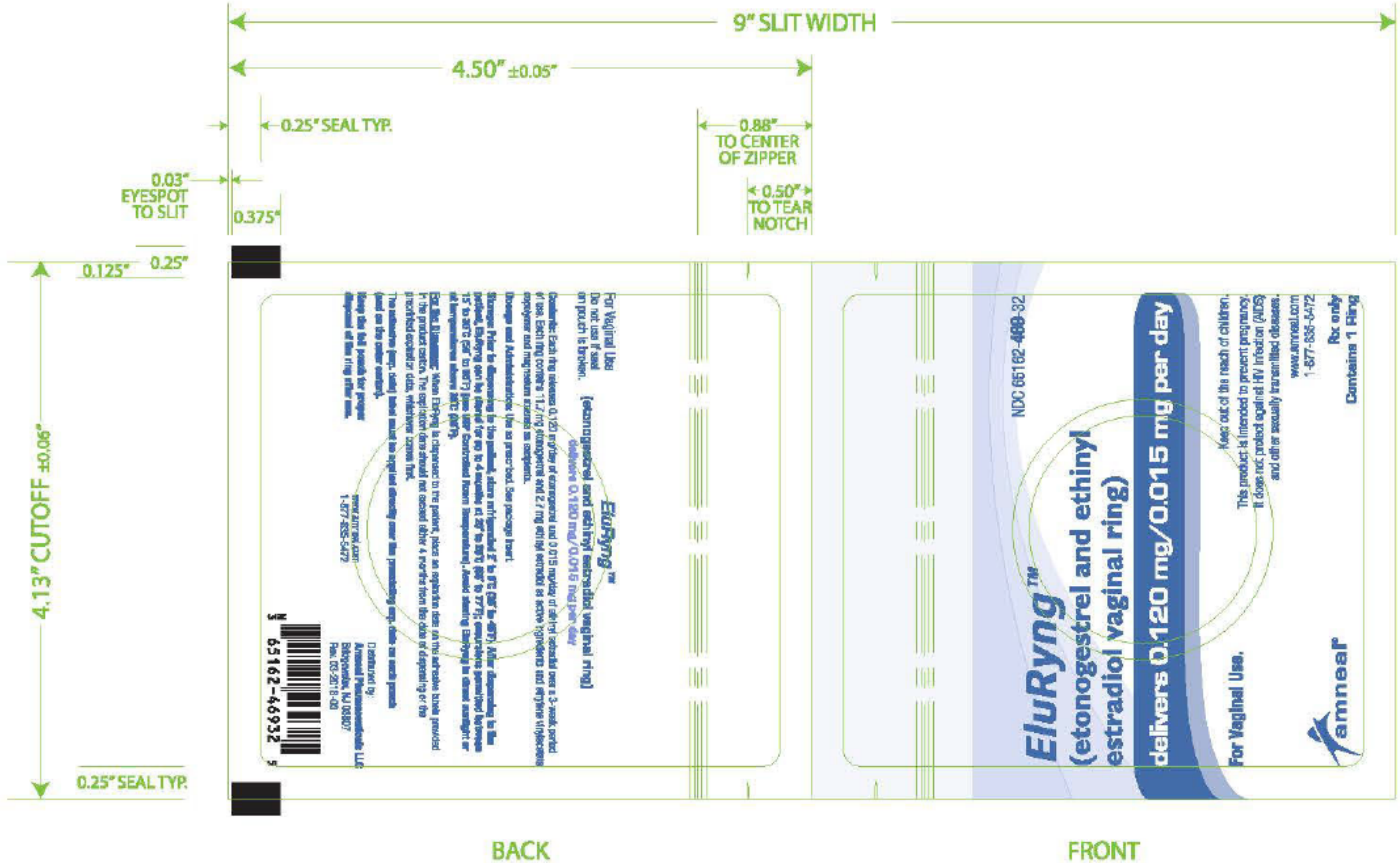
Digitally signed by Denise Toyer McKan
Date: 6/22/2018 03:05:31PM
GUID: 5277df670008860f7e1231f730a8684c

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210830

LABELING


9" SLIT WIDTH
4.50" ±0.05"
0.25" SEAL TYP.
0.88" TO CENTER OF ZIPPER
0.50" TO TEAR NOTCH
0.03" EYESPOT TO SLIT
0.375"
0.125"
0.25"
4.13" CUTOFF ±0.06"
0.25" SEAL TYP.
NDC 65162-469-32
EluRyng™
(etonogestrel and ethinyl estradiol vaginal ring)
delivers 0.120 mg/0.015 mg per day
For Vaginal Use.
Rx only
Contains 1 Ring
amneal
BACK
FRONT

(b) (4)


amneal
EluRyng™
(etonogestrel and ethinyl estradiol vaginal ring)
NDC 65162-469-35
EluRyng™
(etonogestrel and ethinyl estradiol vaginal ring)
delivers 0.120 mg/0.015 mg per day
For the Dispenser: Store refrigerated 2° to 8°C (36° to 46°F).
For Vaginal Use.
Keep out of the reach of children.
This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
Rx only
Contains 3 Rings
amneal
EluRyng™
(etonogestrel and ethinyl estradiol vaginal ring)
For Vaginal Use
Do not use if seal on pouch is broken.
Rx only
EluRyng™
(etonogestrel and ethinyl estradiol vaginal ring)
delivers 0.120 mg/0.015 mg per day
Contents: Each ring releases 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a 3-week period of use. Each ring contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol as active ingredients and ethylene vinylacetate copolymer and magnesium stearate as excipients.
Dosage and Administration: Use as prescribed. See package insert.
Storage: Prior to dispensing to the patient, store refrigerated 2° to 8°C (36° to 46°F). After dispensing to the patient, EluRyng can be stored for up to 4 months at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Avoid storing EluRyng in direct sunlight or at temperatures above 30°C (86°F).
For the Dispenser: When EluRyng is dispensed to the patient, place an expiration date on the adhesive labels provided in the product carton. The expiration date should not exceed either 4 months from the date of dispensing or the preprinted expiration date, whichever comes first.
The adhesive (exp. date) label must be applied directly over the preexisting exp. date on each pouch (and on the outer carton only when all 3 pouches are dispensed).
Distributed by:
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807
Rev. 05-2018-01
www.amneal.com
1-877-835-5472
N 3 65162 46935 6
1

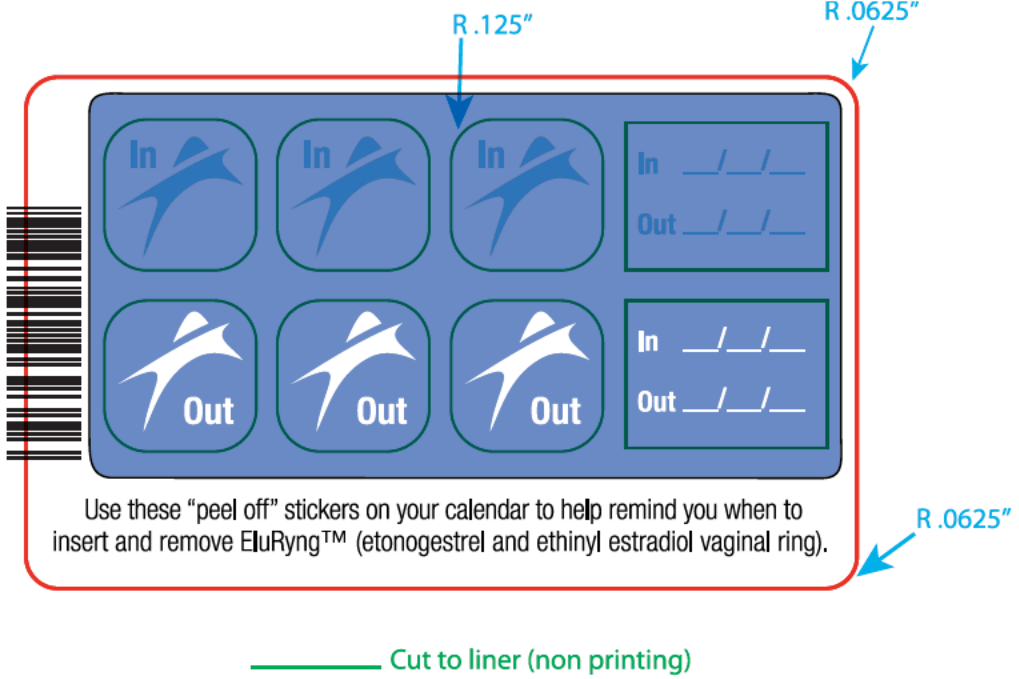
(b) (4)

For the Dispenser:
When EluRyng™ (etonogestrel and ethinyl estradiol vaginal ring) is dispensed to the patient, place the expiration date on an adhesive label provided. The expiration date should not exceed either 4 months from the date of dispensing or the preprinted expiration date, whichever comes first. **The adhesive (exp. date) label must be applied directly over the preexisting exp. date on each pouch (and on the outer carton only when all 3 pouches are dispensed).**

Use this label ↘ to reseal carton

Sealed by your Pharmacy	
Exp:	**Exp:**
Exp:	**Exp:**

(b) (4)



Cut to liner (non printing)

(b) (4)

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

ELURYNG™ (etonogestrel and ethinyl estradiol vaginal ring)
Initial U.S. Approval: 2001

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
See full prescribing information for complete boxed warning.

- **Women over 35 years old who smoke should not use EluRyng. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use. (4)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration
Deviations from the Recommended Regimen (2.3) 12/2018
Warnings and Precautions
Hypersensitivity Reactions (5.6) 12/2018

----------INDICATIONS AND USAGE ----------

EluRyng is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy. (1)

---------- DOSAGE AND ADMINISTRATION ----------

One EluRyng is inserted in the vagina. The ring must remain in place continuously for three weeks, followed by a one-week ring-free interval. (2)

----------DOSAGE FORMS AND STRENGTHS ----------

EluRyng is a polymeric vaginal ring containing 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol, USP, which releases on average 0.12 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol, USP. (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)
- Hypersensitivity, including anaphylaxis and angioedema, to any of the components of EluRyng (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Vascular risks: Stop EluRyng use if a thrombotic event occurs. Stop EluRyng use 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)
- Toxic Shock Syndrome (TSS): If patient exhibits signs or symptoms of TSS, consider the possibility of this diagnosis and initiate appropriate medical evaluation and treatment. (5.2)
- Liver disease: Discontinue EluRyng use if jaundice develops. (5.3)
- High blood pressure: If used in women with well-controlled hypertension, monitor blood pressure and stop EluRyng use if blood pressure rises significantly. (5.5)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.9)
- Headache: Evaluate significant change in headaches and discontinue EluRyng use if indicated. (5.10)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.11)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥2%) in clinical trials were: vaginitis, headache (including migraine), mood changes (e.g., depression, mood swings, mood altered, depressed mood, affect lability), device-related events (e.g., expulsion/discomfort/foreign body sensation), nausea/vomiting, vaginal discharge, increased weight, vaginal discomfort, breast pain/discomfort/tenderness, dysmenorrhea, abdominal pain, acne, and decreased libido. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

Drugs or herbal products that induce certain enzymes, such as 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)

---------- USE IN SPECIFIC POPULATIONS ----------

- Nursing mothers: Not recommended; can decrease milk production. (8.2)

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

Revised: 05/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, CHCs, including EluRyng, should not be used by women who are over 35 years of age and smoke *[see Contraindications (4)]*.

1 INDICATIONS AND USAGE

FOR VAGINAL USE ONLY
EluRyng™ is indicated for use by females of reproductive age to prevent pregnancy.

2 DOSAGE AND ADMINISTRATION

2.1 How to Use EluRyng

To achieve maximum contraceptive effectiveness, EluRyng must be used as directed *[see Dosage and Administration (2.2)]*. One EluRyng is inserted in the vagina. **The ring is to remain in place continuously for**

three weeks. It is removed for a one-week break, during which a withdrawal bleed usually occurs. A new ring is inserted one week after the last ring was removed.

The user can choose the insertion position that is most comfortable to her, for example, standing with one leg up, squatting, or lying down. The ring is to be compressed and inserted into the vagina. The exact position of EluRyng inside the vagina is not critical for its function. The vaginal ring must be inserted on the appropriate day and left in place for three consecutive weeks. This means that the ring should be removed three weeks later on the same day of the week as it was inserted and at about the same time.

EluRyng can be removed by hooking the index finger under the forward rim or by grasping the rim between the index and middle finger and pulling it out. The used ring should be placed in the foil pouch and discarded in a waste receptacle out of the reach of children and pets (do not flush in toilet).

After a one-week break, during which a withdrawal bleed usually occurs, a new ring is inserted on the same day of the week as it was inserted in the previous cycle. The withdrawal bleed usually starts on Day 2 to 3 after removal of the ring and may not have finished before the next ring is inserted. In order to maintain contraceptive effectiveness, the new ring must be inserted exactly one week after the previous one was removed even if menstrual bleeding has not finished.

2.2 How to Start Using EluRyng

IMPORTANT: Consider the possibility of ovulation and conception prior to the first use of EluRyng.

No Hormonal Contraceptive Use in the Preceding Cycle:

The woman should insert EluRyng on the first day of her menstrual bleeding. EluRyng may also be started on Days 2 to 5 of the woman's cycle, but in this case a barrier method, such as male condoms with spermicide, should be used for the first seven days of EluRyng use in the first cycle.

Changing From a CHC:

The woman may switch from her previous CHC on any day, but at the latest on the day following the usual hormone-free interval, if she has been using her hormonal method consistently and correctly, or if it is reasonably certain that she is not pregnant.

Changing From a Progestin-Only Method (progestin-only pill [POP], Implant, or Injection or a Progestin-Releasing Intrauterine System [IUS]):

The woman may switch from the POP on any day; instruct her to start using EluRyng on the day after she took her last POP. She should switch from an implant or the IUS on the day of its removal, and from an injectable on the day when the next injection would be due. In all of these cases, the woman should use an additional barrier method such as a male condom with spermicide, for the first seven days.

Use After Abortion or Miscarriage:

The woman may start using EluRyng within the first five days following a complete first trimester abortion or miscarriage, and she does not need to use an additional method of contraception. If use of EluRyng is not started within five days following a first trimester abortion or miscarriage, the woman should follow the instructions for "No Hormonal Contraceptive Use in the Preceding Cycle." In the meantime, she should be advised to use a non-hormonal contraceptive method.

Start EluRyng no earlier than four weeks after a second trimester abortion or miscarriage, due to the increased risk of thromboembolism *[see Contraindications (4)* and *Warnings and Precautions (5.1)]*.

Following Childbirth:

The use of EluRyng may be initiated no sooner than four weeks postpartum in women who elect not to breastfeed, due to the increased risk of thromboembolism in the postpartum period *[see Contraindications (4)* and *Warnings and Precautions (5.1)]*.

Advise women who are breastfeeding not to use EluRyng but to use other forms of contraception until the child is weaned.

If a woman begins using EluRyng postpartum, instruct her to use an additional method of contraception, such as male condoms with spermicide, for the first seven days. If she has not yet had a period, consider the possibility of ovulation and conception occurring prior to initiation of EluRyng.

2.3 Deviations from the Recommended Regimen

To prevent loss of contraceptive efficacy, advise women not to deviate from the recommended regimen. EluRyng should be left in the vagina for a continuous period of three weeks. Advise women to regularly check for the presence of EluRyng in the vagina (for example, before and after intercourse).

Inadvertent Removal or Expulsion

EluRyng can be accidentally expelled, for example, while removing a tampon, during intercourse, or with straining during a bowel movement. EluRyng should be left in the vagina for a continuous period of three weeks. If the ring is accidentally expelled and is left outside of the vagina for **less than three hours**, contraceptive efficacy is not reduced. EluRyng can be rinsed with cool to lukewarm (not hot) water and **reinserted as soon as possible,** but at the latest within three hours. If EluRyng is lost, a new vaginal ring should be inserted and the regimen should be continued without alteration.

If EluRyng is out of the vagina **for more than three continuous hours:**

During Weeks 1 and 2: Contraceptive efficacy may be reduced. The woman should reinsert the ring as soon as she remembers. A barrier method such as male condoms with spermicides must be used until the ring has been used continuously for seven days.

During Week 3: The woman should discard that ring. One of the following two options should be chosen:

1. Insert a new ring immediately. Inserting a new ring will start the next three-week use period. The woman may not experience a withdrawal bleed from her previous cycle. However, breakthrough spotting or bleeding may occur.

2. Insert a new ring no later than seven days from the time the previous ring was removed or expelled, during which time she may have a withdrawal bleed. This option should only be chosen if the ring was used continuously for at least seven days prior to inadvertent removal/expulsion.

In either case, a barrier method such as male condoms with spermicides must be used until the new ring has been used continuously for seven days.

If EluRyng was out of the vagina for an unknown amount of time, the possibility of pregnancy should be considered. A pregnancy test should be performed prior to inserting a new ring.

Prolonged Ring-Free Interval
If the ring-free interval has been extended beyond one week, consider the possibility of pregnancy, and an additional method of contraception, such as male condoms with spermicide, **MUST** be used until EluRyng has been used **continuously for seven days.**

Prolonged Use of EluRyng
If EluRyng has been left in place for up to one extra week (i.e., up to four weeks total), the woman will remain protected. EluRyng should be removed and the woman should insert a new ring after a one-week ring-free interval.

If EluRyng has been left in place for longer than four weeks, instruct the woman to remove the ring, and rule out pregnancy. If pregnancy is ruled out, EluRyng may be restarted, and an additional method of contraception, such as male condoms with spermicide, **MUST** be used until a new EluRyng has been used **continuously for seven days.**

Ring Breakage
There have been reported cases of EluRyng disconnecting at the weld joint. This is not expected to affect the contraceptive effectiveness of EluRyng. In the event of a disconnected ring, vaginal discomfort or expulsion (slipping out) is more likely to occur. Vaginal injury associated with ring breakage has been reported *[see Adverse Reactions (6.2)]*.

If a woman discovers that her EluRyng has disconnected, she should discard the ring and replace it with a new ring.

2.4 In the Event of a Missed Menstrual Period

1. If the woman has not adhered to the prescribed regimen (EluRyng has been out of the vagina for more than three hours or the preceding ring-free interval was extended beyond one week), consider the possibility of pregnancy at the time of the first missed period and discontinue EluRyng use if pregnancy is confirmed.
2. If the woman has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.
3. If the woman has retained one EluRyng for longer than four weeks, rule out pregnancy.

2.5 Use with Other Vaginal Products

EluRyng may interfere with the correct placement and position of certain female barrier methods such as a diaphragm, cervical cap or female condom. These methods are not recommended as back-up methods with EluRyng use.

Pharmacokinetic data show that the use of tampons has no effect on the systemic absorption of the hormones released by EluRyng.

3 DOSAGE FORMS AND STRENGTHS

EluRyng (etonogestrel and ethinyl estradiol vaginal ring) is a non-biodegradable, flexible, transparent to translucent, colorless to almost colorless, combination contraceptive vaginal ring, with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. It is made of ethylene vinylacetate copolymers and magnesium stearate, and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol, USP. When placed in the vagina, each ring releases on average 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol, USP over a three-week period of use. EluRyng is not made with natural rubber latex.

4 CONTRAINDICATIONS

Do not prescribe EluRyng to women who are known to have or use the following:

- 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 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 inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.5)]*
  - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.9)]*
  - Have headaches with focal neurological symptoms or migraine headaches with aura *[see Warnings and Precautions (5.10)]*
    - Women over age 35 with any migraine headaches *[see Warnings and Precautions (5.10)]*
- Liver tumors, benign or malignant or liver disease *[see Warnings and Precautions (5.3)* and *Use in Specific Populations (8.6)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.11)]*
- Pregnancy, because there is no reason to use CHCs during pregnancy *[see Use in Specific Populations (8.1)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.14)]*
- Hypersensitivity reactions, including anaphylaxis and angioedema, to any of the components of EluRyng *[see Warnings and Precautions (5.6)* and *Adverse Reactions (6)]*
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop EluRyng use if an arterial thrombotic or venous thromboembolic event (VTE) occurs. Stop EluRyng use if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately *[see Adverse Reactions (6)]*.

If feasible, stop EluRyng at least four weeks before and through two weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism, and during and following prolonged immobilization.

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

The use of 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)]*.

Two epidemiologic studies[1, 2, 3] that assessed the risk of VTE associated with the use of EluRyng are described below.

In these studies, which were required or sponsored by regulatory agencies, EluRyng users had a risk of VTE similar to Combined Oral Contraceptives (COCs) users (see Table 1 for adjusted hazard ratios). A large prospective, observational study, the Transatlantic Active Surveillance on Cardiovascular Safety of EluRyng (TASC), investigated the risk of VTE for new users, and women who were switching to or restarting EluRyng or COCs in a population that is representative of routine clinical users. The women were followed for 24 to 48 months. The results showed a similar risk of VTE among EluRyng users (VTE incidence 8.3 per 10,000 WY) and women using COCs (VTE incidence 9.2 per 10,000 WY). For women using COCs that did not contain the progestins desogestrel (DSG) or gestodene (GSD), VTE incidence was 8.9 per 10,000 WY.

A retrospective cohort study using data from 4 health plans in the US (FDA-funded Study in Kaiser Permanente and Medicaid databases) showed the VTE incidence for new users of EluRyng to be 11.4 events per 10,000 WY, for new users of a levonorgestrel (LNG)-containing COC 9.2 events per 10,000 WY, and for users of other COCs available during the course of the study* 8.2 events per 10,000 WY.

* Includes low-dose COCs containing the following progestins: norgestimate, norethindrone, or levonorgestrel.

Table 1: Estimates (Hazard Ratios) of Venous Thromboembolism Risk in Users of EluRyng Compared to Users of Combined Oral Contraceptives (COCs)

Epidemiologic Study (Author, Year of Publication) Population Studied	**Comparator Product(s)**	**Hazard Ratios (HR) (95% CI)**
TASC (Dinger, 2012) Initiators, including new users, switchers and restarters	All COCs available during the course of the study [*] COCs available excluding DSG- or GSD -containing OCs	HR[†]: 0.8 (0.5 to 1.5) HR[†]: 0.8 (0.4 to 1.7)
FDA-funded Study in Kaiser Permanente and Medicaid databases (Sidney, 2011) First use of a combined hormonal contraceptive (CHC) during the study period	COCs available during the course of the study[‡] LNG/0.03 mg ethinyl estradiol	HR[§]: 1.1 (0.6 to 2.2) HR[§]: 1.0 (0.5 to 2.0)

[*] Includes low-dose COCs containing the following progestins: chlormadinone acetate, cyproterone acetate, desogestrel, dienogest, drospirenone, ethynodiol diacetate, gestodene, levonorgestrel, norethindrone, norgestimate, or norgestrel
[†] Adjusted for age, BMI, duration of use, VTE history
[‡] Includes low-dose COCs containing the following progestins: norgestimate, norethindrone, or levonorgestrel
[§] Adjusted for age, site, year of entry into study

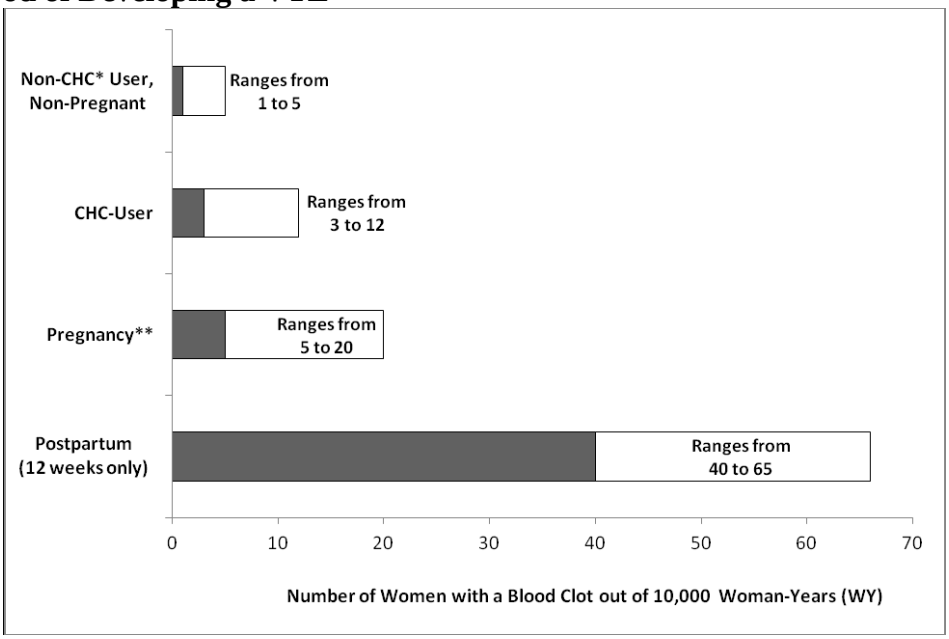
An increased risk of thromboembolic and thrombotic disease associated with the use of CHCs is well-established. Although the absolute VTE rates are increased for users of CHCs compared to non-users, the rates associated with pregnancy are even greater, especially during the post-partum period (see Figure 1).

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

The risk of VTE is highest during the first year of CHC use and after restarting a CHC following a break of at least four weeks. The risk of VTE due to CHCs gradually disappears after use is discontinued.

Figure 1 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 postpartum 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 1: 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 nine months, the rate is 7 to 27 per 10,000 WY.

Several epidemiology studies indicate that third generation oral contraceptives, including those containing desogestrel (etonogestrel, the progestin in EluRyng, is the biologically active metabolite of desogestrel), may be associated with a higher risk of VTE than oral contraceptives containing other progestins. Some of these studies indicate an approximate two-fold increased risk. However, data from other studies have not shown this two-fold increase in risk.

Use of CHCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. CHCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). In general, the risk is greatest among older (>35 years of age), hypertensive women who also smoke.

Use EluRyng with caution in women with cardiovascular disease risk factors.

5.2 Toxic Shock Syndrome (TSS)

Cases of TSS have been reported by EluRyng users. TSS has been associated with tampons and certain barrier contraceptives, and, in some cases the EluRyng users were also using tampons. A causal relationship between the use of EluRyng and TSS has not been established. If a patient exhibits signs or symptoms of TSS, consider the possibility of this diagnosis and initiate appropriate medical evaluation and treatment.

5.3 Liver Disease

Impaired Liver Function
Do not use EluRyng in women with liver disease such as acute viral hepatitis or severe (decompensated) cirrhosis of the liver *[see Contraindications (4)]*. 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 *[see Use in Specific Populations (8.6)]*. Discontinue EluRyng use if jaundice develops.

Liver Tumors
EluRyng 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 per 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 attributable risk of liver cancers in CHC users is less than one case per million users.

5.4 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as CHCs. Discontinue EluRyng prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir *[see Contraindications (4)]*. EluRyng can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.5 High Blood Pressure

EluRyng 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 EluRyng use if blood pressure rises significantly.

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

5.6 Hypersensitivity Reactions

Hypersensitivity reactions of anaphylaxis and angioedema have been reported during use of EluRyng. If anaphylaxis and/or angioedema is suspected, EluRyng should be discontinued and appropriate treatment administered *[see Contraindications (4)]*.

5.7 Vaginal Use

EluRyng may not be suitable for women with conditions that make the vagina more susceptible to vaginal irritation or ulceration. Vaginal/cervical erosion or ulceration in women using EluRyng has been reported. In some cases, the ring adhered to vaginal tissue, necessitating removal by a healthcare provider and in some instances (i.e., when the tissue had grown over the ring), removal was achieved by cutting the ring without incising the overlying vaginal tissue.

Some women are aware of the ring on occasion during the 21 days of use or during intercourse, and sexual partners may feel EluRyng in the vagina.

5.8 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.

5.9 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are using EluRyng. CHCs may decrease glucose tolerance.

Consider alternative contraception for women with uncontrolled dyslipidemia. Some women will have adverse lipid changes while on CHCs.

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

5.10 Headache

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

Consider discontinuation of EluRyng in the case of an increased frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) *[see Contraindications (4)]*.

5.11 Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Unscheduled bleeding (breakthrough or intracyclic) bleeding and spotting sometimes occur in women using CHCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different CHC.

Bleeding patterns were evaluated in three large clinical studies. In the North American study (US and Canada, N=1,177), the percentages of subjects with breakthrough bleeding/spotting ranged from 7.2% to 11.7% during cycles 1-13. In the two non-US studies, the percentages of subjects with breakthrough bleeding/spotting ranged from 2.6% to 6.4% (Europe, N=1,145) and from 2.0% to 8.7% (Europe, Brazil, Chile, N=512).

Amenorrhea and Oligomenorrhea

If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule, consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures.

Occasional missed periods may occur with the appropriate use of EluRyng. In the clinical studies, the percent of women who did not have withdrawal bleeding in a given cycle ranged from 0.3% to 3.8%.

If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

Some women may experience amenorrhea or oligomenorrhea after discontinuing CHC use, especially when such a condition was pre-existent.

5.12 Inadvertent Urinary Bladder Insertion

There have been reports of inadvertent insertions of EluRyng into the urinary bladder, which required cystoscopic removal. Assess for ring insertion into the urinary bladder in EluRyng users who present with persistent urinary symptoms and are unable to locate the ring.

5.13 Depression

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

5.14 Carcinoma of the Breasts and Cervix

EluRyng is contraindicated in women who currently have or have had breast cancer because breast cancer is a hormonally-sensitive tumor *[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 CHCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.15 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 hormones or cortisol therapy may need to be increased.

5.16 Monitoring

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

5.17 Hereditary Angioedema

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

5.18 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 EluRyng.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of CHCs are discussed elsewhere in the labeling.

- Serious cardiovascular events and stroke *[see Boxed Warning* and *Warnings and Precautions (5.1)]*

- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.3)]*

Adverse reactions commonly reported by CHC users 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 practice.

Trials with a duration of 6 to 13 28-day cycles provided safety data. In total, 2,501 women, aged 18 to 41 contributed 24,520 cycles of exposure.

Common Adverse Reactions (≥ 2%): vaginitis (13.8%), headache (including migraine) (11.2%), mood changes (e.g., depression, mood swings, mood altered, depressed mood, affect lability) (6.4%), device-related events (e.g., expulsion/discomfort/foreign body sensation) (6.3%), nausea/vomiting (5.9%), vaginal discharge (5.7%), increased weight (4.9%), vaginal discomfort (4.0%), breast pain/discomfort/tenderness (3.8%), dysmenorrhea (3.5%), abdominal pain (3.2%), acne (2.4%), and decreased libido (2.0%).

Adverse Reactions (≥ 1%) Leading to Study Discontinuation: 13.0% of the women discontinued from the clinical trials due to an adverse reaction; the most common adverse reactions leading to discontinuation were device-related events (2.7%), mood changes (1.7%), headache (including migraine) (1.5%) and vaginal symptoms (1.2%).

Serious Adverse Reactions: deep vein thrombosis *[see Warnings and Precautions (5.1)]*, anxiety, cholelithiasis, and vomiting.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of EluRyng. 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.

Immune system disorders: hypersensitivity reactions, including anaphylaxis and angioedema

Nervous system disorders: stroke/cerebrovascular accident

Vascular disorders: arterial events (including arterial thromboembolism and myocardial infarction), aggravation of varicose veins

Skin and subcutaneous tissue disorders: urticaria, chloasma

Reproductive system and breast disorders: penile disorders, including local reactions on penis (in male partners of women using EluRyng), galactorrhea

General Disorders and Administration Site Conditions: device breakage (including with concomitant use of intravaginal antimycotic, antibiotic, and lubricant products)

Injury, poisoning and procedural complications: vaginal injury (including associated pain, discomfort, and bleeding) associated with ring breakage

7 DRUG INTERACTIONS

Consult the labeling of all 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 CHCs

Substances decreasing the plasma concentrations of CHCs and potentially diminishing the effectiveness 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 CHCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure.

Counsel women to use an alternative non-hormonal method of contraception or a back-up method when enzyme inducers are used with EluRyng, and to continue back-up non-hormonal contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Note: EluRyng may interfere with the correct placement and position of certain female barrier methods such as a diaphragm or female condom. These methods are not recommended as back-up methods with EluRyng use *[see Dosage and Administration (2.5)]*.

The serum concentrations of etonogestrel and ethinyl estradiol were not affected by concomitant administration of oral amoxicillin or doxycycline in standard dosages during 10 days of antibiotic treatment. The effects of other antibiotics on etonogestrel or ethinyl estradiol concentrations have not been evaluated.

Substances increasing the plasma concentrations of CHCs

Co-administration of atorvastatin and certain CHCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20-25%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by inhibition of conjugation. Concomitant administration of strong or moderate CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma estrogen and/or progestin concentrations. Co-administration of vaginal miconazole nitrate and EluRyng increases the serum concentrations of etonogestrel and ethinyl estradiol by up to 40% *[see Clinical Pharmacology (12.3)]*.

Human immunodeficiency virus (HIV) / Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors

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

atazanavir/ritonavir]) /HCV protease inhibitors (decrease [e.g., boceprevir and telaprevir]) or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., efavirenz, nevirapine] or increase [e.g., etravirine]). These changes may be clinically relevant in some cases.

7.2 Effects of CHCs on Other Drugs

CHCs containing ethinyl estradiol 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. A significant decrease in the plasma concentrations 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 concentrations of thyroid-binding globulin increase with use of CHCs.

7.3 Concomitant Use with HCV Combination Therapy - Liver Enzyme Elevation

Do not co-administer EluRyng with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations *[see Warnings and Precautions (5.4)]*.

7.4 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

Risk Summary

EluRyng is contraindicated during pregnancy because there is no need for pregnancy prevention in a woman who is already pregnant. Epidemiologic studies and meta-analyses have not shown an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following maternal exposure to low dose CHCs prior to conception or during early pregnancy. No adverse developmental outcomes were observed in pregnant rats and rabbits with the administration of etonogestrel during organogenesis at doses approximately 300 times the anticipated daily vaginal human dose (~0.002 mg/kg/day).

No adverse developmental outcomes were observed in pregnant rats and rabbits with the co-administration of the combination desogestrel/ethinyl estradiol during organogenesis at desogestrel/ethinyl estradiol doses at least 2/5 times, respectively, the anticipated daily vaginal human dose (~0.002 desogestrel/0.00025 ethinyl estradiol mg/kg/day).

Discontinue EluRyng use if pregnancy is confirmed.

Data

Animal Data

In rats and rabbits at dosages up to 300 times the anticipated dose, etonogestrel is neither embryotoxic nor teratogenic. Co-administration of a maternally toxic dose of desogestrel/ethinyl estradiol to pregnant rats was

associated with embryolethality and wavy ribs at a desogestrel/ethinyl estradiol dose that was 40/130 times, respectively, the anticipated vaginal human dose (0.002 desogestrel/0.00025 ethinyl estradiol mg/kg/day). No adverse embryofetal effects were observed when the combination was administered to pregnant rats at a desogestrel/ethinyl estradiol dose that was 4/13 times, respectively, the anticipated vaginal human dose. When desogestrel/ethinyl estradiol was given to pregnant rabbits, pre-implantation loss was observed at a desogestrel/ethinyl estradiol dose that was 3/10 times, respectively, the anticipated vaginal human dose. No adverse embryofetal effects were observed when the combination was administered to pregnant rabbits at a desogestrel/ethinyl estradiol dose that was 2/5 times the anticipated vaginal human dose.

8.2 Lactation

Risk Summary

Small amounts of contraceptive steroids and/or metabolites, including etonogestrel and ethinyl estradiol are transferred to human milk. Harmful effects have not been observed in breastfed infants exposed to CHCs through breast milk. 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.

When possible, advise the nursing mother to use non-estrogen-containing contraception until she has completely weaned her child. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EluRyng and any potential adverse effects on the breastfed child from EluRyng or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy of EluRyng have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal 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

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

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of EluRyng has not been studied. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal *[see Contraindications (4)* and *Warnings and Precautions (5.3)]*.

8.7 Renal Impairment

The effect of renal impairment on the pharmacokinetics of EluRyng has not been studied.

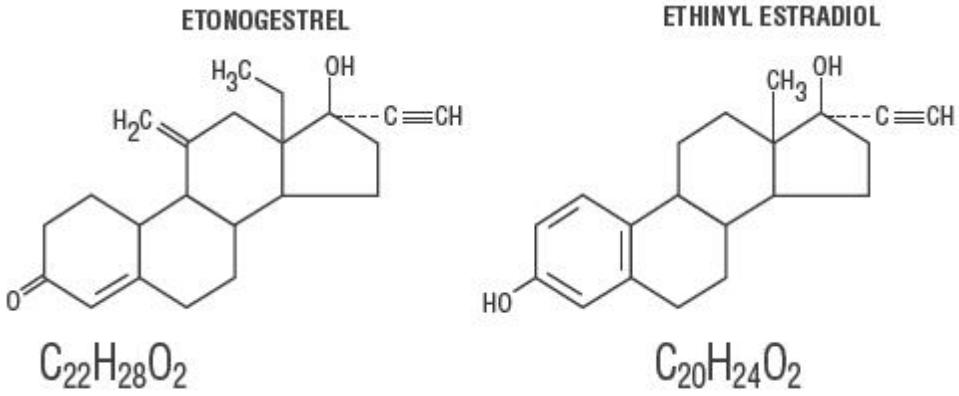
10 OVERDOSAGE

There have been no reports of serious ill effects from overdose of CHCs. Overdosage may cause withdrawal bleeding in females and nausea. If the ring breaks, it does not release a higher dose of hormones. In case of suspected overdose, all EluRyng rings should be removed and symptomatic treatment given.

11 DESCRIPTION

EluRyng (etonogestrel and ethinyl estradiol vaginal ring) is a non-biodegradable, flexible, transparent to translucent , colorless to almost colorless, combination contraceptive vaginal ring containing two active components, a progestin, etonogestrel (13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one) and an estrogen, ethinyl estradiol, USP (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol). When placed in the vagina, each ring releases on average 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol, USP over a three-week period of use. EluRyng is made of ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol, USP. EluRyng is not made with natural rubber latex. EluRyng has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. The molecular weights for etonogestrel and ethinyl estradiol, USP are 324.5 and 296.40, respectively.

The structural formulas are as follows:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Combination hormonal contraceptives act by suppression of gonadotropins. Although the primary effect 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).

12.3 Pharmacokinetics

Absorption
Etonogestrel: Etonogestrel released by EluRyng is rapidly absorbed. The bioavailability of etonogestrel after vaginal administration is approximately 100%. The serum etonogestrel and ethinyl estradiol concentrations observed during three weeks of EluRyng use are summarized in Table 2.

Ethinyl estradiol: Ethinyl estradiol released by EluRyng is rapidly absorbed. The bioavailability of ethinyl estradiol after vaginal administration is approximately 56%, which is comparable to that with oral administration of ethinyl estradiol. The serum ethinyl estradiol concentrations observed during three weeks of EluRyng use are summarized in Table 2.

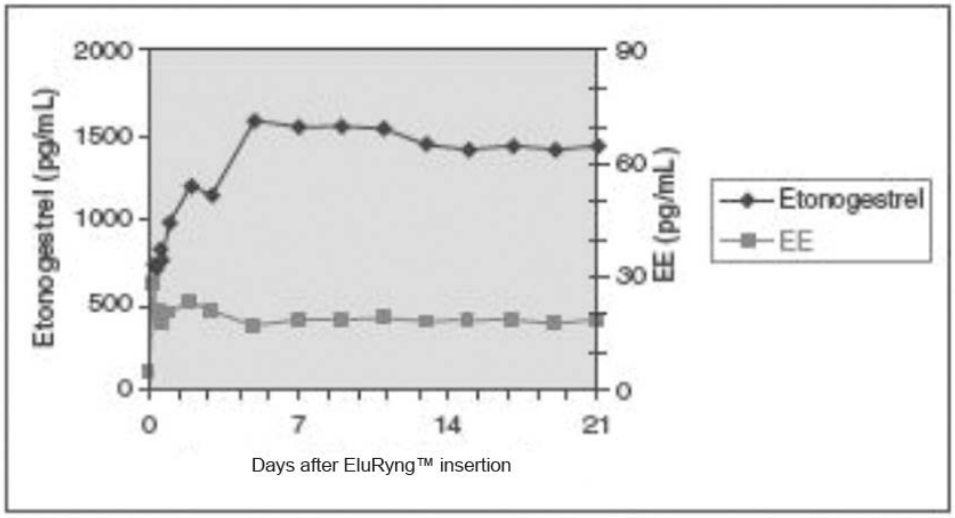
Table 2: Mean (SD) Serum Etonogestrel and Ethinyl Estradiol Concentrations (n=16)

	1 week	2 weeks	3 weeks
etonogestrel (pg/mL)	1578 (408)	1476 (362)	1374 (328)

ethinyl estradiol (pg/mL)	19.1 (4.5)	18.3 (4.3)	17.6 (4.3)

The pharmacokinetic profile of etonogestrel and ethinyl estradiol during use of EluRyng is shown in Figure 2.

Figure 2: Mean Serum Concentration-Time Profile of Etonogestrel and Ethinyl Estradiol during Three Weeks of EluRyng Use



The pharmacokinetic parameters of etonogestrel and ethinyl estradiol were determined during one cycle of EluRyng use in 16 healthy female subjects and are summarized in Table 3.

Table 3: Mean (SD) Pharmacokinetic Parameters of EluRyng (n=16)

Hormone	**C_{max} pg/mL**	**T_{max} hr**	**$t_{1/2}$ hr**	**CL L/hr**
etonogestrel	1716 (445)	200.3 (69.6)	29.3 (6.1)	3.4 (0.8)
ethinyl estradiol	34.7 (17.5)	59.3 (67.5)	44.7 (28.8)	34.8 (11.6)

C_{max}- maximum serum drug concentration
T_{max}- time at which maximum serum drug concentration occurs
$t_{1/2}$ - elimination half-life, calculated by $0.693/K_{elim}$
CL - apparent clearance

Prolonged use of EluRyng: The mean serum etonogestrel concentration at the end of the fourth week of continuous use of EluRyng was 1272 ± 311 pg/mL compared to a mean concentration range of 1578 ± 408 to 1374 ± 328 pg/mL at the end of weeks one to three. The mean serum ethinyl estradiol concentration at the end of the fourth week of continuous use of EluRyng was 16.8 ± 4.6 pg/mL compared to a mean concentration range of 19.1 ± 4.5 to 17.6 ± 4.3 pg/mL at the end of weeks one to three.

Distribution

Etonogestrel: Etonogestrel is approximately 32% bound to sex hormone-binding globulin (SHBG) and approximately 66% bound to albumin in blood.

Ethinyl estradiol: Ethinyl estradiol is highly but not specifically bound to serum albumin (98.5%) and induces an increase in the serum concentrations of SHBG.

Metabolism

In vitro data shows that both etonogestrel and ethinyl estradiol are metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme. Ethinyl estradiol is primarily metabolized by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as sulfate and glucuronide conjugates. The hydroxylated ethinyl estradiol metabolites have weak estrogenic activity. The biological activity of etonogestrel metabolites is unknown.

Excretion

Etonogestrel and ethinyl estradiol are primarily eliminated in urine, bile and feces.

Drug Interactions

[See also Drug Interactions (7).]

The drug interactions of EluRyng were evaluated in several studies.

A single-dose vaginal administration of an oil-based 1200-mg miconazole nitrate capsule increased the serum concentrations of etonogestrel and ethinyl estradiol by approximately 17% and 16%, respectively. Following multiple doses of 200 mg miconazole nitrate by vaginal suppository or vaginal cream, the mean serum concentrations of etonogestrel and ethinyl estradiol increased by up to 40%.

A single-dose vaginal administration of 100-mg water-based nonoxynol-9 spermicide gel did not affect the serum concentrations of etonogestrel or ethinyl estradiol.

The serum concentrations of etonogestrel and ethinyl estradiol were not affected by concomitant administration of oral amoxicillin or doxycycline in standard dosages during 10 days of antibiotic treatment.

Tampon Use
The use of tampons had no effect on serum concentrations of etonogestrel and ethinyl estradiol during use of EluRyng *[see Dosage and Administration (2.5)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 mcg etonogestrel per day, (approximately 0.3 and 0.6 times the systemic steady-state exposure of women using EluRyng), no drug-related carcinogenic potential was observed.

Mutagenesis

Etonogestrel was not genotoxic in the *in vitro* Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the *in vivo* mouse micronucleus test.

Impairment of Fertility

A fertility study was conducted with etonogestrel in rats at approximately 600 times the anticipated daily vaginal human dose (~0.002 mg/kg/day). Treatment did not have any adverse effect on resulting litter parameters after cessation of treatment supporting the return to fertility after suppression with etonogestrel.

14 CLINICAL STUDIES

In three large one-year clinical trials enrolling 2,834 women aged 18 to 40 years, in North America, Europe, Brazil, and Chile, the racial distribution was 93% Caucasian, 5.0% Black, 0.8% Asian, and 1.2% Other. Women with BMI ≥ 30 kg/m^2 were excluded from these studies.

Based on pooled data from the three trials, 2,356 women aged < 35 years completed 23,515 evaluable cycles of EluRyng use (cycles in which no back-up contraception was used). The pooled pregnancy rate (Pearl Index) was 1.28 (95% CI [0.8, 1.9]) per 100 women-years of EluRyng use. In the US study, the Pearl Index was 2.02 (95% CI [1.1, 3.4]) per 100 women-years of EluRyng use.

Study data indicate the return of ovulation and spontaneous menstrual cycles in most women within a month after discontinuation of EluRyng use.

15 REFERENCES

1. Dinger, J et. al., Cardiovascular risk associated with the use of an etonogestrel-containing vaginal ring. Obstetrics & Gynecology 2013; 122(4): 800-808.
2. Sidney, S. et. al., Recent combined hormonal contraceptives (CHCs) and the risk of thromboembolism and other cardiovascular events in new users. Contraception 2013; 87: 93-100.
3. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular endpoints. Sidney, S. (primary author) http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf, accessed 23-Aug-2013.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each EluRyng (etonogestrel and ethinyl estradiol vaginal ring) is individually packaged in a reclosable aluminum laminate pouch consisting of four layers, from outside to inside: polyester, LDPE-EAA coex (low density polyethylene/ethylene acryclic acid copolymer coextrudate laminate), aluminum foil, and EAA-LLDPE coex (ethylene acryclic acid copolymer/ low low density polyethylene coextrudate laminate). The ring should be replaced in this reclosable pouch after use and discarded in a waste receptacle out of the reach of children and pets. It should not be flushed down the toilet.

Carton of 3 pouches NDC 65162-469-35

16.1 Storage

Prior to dispensing to the user, store refrigerated 2° to 8°C (36° to 46°F). After dispensing to the user, EluRyng can be stored for up to 4 months at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Avoid storing EluRyng in direct sunlight or at temperatures above 30°C (86°F).

For the Dispenser: When EluRyng is dispensed to the user, place an expiration date on the label. The date should not exceed either 4 months from the date of dispensing or the expiration date, whichever comes first.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Counsel patients regarding the following:

Increased risk of cardiovascular events

- Advise patients that cigarette smoking increases the risk of serious cardiovascular events from use of EluRyng, and women who are over 35 years old and smoke should not use EluRyng *[see Boxed Warning]*.
- Inform patients that the increased risk of VTE compared to non-users of CHCs is greatest after initially starting a CHC or restarting (following a 4-week or greater CHC-free interval) the same or a different CHC *[see Warnings and Precautions (5.1)]*.

Use and administration

- Inform patients that EluRyng does not protect against HIV infection (AIDS) and other sexually transmitted infections.
- Advise patients on the proper usage of EluRyng and what to do if she does not comply with the labeled timing of insertion and removal *[see Dosage and Administration (2)]*.
- Advise patients to regularly check for the presence of EluRyng in the vagina (for example, before and after intercourse) *[see Dosage and Administration (2.3)]*.

Pregnancy

- Inform patients that EluRyng is not to be used during pregnancy. If pregnancy is planned or occurs during treatment with EluRyng, instruct the patient to discontinue EluRyng use *[see Use in Specific Populations (8.1)]*.

Use of additional contraception

- Inform patients that they need to use a barrier method of contraception when the ring is out for more than three continuous hours until EluRyng has been used continuously for at least seven days *[see Dosage and Administration (2.3)]*.
- Advise patients to use a back-up or alternative method of contraception when enzyme inducers are used with EluRyng *[see Drug Interactions (7.1)]*.
- Inform patients who start EluRyng postpartum and have not yet had a normal period that they should use an additional non-hormonal method of contraception for the first seven days *[see Dosage and Administration (2.2)]*.

Lactation

- Inform patients that CHCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established *[see Use in Specific Populations (8.2)]*.

Amenorrhea

- Inform patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea if EluRyng has been out of the vagina for more than three consecutive hours, if the ring-free interval was extended beyond one week, if the woman has missed a period for two or more consecutive cycles, and if the ring has been retained for longer than four weeks *[see Warnings and Precautions (5.11)]*.

Disposal

- Advise patients on the proper disposal of a used EluRyng *[see How Supplied/Storage and Handling (16)]*.

Distributed by:
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

Rev. 05-2019-02

Patient Information
EluRyng™ (el' ue ring)
(etonogestrel and ethinyl estradiol vaginal ring)

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

Do not use EluRyng if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from combination hormonal contraceptives (CHCs), including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

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 EluRyng?

EluRyng (el' ue ring) is a flexible birth control vaginal ring used to prevent pregnancy.

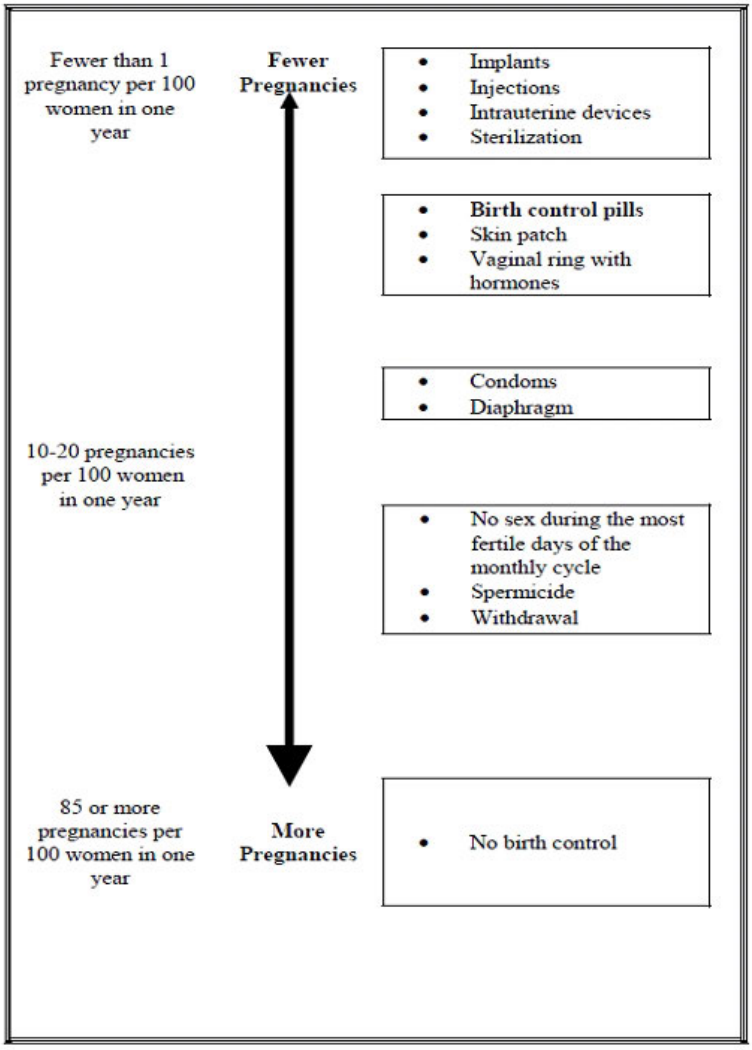
EluRyng contains a combination of a progestin and estrogen, 2 kinds of female hormones. Birth control methods that contain both an estrogen and a progestin are called combination hormonal contraceptives (CHCs).

How well does EluRyng work?

Your chance of getting pregnant depends on how well you follow the directions for using EluRyng. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of a US clinical study, approximately 1 to 3 women out of 100 women may get pregnant during the first year they use EluRyng.

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 EluRyng?

Do not use EluRyng 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 with your blood that makes it 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 can't control
- have diabetes with kidney, eye, nerve, or blood vessel damage
- have 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
- take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme “alanine aminotransferase” (ALT) in the blood
- have unexplained vaginal bleeding
- are pregnant or think you may be pregnant. EluRyng is not for pregnant women.
- have or have had breast cancer or any cancer that is sensitive to female hormones

- are allergic to etonogestrel, ethinyl estradiol or any of the ingredients in EluRyng. See the list of ingredients in EluRyng at the end of this leaflet.

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 conditions listed above. Your healthcare provider can suggest another method of birth control.

What should I tell my healthcare provider before using EluRyng?

Before you use EluRyng tell your healthcare provider if you:

- have any medical conditions
- smoke
- are pregnant or think you are pregnant
- recently had a baby
- recently had a miscarriage or abortion
- have a family history of breast cancer
- have or have had breast nodules, fibrocystic disease, an abnormal breast x-ray, or abnormal mammogram
- use tampons and have a history of toxic shock syndrome
- have been diagnosed with depression
- have had liver problems including jaundice during pregnancy
- have or have had elevated cholesterol or triglycerides
- have or have had gallbladder, liver, heart, or kidney disease
- have diabetes
- have a history of jaundice (yellowing of the skin or eyes) caused by pregnancy (also called cholestasis of pregnancy)
- have a history of scanty or irregular menstrual periods
- have any condition that makes the vagina become irritated easily
- have or have had high blood pressure
- have or have had migraines or other headaches or seizures
- are scheduled for surgery. EluRyng may increase your risk of blood clots after surgery. You should stop using EluRyng at least 4 weeks before you have surgery and not restart it until at least 2 weeks after your surgery.
- 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 EluRyng, may decrease the amount of milk you make. A small amount of hormones from EluRyng may pass into your breast milk. Consider another non-hormonal method of birth control until you are ready to stop breastfeeding.
- have (or have ever had) an allergic reaction while using EluRyng, including hives, swelling of the face, lips, tongue, and/or throat causing difficulty in breathing or swallowing (anaphylaxis and/or angioedema).

Tell your healthcare provider about all medicines and herbal products you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

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

- certain anti-seizure medicines (such as barbiturates, carbamazepine, felbamate, oxcarbazepine, phenytoin, rufinamide and topiramate)
- medicine to treat fungal infections (griseofulvin)
- certain combinations of HIV medicines, (such as nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir)
- certain hepatitis C (HCV) medicines (such as boceprevir and telaprevir)
- non-nucleoside reverse transcriptase inhibitors (such as efavirenz and nevirapine)
- medicine to treat tuberculosis (such as rifampicin and rifabutin)
- medicine to treat high blood pressure in the vessels of the lung (bosentan)
- medicine to treat chemotherapy-induced nausea and vomiting (aprepitant)
- St John's wort

Use an additional barrier contraceptive method (such as a male condom with spermicide) when you take medicines that may make EluRyng less effective. Since the effect of another medicine on EluRyng may last up to 28 days after stopping the medicine, it is necessary to use the additional barrier contraceptive method for that long to help prevent you from becoming pregnant. While using EluRyng, you should not use certain female barrier contraceptive methods such as a vaginal diaphragm, cervical cap or female condom as your back-up method of birth control because EluRyng may interfere with the correct placement and position of a diaphragm, cervical cap or female condom.

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

- the pain reliever acetaminophen
- ascorbic acid (vitamin C)
- medicines that affect how your liver breaks down other medicines (such as itraconazole, ketoconazole, voriconazole, fluconazole, clarithromycin, erythromycin, and diltiazem)
- certain HIV medicines (atazanavir/ritonavir and indinavir)
- non-nucleoside reverse transcriptase inhibitors (such as etravirine)
- medicines to lower cholesterol such as atorvastatin and rosuvastatin

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

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

Ask your healthcare provider if you are not sure if you take any of the medicines listed above. 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 EluRyng?

- Read the **Instructions for Use** at the end of this Patient Information that comes with your EluRyng for information about the right way to use EluRyng.
- Use EluRyng exactly as your healthcare provider tells you to use it.
- EluRyng is used in a 4-week cycle.
    - Insert 1 EluRyng in the vagina and keep it in place for 3 weeks (21 days).
      Regularly check that EluRyng is in your vagina (for example, before and after intercourse) to ensure that you are protected from pregnancy.
    - Remove the EluRyng for a 1-week break (7 days). During the 1-week break (7 days), you will usually have your menstrual period.
      Note: Insert and remove EluRyng on the same day of the week and at the same time:

    - For example, if you insert your EluRyng on a Monday at 8:00 am, you should remove it on the Monday 3 weeks later at 8:00 am.
    - After your 1-week (7 days) break, you should insert a new EluRyng on the next Monday at 8:00 am.
- While using EluRyng, you should not use certain female barrier contraceptive methods such as a vaginal diaphragm, cervical cap or female condom as your back-up method of birth control because EluRyng may interfere with the correct placement and position of a diaphragm, cervical cap or female condom.
- Ring breakage has occurred when also using a vaginal product such as a lubricant or treatment for infection (see "What should I do if my EluRyng comes out of my vagina?"). Use of spermicides or vaginal yeast products will not make EluRyng less effective at preventing pregnancy.
- Use of tampons will not make EluRyng less effective or stop EluRyng from working.
- If EluRyng has been left inside your vagina for more than 4 weeks (28 days), you may not be protected from pregnancy and you should see your healthcare provider to be sure you are not pregnant. Until you know the results of your pregnancy test, you should use an extra method of birth control, such as male condoms with spermicide, until the new EluRyng has been in place for 7 days in a row.
- Do not use more than 1 EluRyng at a time. Too much hormonal birth control medicine in your body may cause nausea, vomiting, or vaginal bleeding.

Your healthcare provider should examine you at least 1 time a year to see if you have any signs of side effects from using EluRyng.

What are the possible side effects of using EluRyng?

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

EluRyng may cause serious side effects, including:

blood clots. Like pregnancy, combination 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 a combination hormonal birth control method or when you restart the same or different combination hormonal birth control method after not using it for a month or more. Talk with your healthcare provider about your risk of getting a blood clot before using EluRyng or before deciding which type of birth control is right for you.

In some studies of women who used EluRyng, the risk of getting a blood clot was similar to the risk in women who used combination birth control pills.

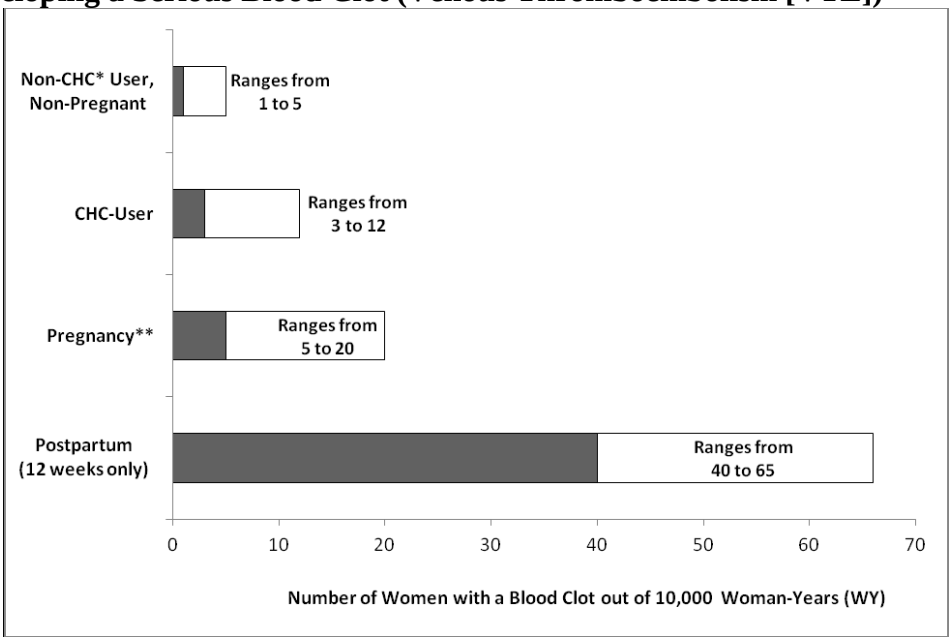
Other studies have reported that the risk of blood clots was higher for women who use combination birth control pills containing desogestrel (a progestin similar to the progestin in EluRyng) than for women who use combination birth control pills that do not contain desogestrel.

It is possible to die or be permanently disabled from a problem caused by a blood clot, such as heart attack or 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 does 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:

- Toxic Shock Syndrome (TSS). Some of the symptoms are much the same as the flu, but they can become serious very quickly. Call your healthcare provider or get emergency treatment right away if you have the following symptoms:
  - sudden high fever
  - vomiting
  - diarrhea
  - a sunburn-like rash
  - muscle aches
  - dizziness
  - fainting or feeling faint when standing up
- allergic reaction, including hives, swelling of the face, lips, tongue, and/or throat causing difficulty in breathing or swallowing (anaphylaxis and or/angioedema).
- liver problems, including liver tumors
- high blood pressure
- gallbladder problems
- accidental insertion into bladder
- symptoms of a problem called angioedema if you already have a family history of angioedema

The most common side effects of EluRyng are:

- tissue irritation inside your vagina or on your cervix
- headache (including migraine)
- mood changes (including depression, especially if you had depression in the past). Call your healthcare provider immediately if you have any thoughts of harming yourself.
- EluRyng problems, including the ring slipping out or causing discomfort
- nausea and vomiting
- vaginal discharge
- weight gain
- vaginal discomfort
- breast pain, discomfort, or tenderness
- painful menstrual periods
- abdominal pain
- acne
- less sexual desire

Some women have spotting or light bleeding during EluRyng use. If these symptoms occur, do not stop using EluRyng. The problem will usually go away. If it doesn't go away, check with your healthcare provider.

Other side effects seen with EluRyng include breast discharge; vaginal injury (including pain, discomfort, and bleeding) associated with broken rings; and penis discomfort of the partner (such as irritation, rash, itching).

Less common side effects seen with combination hormonal birth control include:

- Blotchy darkening of your skin, especially on your face
- High blood sugar, especially in women who already have diabetes
- High fat (cholesterol, triglycerides) levels in the blood

There have been reports of the ring becoming stuck to the vaginal tissue and having to be removed by a healthcare provider. Call your healthcare provider if you are unable to remove your EluRyng.

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 EluRyng. 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 EluRyng and throw away used EluRyngs?

- Store EluRyng at room temperature between 68°F to 77°F (20°C to 25°C).
- Store EluRyng at room temperature for up to 4 months after you receive it. Throw EluRyng away if the expiration date on the label has passed.
- Do not store EluRyng above 86°F (30°C).
- Avoid direct sunlight.
- Place the used EluRyng in the re-closable foil pouch and properly throw it away in your household trash out of the reach of children and pets. Do not flush your used EluRyng down the toilet.

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

General information about the safe and effective use of EluRyng

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information. Do not use EluRyng for a condition for which it was not prescribed. Do not give EluRyng to other people. It may harm them.

This leaflet summarizes the most important information about EluRyng. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about EluRyng that is written for health professionals.

For more information on EluRyng, go to www.amneal.com or call 1-877-835-5472.

What are the ingredients in EluRyng?

Active ingredients: etonogestrel and ethinyl estradiol, USP

Inactive ingredients: ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate.

EluRyng is not made with natural rubber latex.

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, including EluRyng, 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 EluRyng?

When you use EluRyng 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 EluRyng use, but may also occur after you have been using EluRyng for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue using the ring 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 regular scheduled period when using EluRyng?

Some women miss periods on hormonal birth control, even when they are not pregnant. Consider the possibility that you may be pregnant if:

1. you miss a period and EluRyng was out of the vagina for more than 3 hours during the 3 weeks (21 days) of ring use
2. you miss a period and waited longer than 1 week to insert a new ring
3. you have followed the instructions and you miss 2 periods in a row
4. you have left EluRyng in place for longer than 4 weeks (28 days)

What if I want to become pregnant?

You may stop using EluRyng whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop using EluRyng.

Instructions for Use

EluRyng™ (el'ue ring)
(etonogestrel and ethinyl estradiol vaginal ring)

Read these Instructions for Use before you start using EluRyng and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your treatment.

How should I start using EluRyng?

If you are not currently using hormonal birth control, you have 2 ways to start using EluRyng. Choose the best way for you:

- **First Day Start:** Insert EluRyng on the first day of your menstrual period. You will not need to use another birth control method since you are using EluRyng on the first day of your menstrual period.
- **Day 2 to Day 5 Cycle Start:** You may choose to start EluRyng on days 2 to 5 of your menstrual period. Make sure you also use an extra method of birth control (barrier method), such as male condoms with spermicide for the first 7 days of EluRyng use in the first cycle.

If you are changing from a birth control pill or patch to EluRyng:

If you have been using your birth control method correctly and are certain that you are not pregnant, you can change to EluRyng any day. Do not start EluRyng any later than the day you would start your next birth control pill or apply your patch.

If you are changing from a progestin-only birth control method, such as a minipill, implant or injection or from an intrauterine system (IUS):

- You may switch from a minipill on any day. Start using EluRyng on the day that you would have taken your next minipill.
- You should switch from an implant or the IUS and start using EluRyng on the day that you remove the implant or IUS.
- You should switch from an injectable and start using EluRyng on the day when your next injection would be due.

If you are changing from a minipill, implant or injection or from an intrauterine system (IUS), you should use an extra method of birth control, such as a male condom with spermicide during the first 7 days of using EluRyng.

If you start using EluRyng after an abortion or miscarriage:

- **Following a first trimester abortion or miscarriage:** You may start EluRyng within 5 days following a first trimester abortion or miscarriage (the first 12 weeks of pregnancy). <u>You do not need to use an additional birth control method</u>.
- If you do not start EluRyng within 5 days after a first trimester abortion or miscarriage, use a non-hormonal birth control method, such as male condoms and spermicide, while you wait for your period to start. Begin EluRyng at the time of your next menstrual period. Count the first day of your menstrual period as "Day 1" and start EluRyng one of the following 2 ways below.

    - **First Day Start:** Insert EluRyng on the first day of your menstrual period. You will not need to use another birth control method since you are using EluRyng on the first day of your menstrual period.

- **Day 2 to Day 5 Cycle Start:** You may choose to start EluRyng on Days 2 to 5 of your menstrual period. Make sure you also use an extra method of birth control (barrier method), such as male condoms with spermicide for the first 7 days of EluRyng use in the first cycle.
- **Following a second trimester abortion or miscarriage:** You may start using EluRyng no sooner than 4 weeks (28 days) after a second trimester abortion (**after** the first 12 weeks of pregnancy).

If you are starting EluRyng after childbirth:

- You may start using EluRyng no sooner than 4 weeks (28 days) after having a baby if you are not breastfeeding.
- If you have not gotten your menstrual period after childbirth, you should talk to your healthcare provider. You may need a pregnancy test to make sure you are not pregnant before you start using EluRyng.
- Use another birth control method such as male condoms with spermicide for the first 7 days in addition to EluRyng.

If you are breastfeeding you should not use EluRyng. Use other birth control methods until you are no longer breastfeeding.

Step 1. Choose a position for insertion of EluRyng.

- Choose the position that is comfortable for you. For example, lying down, squatting, or standing with 1 leg up **(See Figures A, B, and C)**.

Positions for EluRyng insertion

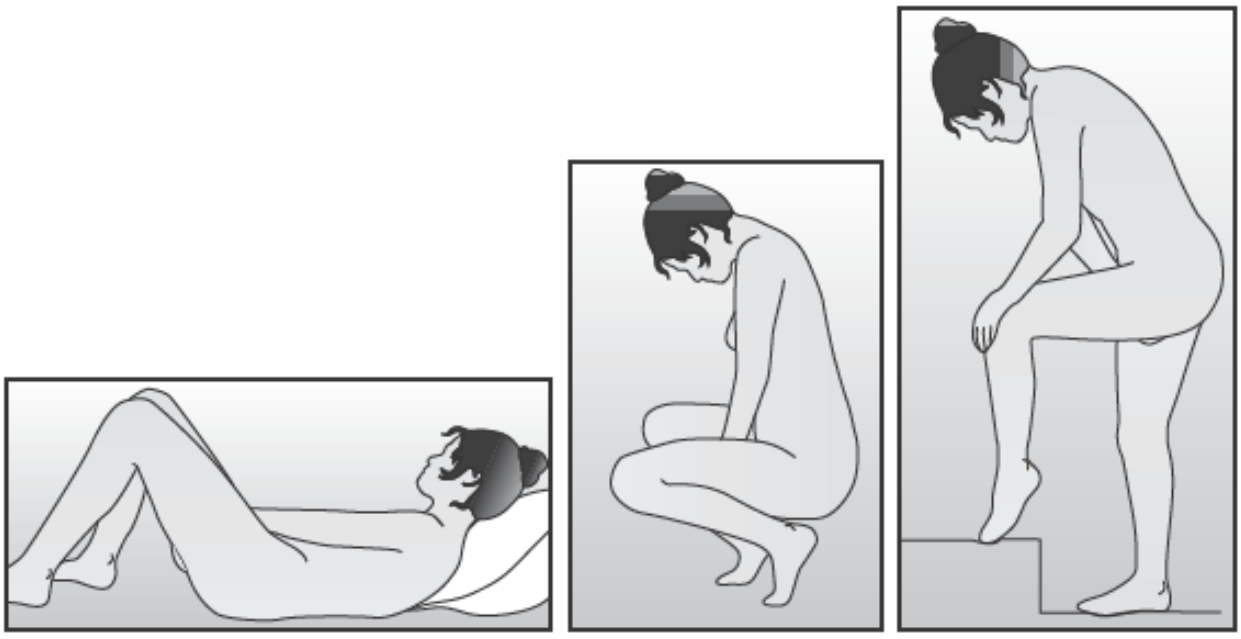


Figure A **Figure B** **Figure C**

Step 2. Open the pouch to remove your EluRyng.

- Each EluRyng comes in a re-sealable foil pouch.
- Wash and dry your hands before removing EluRyng from the foil pouch.
- Open the foil pouch at either notch near the top.
- Keep the foil pouch so you can place your used EluRyng in it before you throw it away in your household trash.

Step 3. Prepare EluRyng for insertion.

- Hold EluRyng between your thumb and index finger and press the sides of the ring together **(See Figures D and E)**.

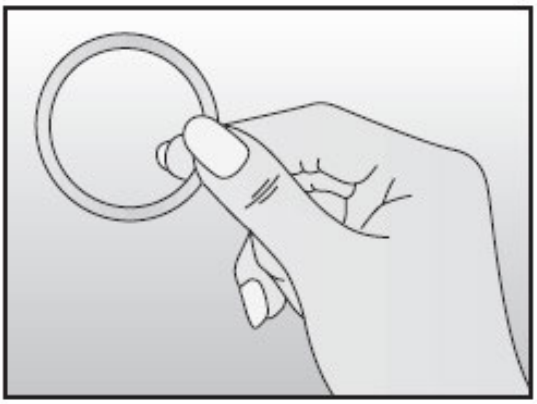


Figure D

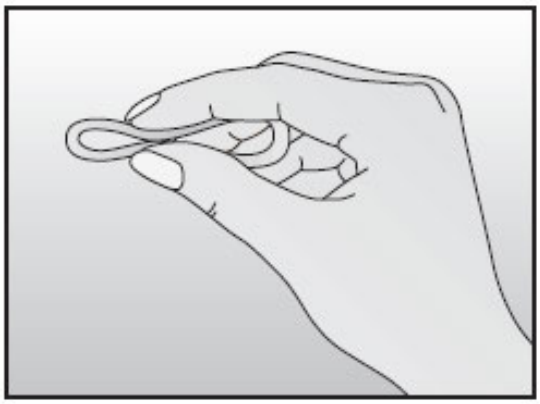


Figure E

Step 4. Insert EluRyng into your vagina.

- Insert the folded EluRyng into your vagina and gently push it further up into your vagina using your index finger **(See Figures F and G).**
- When you insert EluRyng it may be in different positions in your vagina, but EluRyng does not have to be in an exact position for it to work **(See Figures H and I).**
- EluRyng may move around slightly within your vagina. This is normal. Although some women may be aware of EluRyng in the vagina, most women do not feel it when it is in place.

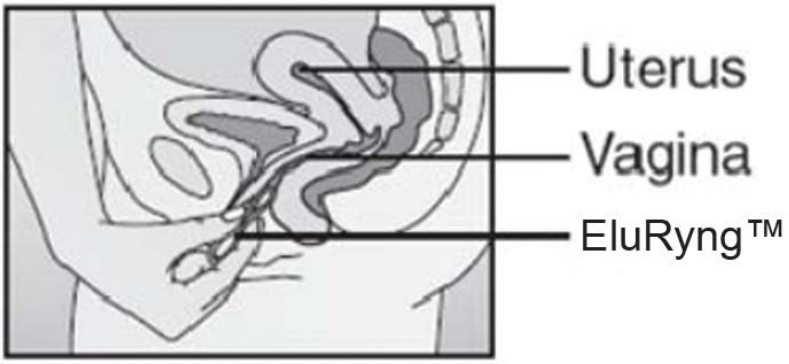


Figure F

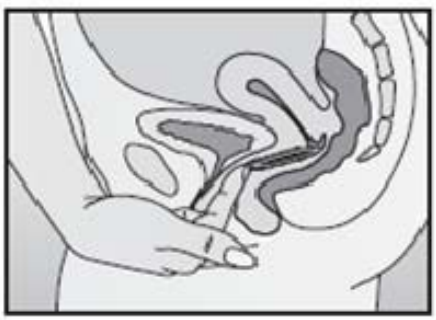


Figure G

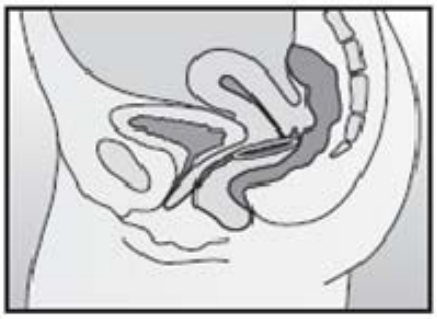


Figure H

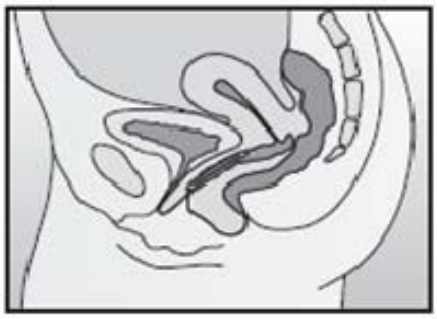


Figure I

Inserting EluRyng (**Figure F, Figure G)** and positioning EluRyng (**Figure H, Figure I)**

Note:

- If the EluRyng feels uncomfortable, you may not have pushed the ring into your vagina far enough. Use your finger to gently push the EluRyng as far as you can into your vagina. There is no danger of EluRyng being pushed too far up in the vagina or getting lost **(See Figure G)**.
- Some women have accidentally inserted EluRyng into their bladder. If you have pain during or after insertion and you cannot find EluRyng in your vagina, call your healthcare provider right away.
- Regularly check that EluRyng is in your vagina (for example, before and after intercourse) to ensure you are protected from pregnancy.

Step 5. How do I remove EluRyng?

- Wash and dry your hands.
- Choose the position that is most comfortable for you **(See Figures A, B, and C)**.
- Put your index finger into your vagina and hook it through the EluRyng. Gently pull downward and forward to remove the EluRyng and pull it out **(See Figure J)**.

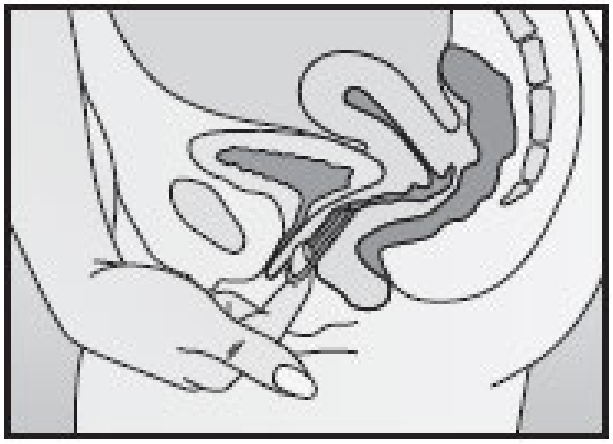


Figure J

Step 6. Throw away the used EluRyng**.**

- Place the used EluRyng in the re-sealable foil pouch and put it in a trash can out of the reach of children and pets.
- Do not throw EluRyng in the toilet.

What else should I know about using EluRyng?

What if I leave EluRyng in too long?

- If you leave EluRyng in your vagina for up to 4 weeks (28 days) you will still be getting pregnancy protection. Remove your old EluRyng for 1 week (7 days) and insert a new EluRyng 1 week (7 days) later **(See Steps 1 through 4)**.
- If you leave EluRyng in your vagina longer than 4 weeks (28 days), remove the ring and check to make sure you are not pregnant.

  If you are not pregnant, insert a new EluRyng **(See Steps 1 through 4).** You must use another birth control method, such as male condoms with spermicide, until the new EluRyng has been used for 7 days in a row.

What should I do if my EluRyng comes out of my vagina?

EluRyng can slip or accidentally come out (expelled) of your vagina, for example, during sexual intercourse, bowel movements, use of tampons, or if it breaks.

- EluRyng may break causing the ring to lose its shape. If the ring stays in your vagina this should not lower EluRyng's effectiveness at preventing pregnancy.
  - If EluRyng breaks and slips out of your vagina, throw the broken ring in your household trash out of the reach of children and pets.
  - Insert a new EluRyng **(See Steps 1 through 4)**.

- You should pay attention when removing a tampon to be sure that your EluRyng is not accidentally pulled out.
  - Be sure to insert EluRyng before inserting a tampon.
  - If you accidentally pull out your EluRyng while using tampons, rinse your EluRyng in cool to lukewarm (not hot) water and insert it again right away.

- EluRyng can be pushed out of (expelled from) your vagina, for example, during sexual intercourse or during a bowel movement.
  - If the expelled ring has been out of your vagina for less than 3 hours, rinse the expelled EluRyng in cool to lukewarm (not hot) water and insert it again right away.
  - If the expelled EluRyng has been out of your vagina for more than 3 continuous hours:
    - **During Weeks 1 and 2,** you may not be protected from pregnancy. Reinsert the ring as soon as you remember **(See Steps 1 through 4)**. Use another birth control method, such as male condoms with spermicide, until the ring has been in place for 7 days in a row.
    - **During Week 3,** do not reinsert the EluRyng that has been out of your vagina; but throw it away in your household trash away from children and pets. Use another birth control method, such as male condoms with spermicide, until the **new EluRyng has been used for 7 days in a row, following one of the two options below:**
      - **Option 1.** Insert a new ring right away to start your next 21 Day EluRyng use cycle. You may not have your regular period, but you may have spotting or vaginal bleeding.
      - **Option 2.** Insert a new ring no later than 7 days from the time the previous ring was removed or expelled. During this time, you may have your period.

      Note: You should only choose to do option 2 if you used EluRyng for 7 days in a row, prior to the day that your previous EluRyng was accidentally removed or expelled.
- If EluRyng was out of the vagina for an unknown amount of time, you may not be protected from pregnancy. Perform a pregnancy test prior to inserting a new ring and consult your healthcare provider.

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

Distributed by:
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

Rev. 05-2019-02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210830

LABELING REVIEWS

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	July 17, 2019
ANDA Number(s)	210830
Review Number	4
Applicant Name	Amneal Pharmaceuticals LLC
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day
Proposed Proprietary Name	EluRyng™ (granted 2/13/18)
Submission Received Date	May 17, 2019 (RLD update)
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments
☒ ACCEPTABLE – Include Post Approval Comments
☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☐ Yes ☒ No

Combined Insert/Outsert ☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

None

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission received May 17, 2019.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

PRESCRIBING INFORMATION
GENERAL COMMENT: Replace your proprietary name, EluRyng, with the established name when referencing studies/data that were not conducted with your drug product.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

Labeling review #3 based on the submissions dated October 19, 2018 and December 4, 2018 determined labeling to be acceptable with a post approval comment.

PRESCRIBING INFORMATION
GENERAL COMMENT: Replace your proprietary name, EluRyng, with the established name when referencing studies/data that were not conducted with your drug product.

The May 17, 2019 submission is provided due to a recent RLD update as the RLD, NDA 021187/S-037, was approved May 8, 2019. The May 17, 2019 submission satisfactorily updates the insert labeling. We will include the still applicable post approval comment. Please refer to section 1.3 above.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

The Pouch, Carton, Expiration Stickers and Calendar Reminder Stickers were found acceptable with the 10/19/18 submission.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page**?** NO

3.2 MODEL LABELING

Table 1: Review Model Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)* **NDA# /Supplement# (S-000 if original):** 021187/S-037 **Supplement Approval Date:** 5/8/2019 **Proprietary Name:** NuvaRing **Established Name:** etonogestrel/ethinyl estradiol vaginal ring **Description of Supplement:** This Prior Approval supplemental new drug application provides for an update to the Adverse Reactions Section, Subsection Postmarketing Experience to report the occurrence of ring breakage based on postmarketing reports. Additionally, corresponding language was updated in the Patient Package Insert section, "How should I use NuvaRing?".
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** (b) (4)

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

We note the approval of NDA 021187/S-027 on 9/30/16 provided for an optional applicator that can be used to insert NuvaRing. (b) (4) 2 DOSAGE AND ADMINISTRATION/2.1 How to Use EluRyng and Patient Information/General information about the safe and effective use of EluRyng and Instructions for Use/Step 4. Insert EluRyng into your vagina.

We will request the following post approval revision:

GENERAL COMMENT: Replace your proprietary name, EluRyng, with the established name when referencing studies/data that were not conducted with your drug product.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 021187/S-034 approved 12/4/17]

Back (glues to front of sachet)

Front

Inside Left

Contents: Each ring releases 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a 3-week period of use. Each ring contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol as active ingredients and ethylene vinylacetate copolymer and magnesium stearate as excipients.

Dosage and Administration: Use as prescribed. See package insert.

Storage: Prior to dispensing to the patient, store refrigerated 2-8°C (36-46°F).
After dispensing to the patient, NuvaRing can be stored for up to 4 months at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Avoid storing NuvaRing in direct sunlight or at temperatures above 30°C (86°F).

IIIIIIIIII-II

Inside Right

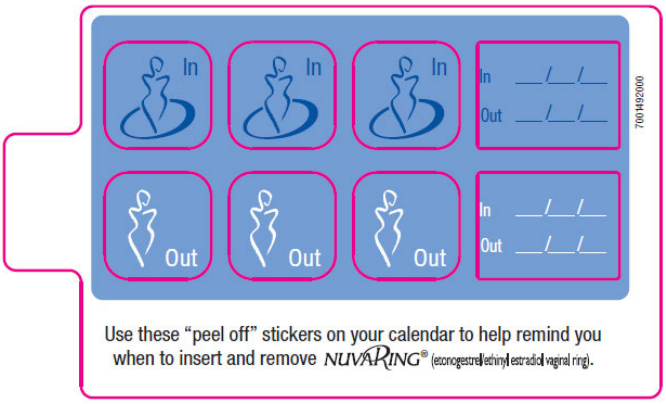
NUVARING®
(etonogestrel/ethinyl estradiol vaginal ring)
delivers 0.120 mg/0.015 mg per day

For Vaginal Use
Do not use if seal on pouch is broken.

Keep the foil pouch for proper disposal of the ring after use.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of **Merck & Co., Inc.**, Whitehouse Station, NJ 08889, USA
Product of The Netherlands

IIIIIIIIII-II



Use these "peel off" stickers on your calendar to help remind you when to insert and remove NUVARING® (etonogestrel/ethinyl estradiol vaginal ring).

For the Dispenser:

When NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) is dispensed to the patient, place the expiration date on an adhesive label provided. The expiration date should not exceed either 4 months from the date of dispensing or the preprinted expiration date, whichever comes first. **The adhesive (exp. date) label must be applied directly over the preexisting exp. date on each sachet pouch (and on the outer carton only when all 3 sachets are dispensed).**

7001491900

Use this label to reseal carton

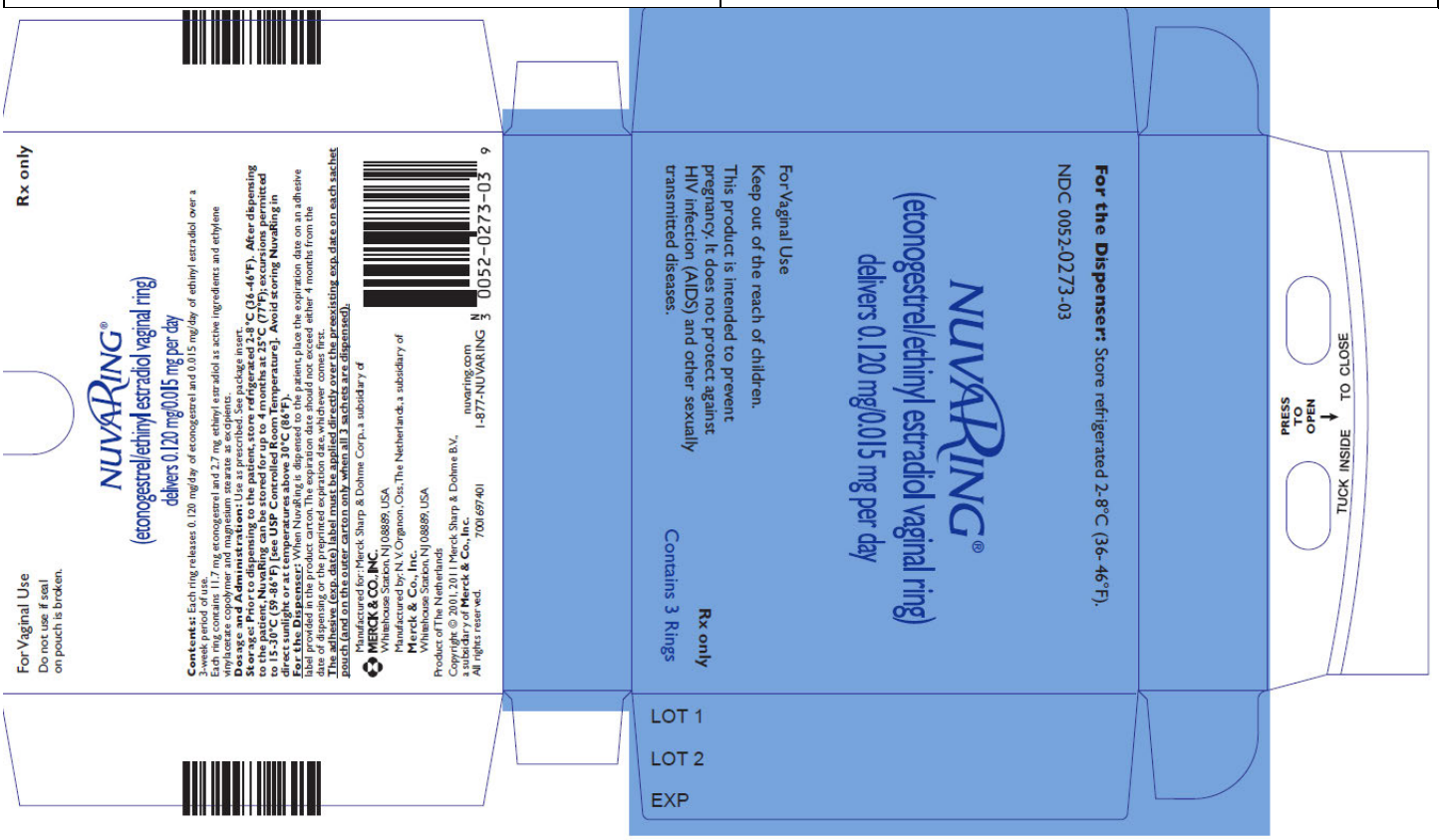
Sealed by your Pharmacy

Exp:

Exp:

Exp:

Exp:



3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 7/18/2019.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

None

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/18/2019.

Table 3 provides Orange Book patents for the Model Labeling NDA 021187 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
NA						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

There are no unexpired patents for this product in the Orange Book database.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NA					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

There is no unexpired exclusivity for this product in the Orange Book database.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
EluRyng is made of ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol, USP. EluRyng is not made with natural rubber latex. EluRyng has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.	EluRyng is made of ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol, USP. EluRyng is not made with natural rubber latex. EluRyng has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.	No change

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Each EluRyng (etonogestrel and ethinyl estradiol vaginal ring) is individually packaged in a reclosable aluminum laminate pouch consisting of four layers, from outside to inside: polyester, LDPE-EAA coex (low density polyethylene/ethylene acrylic acid copolymer coextrudate laminate), aluminum foil, and EAA-LLDPE coex (ethylene acrylic acid copolymer/ low density polyethylene coextrudate laminate). The ring should be replaced in this reclosable pouch after use and discarded in a waste receptacle out of the reach of children and pets. It should not be flushed down the toilet. Carton of 3 pouches NDC 65162-469-35 16.1 Storage Prior to dispensing to the user, store refrigerated 2° to 8°C (36° to 46°F). After dispensing to the user, EluRyng can be stored for up to 4 months at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Avoid storing EluRyng in direct sunlight or at temperatures above 30°C (86°F). For the Dispenser: When EluRyng is dispensed to the user, place an expiration date on the label. The date should not exceed either 4 months from the date of dispensing or the expiration date, whichever comes first.	Each EluRyng (etonogestrel and ethinyl estradiol vaginal ring) is individually packaged in a reclosable aluminum laminate pouch consisting of four layers, from outside to inside: polyester, LDPE-EAA coex (low density polyethylene/ethylene acrylic acid copolymer coextrudate laminate), aluminum foil, and EAA-LLDPE coex (ethylene acrylic acid copolymer/ low density polyethylene coextrudate laminate). The ring should be replaced in this reclosable pouch after use and discarded in a waste receptacle out of the reach of children and pets. It should not be flushed down the toilet. Carton of 3 pouches NDC 65162-469-35 16.1 Storage Prior to dispensing to the user, store refrigerated 2° to 8°C (36° to 46°F). After dispensing to the user, EluRyng can be stored for up to 4 months at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Avoid storing EluRyng in direct sunlight or at temperatures above 30°C (86°F). For the Dispenser: When EluRyng is dispensed to the user, place an expiration date on the label. The date should not exceed either 4 months from the date of dispensing or the expiration date, whichever comes first.	The applicant revised the established name to read "EluRyng". This is acceptable.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 7: Manufacturer/Distributor/Packer Statements		
Distributed by: **Amneal Pharmaceuticals LLC** **Bridgewater, NJ 08807**	**Distributed by:** **Amneal Pharmaceuticals LLC** **Bridgewater, NJ 08807**	**No change**

5. COMMENTS FOR OTHER DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

As noted in labeling review #3:

CDRH consult comments and OPQ comments regarding labeling:

The CDRH recommendations are shown below in blue text, and *my quality assessment comments are shown in red italics*.

The CDRH reviewer recommends that the labeling be updated to reflect the risks associated with the use of intravaginal products. Specifically, (b) (4) tampons. (b) (4)

(b) (4)

- (b) (4) *"Pharmacokinetic data show that the use of tampons has no effect on the systemic absorption of the hormones released by NuvaRing" and 2) "Use of spermicides or vaginal yeast products will not make NuvaRing less effective at preventing pregnancy."]*
- (b) (4)

- (b) (4)

statement in the RLD PI: "Pharmacokinetic data show that the use of tampons has no effect on the systemic absorption of the hormones released by NuvaRing."]

(b) (4)

A meeting with CDRH and OPQ occurred 1/11/19. Labeling informed CDRH and OPQ that labeling must be the "same as" the RLD except for acceptable differences and the labeling is currently in line with the RLD. Agreement among DLR, CDRH, and OPQ was reached that labeling revisions will be not requested.

4/5/19 Drug Product review does not have any labeling issues.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	1 vaginal ring	10/19/18	Satisfactory
Carton	Final	3 Pouches (each pouch contains 1 vaginal ring)	10/19/18	Satisfactory
Expiration Stickers	Final	NA	10/19/18	Satisfactory
Calendar Reminder Stickers	Final	NA	10/19/18	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: 05/2019	5/17/19	Satisfactory*
Medication Guide	NA			
Patient Information & Instructions for Use	Draft	Rev. 05-2019-02	5/17/19	Satisfactory
SPL Data Elements		Revised: 5/2019	5/17/19	Satisfactory

*Post approval revision

Esther Kim

Digitally signed by Esther Kim
Date: 7/18/2019 02:36:30PM
GUID: 5423006c00721ec9406da22c031498a2

Alison Park

Digitally signed by Alison Park
Date: 7/19/2019 12:27:56PM
GUID: 5063541100000db251c2d2cd0f7476af

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	January 7, 2019
ANDA Number(s)	210830
Review Number	3
Applicant Name	Amneal Pharmaceuticals LLC
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day
Proposed Proprietary Name	EluRyng™ (granted 2/13/18)
Submission Received Date	October 19, 2018 (amendment), December 10, 2018 (RLD update)
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments
☒ ACCEPTABLE – Include Post Approval Comments
☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☐ Yes ☒ No
Combined Insert/Outsert ☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

None

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission(s) received October 19, 2018 and December 10, 2018.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

PRESCRIBING INFORMATION
GENERAL COMMENT: Replace your proprietary name, EluRyng, with the established name when referencing studies/data that were not conducted with your drug product.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

Labeling review #2 based on the submissions dated December 15, 2017 and February 28, 2018 determined the labeling with the established name acceptable; however, the applicant has a proprietary name, EluRyng, which was found conditionally acceptable on February 13, 2018. Thus, labeling review #2 requested the applicant provide labeling with their proprietary name if their intent is to market with the proprietary name. The October 19, 2018 submission provides labeling pieces with the proprietary name.

The December 10, 2018 submission provides for updated insert labeling to be in line with the most recently approved RLD insert labeling approved December 4, 2018. This submission supersedes the October 19, 2018 submission.

The applicant has satisfactorily updated the labeling pieces to reflect the proprietary name with the October 19, 2018 submission and RLD update with the December 4, 2018 submission.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

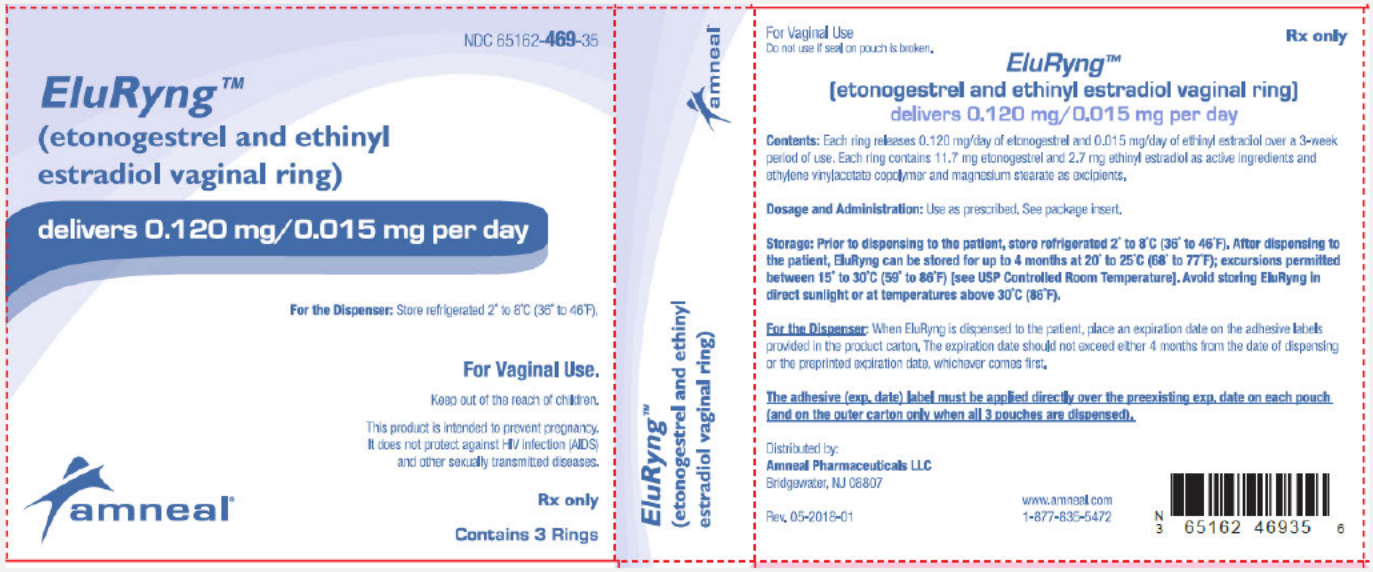
(b) (4)

Currently proposed Pouch

Previously submitted Carton

(b) (4)

Currently proposed Carton



(b) (4)

Currently proposed Expiration Sticker

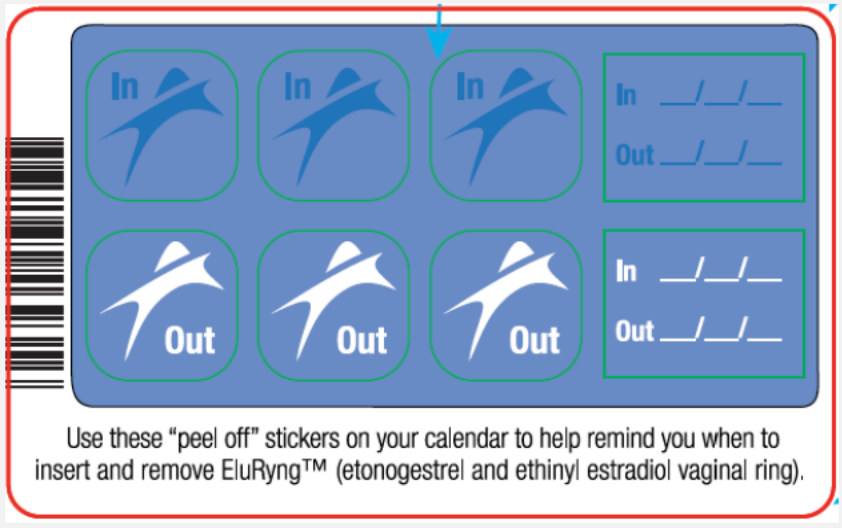
For the Dispenser:
When EluRyng™ (etonogestrel and ethinyl estradiol vaginal ring) is dispensed to the patient, place the expiration date on an adhesive label provided. The expiration date should not exceed either 4 months from the date of dispensing or the preprinted expiration date, whichever comes first. **The adhesive (exp. date) label must be applied directly over the preexisting exp. date on each pouch (and on the outer carton only when all 3 pouches are dispensed).**

Use this label ↘ to reseal carton

Sealed by your Pharmacy	
Exp:	**Exp:**
Exp:	**Exp:**

(b) (4)

Currently proposed Calendar Reminder Stickers



Use these "peel off" stickers on your calendar to help remind you when to insert and remove EluRyng™ (etonogestrel and ethinyl estradiol vaginal ring).

The applicant appropriately added the proprietary name to the labeling pieces. We find the Pouch, Carton, Expiration Stickers and Calendar Reminder Stickers acceptable.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:
None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA# /Supplement# (S-000 if original): 021187/S-035 and S-036

Supplement Approval Date: 12/4/2018

Proprietary Name: NuvaRing

Established Name: etonogestrel/ethinyl estradiol vaginal ring

Description of Supplement: These Prior Approval supplemental new drug applications provide for (S-035), to add subsection Vaginal Injury (5.18) under Recent Major Changes, Full Prescribing Information and Warning and Precautions Section, and Adverse Reactions Section, Subsection Postmarketing Experience. These changes were also incorporated in the "What should I tell my healthcare provider before using NuvaRing?," and "What are the possible side effects of using NuvaRing?," sections of the Patient Package Insert (PPI).
In addition, for (S-036), changes were made to Hypersensitivity Reactions (5.6) under the Contraindications, Warnings and Precautions, and Adverse Reactions Sections, Subsection Postmarketing Experience to add anaphylaxis and angioedema to the Immune system disorders. These changes were also incorporated in the "What should I tell my healthcare provider before using NuvaRing?," and "What are the possible side effects of using NuvaRing?," and "Other serious risks," sections of the Patient Package Insert (PPI).

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.

Table 1: Review Model Labeling (Check the box used as the Model Labeling)
☐ OTHER (Describe): (b) (4)

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

We note the approval of NDA 021187/S-027 on 9/30/16 provided for an optional applicator that can be used to insert NuvaRing. (b) (4) 2 DOSAGE AND ADMINISTRATION/2.1 How to Use Etonogestrel/Ethinyl Estradiol Vaginal Ring and Patient Information/General information about the safe and effective use of etonogestrel/ethinyl estradiol vaginal ring and Instructions for Use/Step 4. Insert etonogestrel/ethinyl estradiol vaginal ring into your vagina.

We will request the following post approval revision:

GENERAL COMMENT: Replace your proprietary name, EluRyng, with the established name when referencing studies/data that were not conducted with your drug product.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 021187/S-034 approved 12/4/17]

Back (glues to front of sachet)

Front

Inside Left

Contents: Each ring releases 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a 3-week period of use. Each ring contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol as active ingredients and ethylene vinylacetate copolymer and magnesium stearate as excipients.

Dosage and Administration: Use as prescribed. See package insert.

Storage: Prior to dispensing to the patient, store refrigerated 2-8°C (36-46°F).
After dispensing to the patient, NuvaRing can be stored for up to 4 months at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Avoid storing NuvaRing in direct sunlight or at temperatures above 30°C (86°F).

XXXXXXXXX-XX

Inside Right

NUVARING®
(etonogestrel/ethinyl estradiol vaginal ring)
delivers 0.120 mg/0.015 mg per day

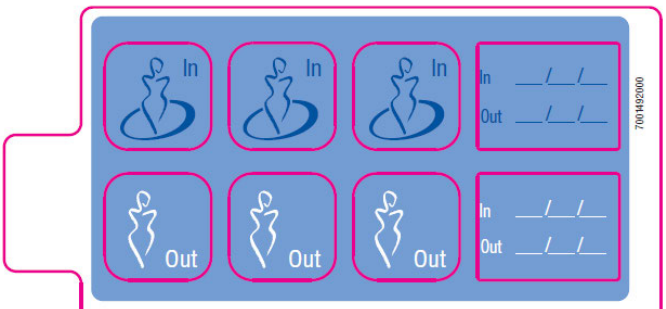
For Vaginal Use
Do not use if seal on pouch is broken.

Keep the foil pouch for proper disposal of the ring after use.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of **Merck & Co., Inc.**, Whitehouse Station, NJ 08889, USA
Product of The Netherlands

XXXXXXXXX-XX

NDA 021187 AR-16 DARRTS 11/22/16 submission



Use these "peel off" stickers on your calendar to help remind you when to insert and remove NUVARING® (etonogestrel/ethinyl estradiol vaginal ring).

For the Dispenser:

When NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) is dispensed to the patient, place the expiration date on an adhesive label provided. The expiration date should not exceed either 4 months from the date of dispensing or the preprinted expiration date, whichever comes first. **The adhesive (exp. date) label must be applied directly over the preexisting exp. date on each sachet pouch (and on the outer carton only when all 3 sachets are dispensed).**

7001491900

Use this label to reseal carton

Sealed by your Pharmacy

Exp:
Exp:
Exp:
Exp:

3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 1/7/2019.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

None

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 1/7/2019.

Table 3 provides Orange Book patents for the Model Labeling NDA 021187 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact (enter Carve-out or None)**
5989581	Apr 8, 2018			III	8/25/17	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

None

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter Carve-out or None)**
NA					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

There is no unexpired exclusivity for this product in the Orange Book database.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)	**EluRyng is made of ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol, USP. EluRyng is not made with natural rubber latex. EluRyng has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.**	**The applicant revised the established name to read "EluRyng". This is acceptable.**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
(b) (4)	Each EluRyng (etonogestrel and ethinyl estradiol vaginal ring) is individually packaged in a reclosable aluminum laminate pouch consisting of four layers, from outside to inside: polyester, LDPE-EAA coex (low density polyethylene/ethylene acrylic acid copolymer coextrudate laminate), aluminum foil, and EAA-LLDPE coex (ethylene acrylic acid copolymer/ low low density polyethylene coextrudate laminate). The ring should be replaced in this reclosable pouch after use and discarded in a waste receptacle out of the reach of children and pets. It should not be flushed down the toilet. Carton of 3 pouches NDC 65162-469-35 16.1 Storage Prior to dispensing to the user, store refrigerated 2° to 8°C (36° to 46°F). After dispensing to the user, EluRyng can be stored for up to 4 months at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Avoid storing EluRyng in direct sunlight or at temperatures above 30°C (86°F). For the Dispenser: When EluRyng is dispensed to the user, place an expiration date on the label. The date should not exceed either 4 months from the date of dispensing or the expiration date, whichever comes first.	The applicant revised the established name to read "EluRyng". This is acceptable.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	Currently Proposed	Assessment
Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807	Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807	No change

5. COMMENTS FOR OTHER DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

CDRH consult comments and OPQ comments regarding labeling:

The CDRH recommendations are shown below in blue text, and *my quality assessment comments are shown in red italics*.

The CDRH reviewer recommends that the labeling be updated to reflect the risks associated with the use of intravaginal products. Specifically, (b) (4) tampons. (b) (4)

(b) (4)

- (b) (4) *"Pharmacokinetic data show that the use of tampons has no effect on the systemic absorption of the hormones released by NuvaRing" and 2) "Use of spermicides or vaginal yeast products will not make NuvaRing less effective at preventing pregnancy."]*
- (b) (4)
- (b) (4) *statement in the RLD PI: "Pharmacokinetic data show that the use of tampons has no effect on the systemic absorption of the hormones released by NuvaRing."]*

(b) (4)

A meeting with CDRH and OPQ occurred 1/11/19. Labeling informed CDRH and OPQ that labeling must be the "same as" the RLD except for acceptable differences and labeling is currently in line with the RLD. Agreement among DLR, CDRH, and OPQ reached that labeling revisions will be not requested.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	1 vaginal ring	10/19/18	Satisfactory
Carton	Final	3 Pouches (each pouch contains 1 vaginal ring)	10/19/18	Satisfactory
Expiration Stickers	Final	NA	10/19/18	Satisfactory
Calendar Reminder Stickers	Final	NA	10/19/18	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	Revised: 12/2018	12/10/18	Satisfactory*
Medication Guide	NA			
Patient Information & Instructions for Use	Final	Rev. 12-2018-01	12//10/18	Satisfactory
SPL Data Elements		Revised: 12/2018	12/10/18	Satisfactory

*Post approval revision

Esther Kim

Digitally signed by Esther Kim
Date: 1/30/2019 09:19:28AM
GUID: 5423006c00721ec9406da22c031498a2

Lisa Kwok

Digitally signed by Lisa Kwok
Date: 1/31/2019 08:39:49AM
GUID: 508da70800028c5cddf24c815a550d26

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	4/6/18
ANDA Number(s)	210830
Review Number	2
Applicant Name	Amneal Pharmaceuticals LLC
Established Name & Strength(s)	Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day
Proposed Proprietary Name	EluRyng™ (granted 2/13/18)
Submission Received Date	12/15/17 (DRL response), 2/28/18 (RLD update)
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Lisa Kwok

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☐YES ☒NO

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on April 9, 2018 based on your submission(s) dated December 15, 2017 and February 28, 2018:

1. GENERAL COMMENT
   We note that you have submitted a proprietary name for this product. It had been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Safety and Epidemiology and found conditionally acceptable on February 13, 2018. If you intend to market with the proprietary name, please submit all labeling pieces with the proprietary name for our review. Please note that your labeling pieces containing the established name, etonogestrel and ethinyl estradiol vaginal ring, are found acceptable.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

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. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

NA

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

CONTAINER LABEL
We acknowledge the revisions made to the RLD are editorial in nature; we recommend revising your pouch to be in accordance with the pouch for the reference listed drug (RLD), NuvaRing, NDA 021187/S-034 approved December 4, 2017.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Labeling review #1 based on the submission date August 25, 2017 determined deficiencies and recommendations for Container, Carton, and Prescribing Information as well as a request to revise the presentation of the established name.

Reviewer Comments:

The applicant has satisfactorily addressed the deficiencies and recommendations for Container, Carton, and Prescribing Information as well as revised the presentation of the established name as requested. We note the applicant's proprietary name has been approved by DMEPA on 2/13/18; therefore, we will request the applicant submit their labeling pieces containing the proprietary name.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

(b) (4)

(b) (4)

We find the Pouch and Carton for the established name acceptable. We note the applicant has proprietary name, EluRyng, approved 2/13/18. (b) (4)

(b) (4)

We note the RLD has updated their Container (sachet) label to use a (b) (4) configuration. (b) (4)

(b) (4)

The front of the label now includes

"see dispensing information on carton and Dispensing Instructions Sticker Sheet". This supplement did not provide revision to the sticker sheet or carton. (b) (4) (b) (4) request for ANDA 207577.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** (*If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)* **NDA# /Supplement# (S-000 if original):** 021187/S-031 **Supplement Approval Date:** 2/12/18 **Proprietary Name:** NuvaRing **Established Name:** etonogestrel/ethinyl estradiol vaginal ring **Description of Supplement:** This Prior Approval supplemental new drug application provides for changes to the Prescribing Information (PI) for NuvaRing to update 1) Dosage and Administration Section, subsection, Use with Other Vaginal Products, 2) Contraindications Section, 3) Warnings and Precautions Section, subsection Vaginal Use, and 4) Adverse Reactions Section, subsection Postmarketing Experience. Additionally, corresponding changes were made to the Patient Package Insert (PPI) to update the following information: 1) Tell your healthcare provider about all medicines and herbal products you take Section, 2) How should I use NuvaRing other serious risk include Section, 3) Other side effects text, and 4) Less common side effects text.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☐ **OTHER (Describe):** **S-032** is a labeling supplement approved 8/9/17 that provides for safety information that should be included in the labeling for the class of ethinyl estradiol containing combination hormonal contraceptive products pertaining to the risk of elevations of the liver enzyme alanine aminotransferase (ALT) in patients using ethinyl estradiol containing products concomitantly with direct-acting antiviral combination products that contain ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. **S-033** is an approved CMC supplement that provides for the addition of an alternate site for microbial testing for etonogestrel. **S-034** is a labeling supplement approved 12/4/17 that provides for modification of the current NuvaRing primary packaging (sachet) label configuration to use a (b) (4) configuration. We note no revisions were made to the prescribing information or patient labeling. **S-035** is a pending labeling supplement that provides for revision to add vaginal injury associated with ring breakage to the Warnings and Precautions and Adverse Reactions sections of the label.

Reviewer Assessment:

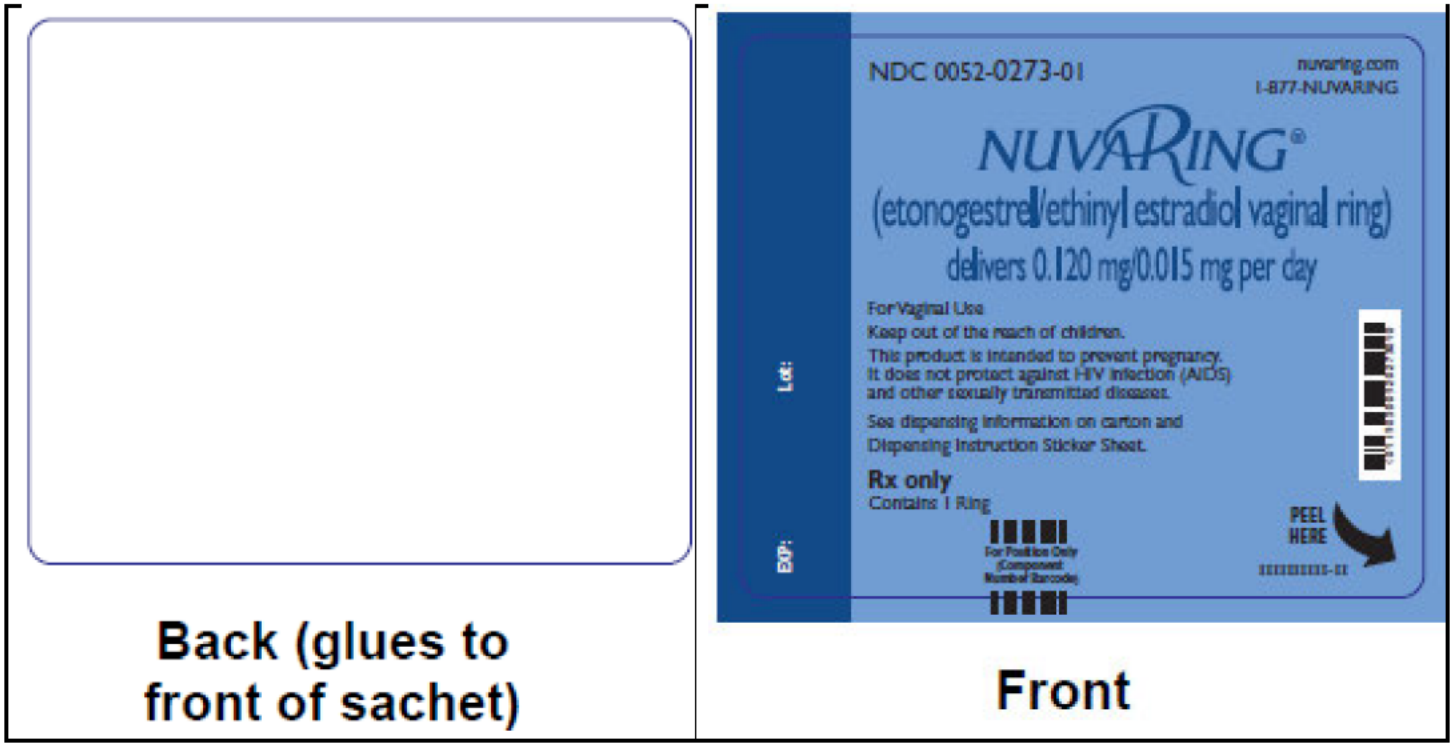
Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

We note the approval of NDA 021187/S-027 on 9/30/16 provided for an optional applicator that can be used to insert NuvaRing. (b) (4) 2 DOSAGE AND ADMINISTRATION/2.1 How to Use Etonogestrel/Ethinyl Estradiol Vaginal Ring and Patient Information/General information about the safe and effective use of etonogestrel/ethinyl estradiol vaginal ring and Instructions for Use/Step 4. Insert etonogestrel/ethinyl estradiol vaginal ring into your vagina.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 021187/S-034 approved 12/4/17]



Inside Left

Contents: Each ring releases 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a 3-week period of use. Each ring contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol as active ingredients and ethylene vinylacetate copolymer and magnesium stearate as excipients.

Dosage and Administration: Use as prescribed. See package insert.

Storage: Prior to dispensing to the patient, store refrigerated 2-8°C (36-46°F).
After dispensing to the patient, NuvaRing can be stored for up to 4 months at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Avoid storing NuvaRing in direct sunlight or at temperatures above 30°C (86°F).

XXXXXXXXX-XX

Inside Right

NUVARING®
(etonogestrel/ethinyl estradiol vaginal ring)
delivers 0.120 mg/0.015 mg per day

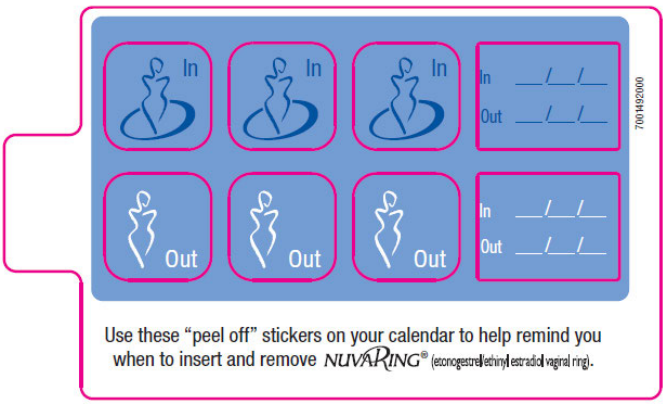
For Vaginal Use
Do not use if seal on pouch is broken.

Keep the foil pouch for proper disposal of the ring after use.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of **Merck & Co., Inc.**, Whitehouse Station, NJ 08889, USA
Product of The Netherlands

XXXXXXXXX-XX

NDA 021187 AR-16 DARRTS 11/22/16 submission



Use these "peel off" stickers on your calendar to help remind you when to insert and remove NUVARING® (etonogestrel/ethinyl estradiol vaginal ring).

For the Dispenser:

When NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) is dispensed to the patient, place the expiration date on an adhesive label provided. The expiration date should not exceed either 4 months from the date of dispensing or the preprinted expiration date, whichever comes first. **The adhesive (exp. date) label must be applied directly over the preexisting exp. date on each sachet pouch (and on the outer carton only when all 3 sachets are dispensed).**

7001491900

Use this label to reseal carton

Sealed by your Pharmacy

Exp:
Exp:
Exp:
Exp:

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

The USP was searched on 4/9/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	NO		NA	NA
Pending Monograph Proposed	NO	5/1/2018 8/1/2018	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

None

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 4/9/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 021187 and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
5989581	Apr 8, 2018			III	8/25/17	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

None

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NA					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

There is no unexpired exclusivity for this product in the Orange Book database.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment
(b) (4)		

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment
(b) (4)		

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	Currently Proposed	Assessment
Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807	Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807	No change

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline (e.g., OPQ, OB) reviewer(s):

Reviewer Comments:

The Chemistry review finds the DESCRIPTION and HOW SUPPLIED sections accurate.

OPQ issued a consult to CDRH:

Requesting a reviewer assignment for a team review of the quality of the proposed generic vaginal ring product. The generic formulation is qualitatively and quantitatively similar to the Referenced Listed Drug (NDA 21187 - NuvaRing). Further, the quality controls (tests and acceptance criterion) and manufacturing processes are similar to the RLD (NDA 21187 - NuvaRing). We are requesting this consult to identify any general concerns CDRH reviewers may have with a vaginal ring type product from a device perspective (We have drug-product samples in house that can be provided once a reviewer is assigned).

The consult states:

From a clinical perspective, DCR considers the differences in the size dimensions, compression force, color, labeling, foil pouch opening, carton opening and patient package inserts to be minor and acceptable.

Therefore, DCR has no comments after completing its review.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	1 vaginal ring	12/15/17	Satisfactory*
Blister	Final	3 Pouches (each pouch contains 1 vaginal ring)	12/15/17	Satisfactory*
Expiration Stickers	Final	NA	8/25/17	Satisfactory
Calendar Reminder Stickers	Final	NA	8/25/17	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	Revised: 02/2018	2/28/18	Satisfactory
Medication Guide	NA			
Patient Information & Instructions for Use	Final	Rev. 02-2018-00	2/28/18	Satisfactory
SPL Data Elements		Revised: 2/2018	2/28/18	Satisfactory

*Post approval revision

(b) (4)

Esther Kim

Digitally signed by Esther Kim
Date: 4/23/2018 08:49:33AM
GUID: 5423006c00721ec9406da22c031498a2

Lisa Kwok

Digitally signed by Lisa Kwok
Date: 4/23/2018 02:10:48PM
GUID: 508da70800028c5cddf24c815a550d26

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	11/16/17
ANDA Number(s)	210830
Review Number	1
Applicant Name	Amneal Pharmaceuticals LLC
Established Name & Strength(s)	Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day
Proposed Proprietary Name	EluRyng™ (pending DMEPA review)
Submission Received Date	8/25/17 (original)
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Lisa Kwok

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☐ Yes	☒ No
Acceptable for Filing	☒ Yes	☐ No

TABLE OF CONTENTS

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on November 20, 2017 based on your submission dated August 25, 2017:

1. GENERAL COMMENTS
    a. We note that you have submitted a proprietary name for this product. It will be reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Safety and Epidemiology. Additional labeling comments may be forthcoming after review of the name by DMEPA.
    b. We recommend revising the established name from “etonogestrel/ethinyl estradiol vaginal ring” to read “etonogestrel and ethinyl estradiol vaginal ring” on your labels and labeling. [Note the revision of “/” to read “and”.]

(b) (4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

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. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission(s) dated (add date).

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

None

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain.
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

2.2 MODEL LABELING

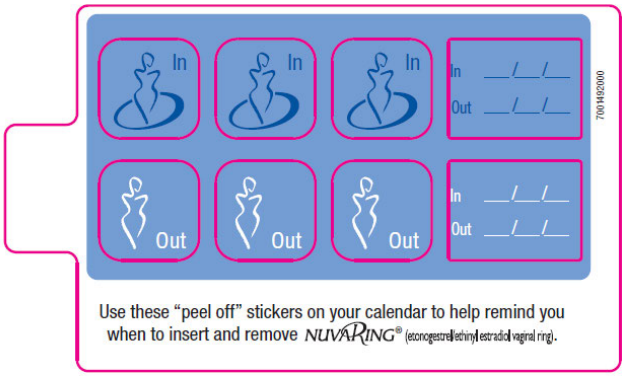
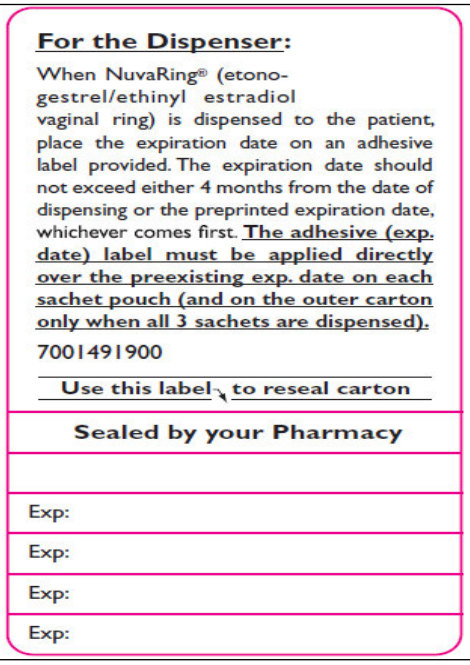
2.2.1 MODEL PRESCRIBING INFORMATION

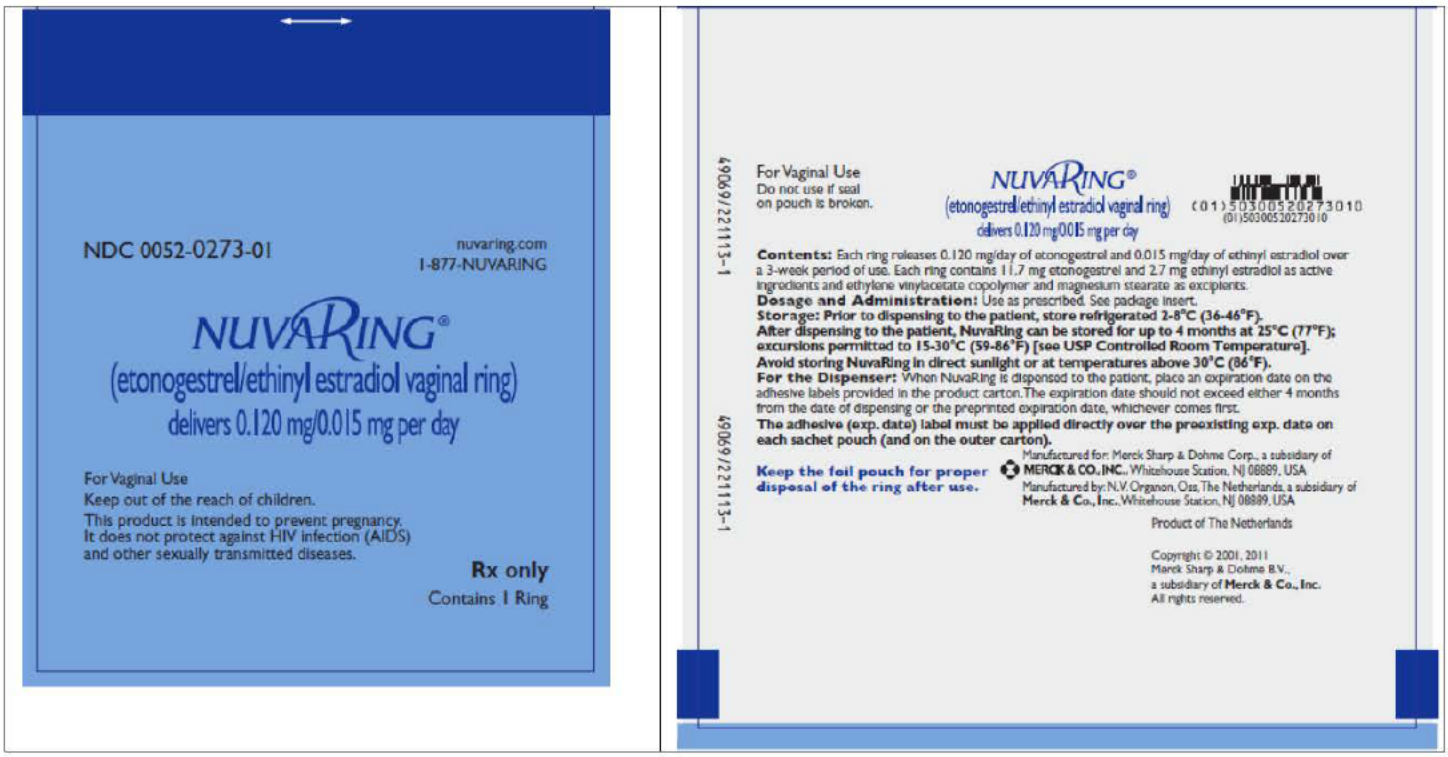
Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original):** 021187/S-032 **Supplement Approval Date:** 8/9/17 **Proprietary Name:** NuvaRing **Established Name:** etonogestrel/ethinyl estradiol vaginal ring **Description of Supplement:** This supplement provides for safety information that should be included in the labeling for the class of ethinyl estradiol containing combination hormonal contraceptive products pertaining to the risk of elevations of the liver enzyme alanine aminotransferase (ALT) in patients using ethinyl estradiol containing products concomitantly with direct-acting antiviral combination products that contain ombitasvir/paritaprevir/ritonavir, with or without dasabuvir.

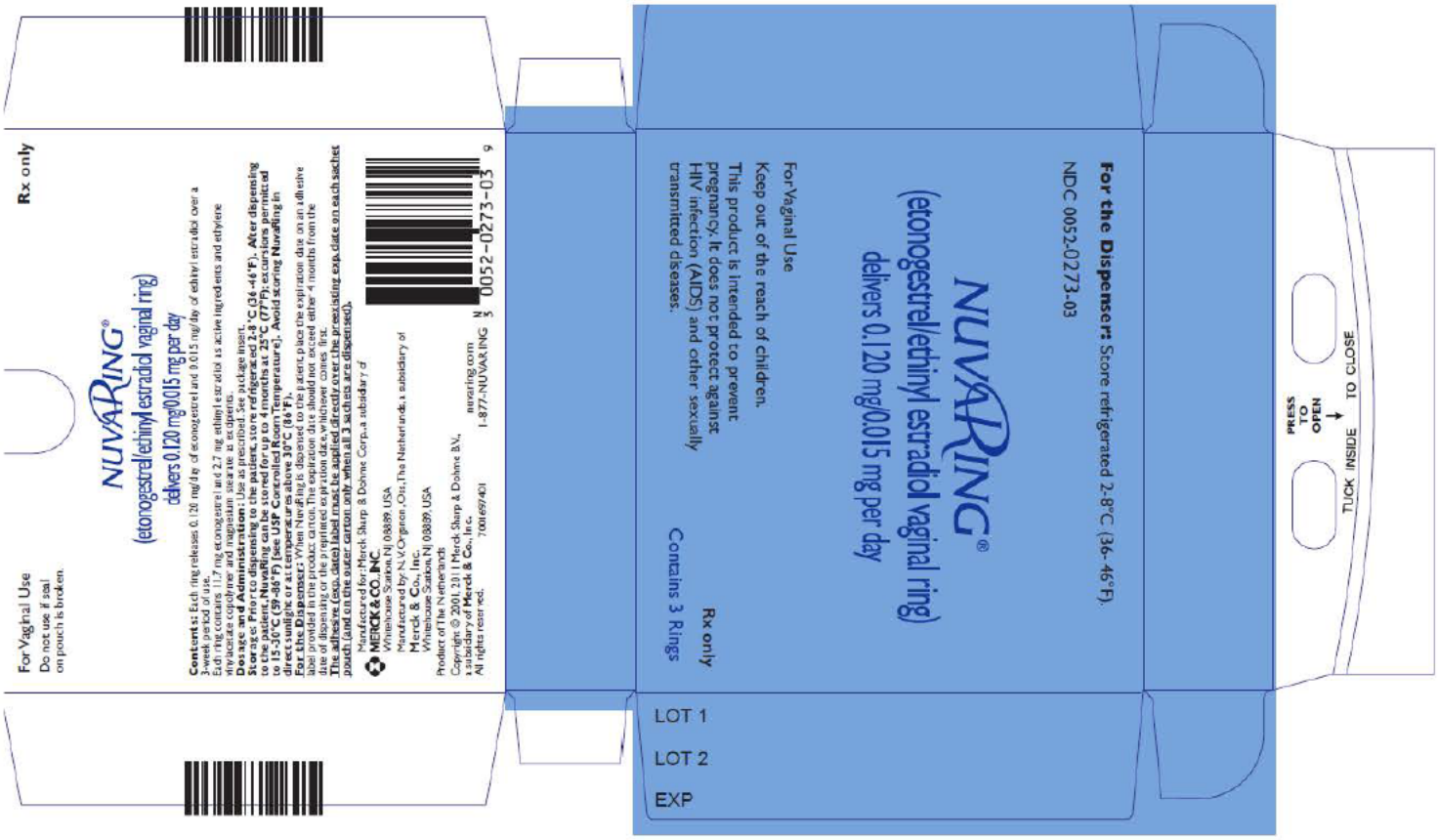
Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** S-033 is a pending CMC supplement that provides for changes in the Chemistry Section to provide for the addition of an alternate site for microbial testing for etonogestrel. S-034 is a pending labeling supplement that provides for modification of the current NuvaRing primary packaging (sachet) label configuration to use a (b) (4) configuration.

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: NDA 021187 AR-16 DARRTS 11/22/16 submission**)**

	
Sachet Front	Sachet Back


NDC 0052-0273-01
nuvaring.com
1-877-NUVARING
NUVARING®
(etonogestrel/ethinyl estradiol vaginal ring)
delivers 0.120 mg/0.015 mg per day
For Vaginal Use
Keep out of the reach of children.
This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
Rx only
Contains 1 Ring
49069/221113-1
For Vaginal Use
Do not use if seal on pouch is broken.
NUVARING®
(etonogestrel/ethinyl estradiol vaginal ring)
delivers 0.120 mg/0.015 mg per day
(01)50300520273010
(01)50300520273010
Contents: Each ring releases 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a 3-week period of use. Each ring contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol as active ingredients and ethylene vinylacetate copolymer and magnesium stearate as excipients.
Dosage and Administration: Use as prescribed. See package insert.
Storage: Prior to dispensing to the patient, store refrigerated 2-8°C (36-46°F).
After dispensing to the patient, NuvaRing can be stored for up to 4 months at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Avoid storing NuvaRing in direct sunlight or at temperatures above 30°C (86°F).
For the Dispenser: When NuvaRing is dispensed to the patient, place an expiration date on the adhesive labels provided in the product carton. The expiration date should not exceed either 4 months from the date of dispensing or the preprinted expiration date, whichever comes first.
The adhesive (exp. date) label must be applied directly over the preexisting exp. date on each sachet pouch (and on the outer carton only when all 3 sachets are dispensed).
Keep the foil pouch for proper disposal of the ring after use.
Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of Merck & Co., Inc. Whitehouse Station, NJ 08889, USA
Product of The Netherlands
Copyright © 2001, 2011
Merck Sharp & Dohme B.V.,
a subsidiary of Merck & Co., Inc.
All rights reserved.
49069/221113-1


Rx only
NUVARING®
(etonogestrel/ethinyl estradiol vaginal ring)
delivers 0.120 mg/0.015 mg per day
For Vaginal Use
Do not use if seal on pouch is broken.
Contents: Each ring releases 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a 3-week period of use. Each ring contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol as active ingredients and ethylene vinylacetate copolymer and magnesium stearate as excipients.
Dosage and Administration: Use as prescribed. See package insert.
Storage: Prior to dispensing to the patient, store refrigerated 2-8°C (36-46°F). After dispensing to the patient, NuvaRing can be stored for up to 4 months at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Avoid storing NuvaRing in direct sunlight or at temperatures above 30°C (86°F).
For the Dispenser: When NuvaRing is dispensed to the patient, place the expiration date on an adhesive label provided in the product carton. The expiration date should not exceed either 4 months from the date of dispensing or the preprinted expiration date, whichever comes first.
The adhesive (exp. date) label must be applied directly over the preexisting exp. date on each sachet pouch (and on the outer carton only when all 3 sachets are dispensed).
Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA
Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of
Merck & Co., Inc.
Whitehouse Station, NJ 08889, USA
Product of The Netherlands
Copyright © 2001, 2011 Merck Sharp & Dohme B.V., a subsidiary of Merck & Co., Inc. All rights reserved.
700169701
nuvaring.com
1-877-NUVARING
N 5 0052-0273-03 9
For the Dispenser: Store refrigerated 2-8°C (36-46°F).
NDC 0052-0273-03
NUVARING®
(etonogestrel/ethinyl estradiol vaginal ring)
delivers 0.120 mg/0.015 mg per day
For Vaginal Use
Keep out of the reach of children.
This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
Rx only
Contains 3 Rings
LOT 1
LOT 2
EXP
PRESS TO OPEN
TUCK INSIDE TO CLOSE

NDA 021187/S-034 (pending approval CBE-30)

Back (glues to front of sachet)

Front

Inside Left

Contents: Each ring releases 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a 3-week period of use. Each ring contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol as active ingredients and ethylene vinylacetate copolymer and magnesium stearate as excipients.

Dosage and Administration: Use as prescribed. See package insert.

Storage: Prior to dispensing to the patient, store refrigerated 2-8°C (36-46°F).
After dispensing to the patient, NuvaRing can be stored for up to 4 months at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Avoid storing NuvaRing in direct sunlight or at temperatures above 30°C (86°F).

Inside Right

NUVARING®
(etonogestrel/ethinyl estradiol vaginal ring)
delivers 0.120 mg/0.015 mg per day

For Vaginal Use
Do not use if seal on pouch is broken.

Keep the foil pouch for proper disposal of the ring after use.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO.,INC., Whitehouse Station, NJ 08889, USA
Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of **Merck & Co., Inc.**, Whitehouse Station, NJ 08889, USA
Product of The Netherlands

(b) (4)

2.3 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 11/16/2017.

Table 2: USP

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	NO		NA	NA

Pending Monograph Proposed	NO	12/1/2017	NA	NA

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 11/16/2017.

Table 3 provides Orange Book patents for the Model Labeling (NDA 021187) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact (enter Carve-out or None)**
5989581	Apr 8, 2018			III	8/25/17	None

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter Carve-out or None)**
NA					

2.5 MANUFACTURING FACILITY

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	**Name and Address on ANDA Container/Carton**	**Name and Address on ANDA Prescribing Information**
(b) (4)	Pouch: Distributed by: **Amneal Pharmaceuticals LLC** Bridgewater, NJ 08807 Carton: Distributed by: **Amneal Pharmaceuticals LLC** Bridgewater, NJ 08807	Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807

3. ASSESSMENT OF ANDA LABELING AND LABELS

Is this product Rx or OTC? Please check one.

☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT.)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**
Is the established name the same as the USP monograph title appearing in section 2.3? **NA**
Is the established name the same as the RLD's nonproprietary name? **YES**
If YES is answered to both questions, then continue with review.
If NO is answered to EITHER questions, then advise firm to revise to the USP name (if applicable) and include justification language under Reviewer Comments.
Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **NO**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the Manufacturer statement acceptable? **YES**

Reviewer Comments:
We note the approval of NDA 021187/S-027 on 9/30/16 provided for an optional applicator that can be used to insert NuvaRing. (b) (4) DOSAGE AND ADMINISTRATION/2.1 How to Use Etonogestrel/Ethinyl Estradiol Vaginal Ring and Patient Information/General information about the safe and effective use of etonogestrel/ethinyl estradiol vaginal ring and Instructions for Use/Step 4. Insert etonogestrel/ethinyl estradiol vaginal ring into your vagina.

3.1.1.1 RX: DESCRIPTION

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling Inactive Ingredients	ANDA Labeling Inactive Ingredients
NuvaRing is made of ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol. NuvaRing is not made with natural rubber latex.	Etonogestrel/ethinyl estradiol vaginal ring is made of ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol, USP. Etonogestrel/ethinyl estradiol vaginal ring is not made with natural rubber latex.

From 3.2.P.1 QOS:

Table 1. Composition of Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day

Ingredients	mg/Unit	% w/w	Component Function
Ethinyl Estradiol, USP (b) (4)	2.700	(b) (4)	Active
Etonogestrel (b) (4)	11.700		Active
Ethylene Vinylacetate Copolymer, 28% Vinylacetate (b) (4)	(b) (4)		(b) (4)
Ethylene Vinylacetate Copolymer, 9% Vinylacetate (b) (4)			
Magnesium Stearate, NF			
			(b) (4)
Total	(b) (4)	**100.0**	

Notes:

(b) (4)

Please note that as per the Controlled Correspondence # 42491 (Refer to Appendix 1 and Appendix 2) with the Agency, Amneal's proposed generic drug Product i.e. Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day is Qualitatively (Q1) and Quantitatively (Q2) same as the RLD, NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) delivers 0.120 mg / 0.150 mg per day.

Reviewer Assessment:

Are the inactive ingredients accurate? **PENDING CHEMISTRY REVIEW**

For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **YES**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**
Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling? **NA**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **YES** Has the statement been verified by chemistry? **YES**

Reviewer Comments:
From 3.2.P.1 QOS, the applicant provided the controlled correspondence response that their formulation is Q1/Q2 with the RLD; therefore, the "is not made with natural rubber latex" statement should be accurate.

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

Table 7: Comparison of Model Labeling to ANDA Labeling

Model Labeling	Each NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) is individually packaged in a reclosable aluminum laminate sachet consisting of three layers, from outside to inside: polyester, aluminum foil, and low-density polyethylene. The ring should be replaced in this reclosable sachet after use and discarded in a waste receptacle out of the reach of children and pets. It should not be flushed down the toilet. Box of 3 sachets NDC 0052-0273-03 16.1 Storage Prior to dispensing to the user, store refrigerated 2-8°C (36-46°F). After dispensing to the user, NuvaRing can be stored for up to 4 months at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Avoid storing NuvaRing in direct sunlight or at temperatures above 30°C (86°F). For the Dispenser: When NuvaRing is dispensed to the user, place an expiration date on the label. The date should not exceed either 4 months from the date of dispensing or the expiration date, whichever comes first.
ANDA Labeling	(b) (4)

Reviewer Assessment:

Are all of the submitted labels and labeling reflected in the How Supplied section? **YES**
Is the description (scoring, color and imprint) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? **PENDING CHEMISTRY REVIEW**
Does the ANDA require the same color coding as the Model Labeling? **NO**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **YES**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**
Is the storage or dispensing statement acceptable as compared to the USP? **NA**

Reviewer Comments:
We note the pouch of the RLD contains 3 layers; whereas, subject ANDA contains 4 layers. We will await the Chemistry review for potential comment.

(b) (4)

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **CLICK HERE**
Is the Medication Guide same as the model labeling, except for allowable differences? **CLICK HERE**
Has the Applicant committed to provide a sufficient number of medication guides? **CLICK HERE**
Is the phonetic spelling of the proprietary or established name present? **CLICK HERE**

Is FDA 1-800-FDA-1088 phone number included? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **YES**
Is the patient labeling the same as the model labeling, except for allowable differences? **YES**

Reviewer Comments:
None

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES**
(For BLISTER labels go to section 3.1.5.)

Reviewer Assessment:

Is the established name acceptable? **YES**
Is title case used in expressing the established name? **YES**
Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**
If the container label is too small to contain all required information, does it meet the "too small" exemption found in 21 CFR 201.10(i)? **NA**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**
Is the following information properly displayed?
- Net quantity statement: **YES**
- Route(s) of administration (other than oral): **YES**
- Warnings (if any) or cautionary statements (if any): **YES**
- Medication Guide Pharmacist instructions per 21 CFR 208.24(d): **NA**
- Controlled substance symbol: **NA**
- Usual Dosage statement: **YES**
- Product strength equivalency statement: **NA**
- NDC: **YES**
- Bar code per 21 CFR 201.25(c)(2): **YES**

Is the Manufacturer/Distributor/Packager statement acceptable? **YES**
For foreign manufacturers, does the labeling have the country of origin? **NA**
Are the USP recommendations and/or differences in test methods (e.g., organic impurities, assay) reflected on the label(s)? **NA**
Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **NA**
Does the ANDA require the same color coding as the Model Labeling? **NO**
Are requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100)? **YES**

Reviewer Comments:
We note the applicant has requested the review of proposed proprietary name, EluRyng; however, the applicant has not submitted labeling with the proposed proprietary name.

- We note the RLD uses a "/" to separate the drug products that comprise NuvaRing; however, we will recommend revision of the established name to read "etonogestrel and ethinyl estradiol vaginal ring".
- (b) (4)
- We will request the applicant increase the prominence of "For Vaginal Use."

Although the strength statement "delivers 0.120 mg/0.015 mg per day" contains a terminal zero "0.120 mg", this presentation is consistent with the RLD; therefore, we will not request any revision by subject ANDA.

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **CLICK HERE**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable (other than Pharmacy Bulk Package)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **CLICK HERE**
Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **CLICK HERE**
Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **CLICK HERE**
Does the container label include graduation marks? **CLICK HERE**
Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **CLICK HERE**
Do proprietary name, established name, strength, bar code, and manufacturer appear accurately on each blister cell? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **YES** If no, please explain the differences in the Reviewer Comments section.
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **NA**
If country of origin is not on Container, does it appear on outer packaging labeling? **NA**

Reviewer Comments:

(b) (4)

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **CLICK HERE**
Does "Questions?" have a toll-free number no less than 6 pt. font size per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" per 21 CFR 201.66 (c)(5)(vii)? **CLICK HERE**
Did firm submit a Labeling Format Information Table to evaluate the font size? **CLICK HERE**
Is the applicant's "patent carve out" acceptable? **CLICK HERE**
Is the applicant's "exclusivity carve out" acceptable? **CLICK HERE**
Is the established name for this ANDA acceptable? **CLICK HERE**
Is title case used in expressing the established name? **CLICK HERE**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **CLICK HERE**
Is the following information properly displayed?

- Pharmacological category: **CLICK HERE**
- Net quantity statement: **CLICK HERE**
- Route(s) of administration (other than oral): **CLICK HERE**
- Warnings (if any) or cautionary statements (if any): **CLICK HERE**
- NDC: **CLICK HERE**
- Bar code per 21 CFR 201.25(c)(2): **CLICK HERE**

Is the Manufacturer/Distributor/Packager statement acceptable? **CLICK HERE**
For foreign manufacturers, does the labeling have the country of origin? **CLICK HERE**

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling? **CLICK HERE**
Is the storage statement acceptable? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
Are multiple strengths differentiated by use of different color or other acceptable means? **CLICK HERE**
Are the labels of related products differentiated to avoid selection errors? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients	**ANDA Inactive Ingredients**
Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? **CLICK HERE**
Are the inactive ingredients listed in alphabetical order? **CLICK HERE**
For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **CLICK HERE** Has the statement been verified by chemistry? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

Table 9: Comparison of Model Labeling to ANDA finished product	
Model Labeling	**Description of Finished Product** (Source: Click here to enter text.) Click here to enter text. **Package Configurations** (Source: Click here to enter text.) Click here to enter text. **Storage Conditions** (Source: Click here to enter text.) Click here to enter text.
ANDA	**Description of Finished Product** (Source: Click here to enter text.) Click here to enter text. **Package Configurations** (Source: Click here to enter text.) Click here to enter text. **Storage Conditions** (Source: Click here to enter text.) Click here to enter text.

Reviewer Assessment:

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **CLICK HERE**

Is there any difference in scoring configuration between the ANDA and the Model Labeling? **CLICK HERE**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **CLICK HERE**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **CLICK HERE**
Is the storage statement acceptable as compared to the Model Labeling? **NA**
Is the storage statement acceptable as compared to USP? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.2 OTC: PATIENT LABELING

Is patient labeling required? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was patient labeling submitted? **CLICK HERE**
Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.3 CONTAINER/CLOSURE

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.
Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **NO**
Are the tamper evident requirements met for OTC, Ophthalmic and Controlled Substances **NA**

For ophthalmic products:

Does this ophthalmic product cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**

For parenteral products:

Is there text on the cap/ferrule overseal of this injectable product? **NA**
If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**
What is the cap color? **NA**
NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:
We note the labeling for the RLD and subject ANDA state that the sachet/pouch is "re-closable".
From 3.2.P.7 QOS:

(b) (4)

[redacted]

3.4 CALCULATIONS FOR CONTENTS AND VERIFICATION OF ALUMINUM CONTENT (b) (4)

Is calculation of ingredient(s) or verification of aluminum content required? **CLICK HERE**

Table 10: Ingredients		
Ingredient	**Stated Content**	**Location of the Information**
Click here to enter text.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the stated contents in the table above acceptable? **CLICK HERE**
Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per 21 CFR 201.323.
Did the chemistry reviewer verify the aluminum content? **CLICK HERE**
Are the labeling requirements met per 21 CFR 201.323? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

Was SPL submitted? **YES**

Table 11: ANDA Tablet/Capsule Size and Imprint		
Tablet/Capsule Strength	**ANDA Tablet/Capsule Size (mm) and imprint code from SPL**	**ANDA Tablet/Capsule Size (mm) and imprint code (Cite source: e.g., Chemistry Review, Product Specification in 3.2.P.5.1, and Commercial Batch Record in 3.2.P.3.3)**
NA	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **NA**
Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

Reviewer Comments:

From 3.2.P.1 QOS:

Table 3. Physical Description of Amneal's Generic Drug Product and RLD			
Parameter		Amneal's Product Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day	RLD's Product [NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) delivers 0.120mg/0.150 mg per day]
Dimensions N = 10	Average Weight (mg)	(b) (4)	
	Average Outer Diameter of Ring (mm)		
	Average Cross Sectional Diameter (mm)		
	Surface Area (mm^2)		
	Volume (mm^3)		
Packaging Configurations		Box of 3 sachets (3 pouches in 1 carton)	Box of 3 sachets (3 pouches in 1 carton)

We note the outer diameter of subject ANDAs vaginal ring is the same as the RLD.

4. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other review discipline (e.g., OPQ, OB) reviewer(s):

Reviewer Comments:

We note that OPQ has issued a consult to CDRH:

Requesting a reviewer assignment for a team review of the quality of the proposed generic vaginal ring product. The generic formulation is qualitatively and quantitatively similar to the Referenced Listed Drug (NDA 21187 - NuvaRing). Further, the quality controls (tests and acceptance criterion) and manufacturing processes are similar to the RLD (NDA 21187 - NuvaRing). We are requesting this consult to identify any general concerns CDRH reviewers may have with a vaginal ring type product from a device perspective (We have drug-product samples in house that can be provided once a reviewer is assigned).

5. SPECIAL CONSIDERATIONS

Click here to enter text.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	1 vaginal ring	8/25/17	Revise
Carton	Draft	3 Pouches (each pouch contains 1 vaginal ring)	8/25/17	Revise
Expiration Stickers	Draft	NA	8/25/17	Satisfactory
Calendar Reminder Stickers	Draft	NA	8/25/17	Satisfactory
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: 08/2017	8/25/17	Revise
Medication Guide	NA			
Patient Information & Instructions for Use	Draft	Rev. 08-2017-00	8/25/17	Satisfactory
SPL Data Elements		Revised: 8/2017	8/25/17	Satisfactory

Esther Kim

Digitally signed by Esther Kim
Date: 12/01/2017 03:11:37PM
GUID: 5423006c00721ec9406da22c031498a2

Lisa Kwok

Digitally signed by Lisa Kwok
Date: 12/01/2017 03:20:43PM
GUID: 508da70800028c5cddf24c815a550d26

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210830

CLINICAL REVIEWS

Clinical Review of Comparative (Threshold) Analyses for Drug-Device Combination Products

Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

ANDA	210830
Drug Product/Strength(s)	Etonogestrel/ethinyl estradiol vaginal ring delivers 0.120 mg/0.115 mg per day
ANDA Applicant	Amneal Pharmaceuticals
RLD #/ Name	N021187/NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) delivers 0.120 mg/0.015 mg per day.
RLD Sponsor	Organon USA Inc.
Primary Reviewer	Karyn L. Berry, MD, MPH Medical Officer
Secondary Reviewer	Nancy Snow, DO, MPA Team Leader
Tertiary Reviewer	Mark Ritter, MD Associate Director
Submission Date	08/25/2017
Date of Review	03/29/2018
GDUFA Goal Date	06/24/2018
DCR Comparative Analyses Conclusion	☐ No Design Differences ☒ Minor Design Differences ☒ Acceptable ☐ Not acceptable Explain: From a clinical perspective, DCR considers the differences in the size dimensions, compression force, color, labeling, carton opening and patient package inserts to be minor and acceptable.
Deficiency Classification	☐ Major ☐ Minor **(See section 4 for Recommendation)** ☒ N/A (Review is Adequate)

1 INTRODUCTION AND BACKGROUND

1.1 Summary of Drug Product Information Pertinent to Review

This review focuses on the analysis of the user interface[1] for the drug-device combination product (drug and a delivery device intended to administer a drug) comparing the proposed generic product ANDA 210830 etonogestrel/ethinyl estradiol vaginal ring and the Reference Listed Drug (RLD) NDA 021187 NuvaRing (etonogestrel/ethinyl estradiol vaginal ring).

The RLD was approved on 10/03/2001 under NDA 021187 and is marketed by Organon USA Inc.. The most current package insert (PI) and patient package insert information for use (IFU) for NuvaRing was approved on 02/12/2018 under Supplement-31.[2]

NuvaRing is a combination hormonal contraceptive that is indicated for use by women to prevent pregnancy. NuvaRing is inserted in the vagina and must remain in place continuously for three weeks, followed by one week ring-free interval. It is a polymeric vaginal ring which contains 11.7 mg etonogestrel and 2.7 mg ethynyl estradiol, which releases on average 0.12 mg/day of etonogestrel and 0.015 mg/day of ethynyl estradiol. Each NuvaRing is individually packaged in a reclosable aluminum laminate sachet consisting of three layers, from outside to inside: polyester, aluminum foil and low-density polyethylene. NuvaRing is self-inserted by the patient.

Amneal Pharmaceuticals submitted an ANDA 210830 for etonogestrel/ethinyl estradiol vaginal ring on 08/25/2017. To date, there are (b) (4) ANDAs under review (b) (4) See Table 1 in section 1.2

On 01/09/2018, DCR sent an Information Request (IR) to the applicant requesting the submission of the results of the three threshold analyses (e.g. comparative labeling analyses, comparative task analyses, comparison in the design of the delivery device constituent) as well as the applicant's overall assessment of any identified differences for their proposed generic product when compared to the RLD.[3] On 01/22/2018, the applicant submitted a complete written response which included the threshold analyses.[4]

1.2 Other Relevant Information

On 10/30/2017, OPQ/OPRO consulted the Center for Devices and Radiological Health (CDRH)/ODE/DRGUD/OGDB) to evaluate if the proposed combination product is comparable to the RLD from a device performance perspective. CDRH reviewed the product specifications as they related to the physical properties of the ring, the biocompatibility of the product, mechanical performance and compatibility with other intravaginal products and devices.

[1] User interface refers to all components of the combination product with which a user interacts.
[2] Drugs@FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process
[3] Panorama ANDA 210830; file:///C:/Users/BERRYK/Downloads/ANDA%20210830%20IR%20for%20Comparative%20Analysis%20(2).pdf
[4] Global Submit Review ANDA 210830; \\cdsesub1\evsprod\anda210830\0007\m1\us\1-2-cover-letter-word-seq-0007-20180122.docx

In its' review dated 12/20/2017, (b) (4) (b) (4) (b) (4).[5] The applicant's response is pending.

The Electronic Orange Book was reviewed and there are no generic products approved for the RLD NuvaRing (etonogestrel/ethynyl estradiol vaginal ring).[6] (b) (4) including ANDA 210830, that are either under review or have a status of "Complete Response."

Table 1: ANDAs for etonogestrel/ethynyl estradiol vaginal ring

Application #	Product Name	Applicant	Dosage Form	Status	Comments
A210830*	Etonogestrel/Ethinyl Estradiol	Amneal Pharm, LLC	Vaginal Ring	Under review	
A207577	Etonogestrel/Ethinyl Estradiol	Dr. Reddy's Lab	Vaginal Ring	Complete Response 11/07/2016	(b) (4)
A204305	Etonogestrel/Ethinyl Estradiol	Warner Chilcott Co., LLC	Vaginal Ring	Complete Response 01/25/2017	
A211328	Etonogestrel/Ethinyl Estradiol	Mayne Pharma, Inc.	Vaginal Ring	Under review 1/19/2018	
(b) (4)					

*Subject of this review

2 COMPARATIVE (THRESHOLD) ANALYSES REVIEW

DCR conducted a comparative analysis of the user interface of the proposed generic combination product and the RLD NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) NDA 021187.

(b) (4)

[6] Electronic Orange Book: https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

2.1 Labeling comparison of the delivery device constituent part: RLD vs. Proposed

The original product label for the RLD NuvaRing (NDA 021187) was approved on 10/03/2011 and the most current PI with the patient Instructions For Use (IFU) label was approved on 02/12/2018 under Supplement-31.[7] The most updated PI with the Patient IFU for the proposed generic etonogestrel/ethinyl estradiol vaginal ring was submitted by the applicant on 02/28/2018.[8] This was done in response to the RLD label update (02/12/2018).

Delivery device constituent part labeling: RLD vs. Proposed	Yes/No
(1) Any difference in the **description/design**?	Yes
(2) Any difference in the **illustration(s)/figure(s)**?	No
(3) Any difference in the **administration or directions for use**?	Yes
(4) Any difference in the **IFU**?	Yes
(5) Other (Carton)	Yes

2.2 Differences in the delivery device constituent part: RLD vs. Proposed

The following tables present side-by-side comparison of the labeling differences only. The differences are highlighted in yellow.

Table 2: Comparison of PI Labels – RLD NuvaRing (NDA 021187) and Proposed Product (ANDA 210830)

RLD NuvaRing (NDA 021187) PI Section	Proposed Product (ANDA 210830) label dated 02/28/2018 PI Section
Description (section 11)	
NuvaRing (etonogestrel/ethinylestradiol vaginal ring) is a non-biodegradable, flexible, transparent, colorless to almost colorless, combination contraceptive vaginal ring, with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.	(b) (4)
Reviewer Comments: (b) (4) *The coloring description of the proposed generic drug to include translucent is a minor difference and is acceptable.*	

[7] Drugs@FDA; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process
[8] Global Submit Review ANDA (b) (4) \\cdsesub1\evsprod\anda210830\0009\ml\us\1-14-3-1-annotated-comparison-with-amneal-previous.pdf

RLD NuvaRing (NDA 021187) PI Section	Proposed Product (ANDA 210830) label dated 02/28/2018 PI Section
Administration (section 2 Dosage and Administration)	
An optional alternative is to insert the ring using the applicator for NuvaRing *[see Applicator for NuvaRing Instructions for Use]*.	
Reviewer Comments: (b) (4)	
How Supplied (Section 16) Each NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) is individually packaged in a reclosable aluminum laminate sachet consisting of three layers, from outside to inside: polyester, aluminum foil, and low-density polyethylene. Box of 3 sachets NDC 0052-0273-03 Box of 3 sachets NDC 0052-0273-05	(b) (4)
Reviewer Comments: (b) (4) (b) (4)	

Table 3: Comparison of IFU Labels – RLD NuvaRing (NDA 021187) and Proposed

Product (ANDA 210830)

RLD NuvaRing (NDA 021187) IFU Section ---	Proposed Product (ANDA 210830) IFU Section ---
Alternatively, the applicator for NuvaRing (available separately) may be used to help you insert the ring *[see Applicator for NuvaRing Instructions for Use]*.	(b) (4)
Reviewer Comments: *The optional applicator is not a part of the packaging for the RLD,* (b) (4) *In general, the IFU contains very few differences in the language used between the two products. The generic follows the same instructions and does not introduce any new steps compared to the RLD. The graphics in the proposed generic IFU are similar to the RLD.*	

Table 4: Carton

RLD NuvaRing (NDA 021187)	Proposed Product (ANDA 210830)
The RLD carton has an instruction "PRESS TO OPEN" Each box comes with three devices and three patient inserts. The RLD patient inserts are stuck together with an adhesive material which requires pulling them apart.	(b) (4) Each box comes with three devices and three patient inserts. The generic patient inserts are bound together with a piece of paper that requires sliding the paper off or breaking it to release the inserts.
Reviewer Comments: *These differences between the two products are minor and acceptable. The applicant submitted cartons (1 vaginal ring/pouch and 3 pouches per carton) for each of the ANDA submission batches.* (b) (4)	

2.3 Physical comparison of the product samples: RLD vs. Proposed

DCR examined the delivery device constituent part of the RLD and proposed generic product using samples provided by the applicant.

The visual appearance of the proposed generic product vaginal ring and the foil pouch that contains the vaginal ring are similar in design to the RLD. When DCR reviewers manipulated, flexed and bent the proposed vaginal ring there were no significant difference compared with the RLD.

While the pouch foil designs are similar, opening of the generic product foil pouch is much more difficult compared to the RLD foil pouch. DCR reviewers evaluated five generic and five RLD pouches. All five of the RLD pouches were easy to open at the notch and retrieval of the vaginal

ring was as per the IFU. None of the five generic product pouches were opened as per the IFU. When torn at the notch, the generic foil pouches could not be opened. The foil pouch had to be cut with scissors to open and retrieve the vaginal ring.

Figure 1: Comparison of Actual Samples – Photos of RLD NuvaRing (NDA 021187) and Proposed Product ANDA 210830

RLD NuvaRing (NDA 021187)	Proposed (ANDA 210830)
(b) (4)	(b) (4)

Photos taken by DCR reviewer on 03/22/18.

Reviewer Comments:

- *The samples are accurately represented and described in the proposed product's labeling.*
- *While DCR reviewers were unable to open the proposed generic product's foil pouch at the notch, the pouch was easily opened with scissors. There was adequate space between the top of the foil pouch opening to prevent accidental damage to the vaginal ring. Cutting with scissors though prevents resealing of the pouch once the used ring is placed inside after use. As a drug product that is not indicated for emergency or urgent use, the additional time needed to obtain and use scissors to open this product, if necessary, is acceptable.*

2.4 Applicant's Comparative Task Analysis

In response to an IR, the applicant submitted a Threshold Analysis (TA) on 01/22/2018 to compare the proposed generic combination product to the RLD.[9] The purpose of the TA is to analyze the user interfaces of the two products in order to determine if there are any significant differences that would impact critical task performance and require a comparative use human factors study. The applicant's submission includes: physical comparison of the delivery device constituent, labeling comparison and comparative task analysis.

The applicant concluded the following:

[9] Global Submit Review ANDA 210830; \\cdsesub1\evsprod\anda210830\0007\m5\53-clin-stud-rep\535-rep-effic-safety-stud\prevent-pregnancy\5354-other-stud-rep\469-ta\threshold-analysis-report.pdf

The differences identified between the generic device and the RLD device are "minor", no critical tasks have been affected, no new demands have been placed on the user, and no new use-related hazards have been introduced as a result of any differences.

DCR agrees with the applicant's conclusions. Differences between the two products do not place new perceptual, cognitive, or physical demand on the end-users. Therefore, a comparative use human factors study is not required.

Table 5: Classification of differences between the RLD and the proposed generic product

Feature	Ortho® (RLD)	Generic	Classification
Size dimensions	(b) (4)		Minor
Compression force	(b) (4)		Minor
Color	Translucent	Translucent	Minor
Labeling	RLD name Reference to separate applicator	Generic name (b) (4)	Minor
Carton opening	Press open	Press not required	Minor
Patient inserts	Adhesive bound	Paper bound	Minor

Source: Applicant's table from Threshold Analyses, pg.14/15

3 CONCLUSION

From a clinical perspective, DCR considers the differences in the size dimensions, compression force, color, labeling, foil pouch opening, carton opening and patient package inserts to be minor and acceptable.

Internal Recommendation: None

4 RECOMMENDATION

CLINICAL COMMENTS TO BE CONVEYED BY THE RPM TO THE APPLICANT

The Clinical Discipline has completed its review of the comparative (threshold) analyses and has:

No comments at this time.

Karyn Berry

Digitally signed by Karyn Berry
Date: 6/22/2018 10:36:06AM
GUID: 508da6f100027afa7fe6c8d55654a0e5

Nancy Snow

Digitally signed by Nancy Snow
Date: 6/22/2018 10:23:54AM
GUID: 508da6f100027b2a80a136409d193d74

Mark Ritter

Digitally signed by Mark Ritter
Date: 6/22/2018 10:24:31AM
GUID: 508da6e80002732e6afdd41c9bb5d417

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210830

PRODUCT QUALITY REVIEWS

OPQ QUALITY ENDORSEMENT CHECKLIST (See Reference Guide for details):

ANDA# 210830 - Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day by Amneal Pharmaceuticals LLC

Function	**Performed By (Initial and Date)**	**Check appropriate box**
Is the final review signed and archived in the current IT platform?	SY 12/2/19	☒ Yes ☐ No
DMF adequate and review up to date?	SY 12/2/19	☒ Yes ☐ No *(see comments)
Are consults complete and adequate?	SY 12/2/19	☒ Yes *(see comments) ☐ No ☐ N/A
Are all facility inspections acceptable?	SY 12/2/19	☒ Yes ☐ No
Is microbiology recommendation adequate for sterile products?	SY 12/2/19	☒ Yes ☐ No ☐ N/A
Final recommended dissolution method/specification acknowledged by Firm?	See executive summary	☐ Yes ☐ No ☐ N/A
Are there comparability protocols provided? If yes, how many?	See executive summary	☐ Yes How many:_____ ☐ No
If USP monograph exists, do the specifications conform to the current USP?	See executive summary	☐ Yes ☐ No *(see comments) ☐ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	See executive summary	☐ Yes ☐ No *(see comments) ☐ N/A

DMF (b) (4) – Adequate (12/24/18), sd 7
DMF (b) (4) – NAI (5/17/17), sd 208

Division	Name	Date
See executive summart	See executive summary	

Steven Yang

Digitally signed by Steven Yang
Date: 12/02/2019 02:14:03PM
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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Complete Response-Minor
☐ Complete Response-Major
☐ Complete Response-Major-Facilities Only

ANDA 210830
Assessment #3

Drug Product Name	Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day (EluRyng™)
Dosage Form	Vaginal Ring
Strength	0.120 mg/0.015 mg per day
Route of Administration	Vaginal
Rx/OTC Dispensed	Rx
Applicant	Amneal Pharmaceuticals LLC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
0012 – Response to CRL	10/19/2018	All
0013 – Response to Process IR	11/02/2018	DP, Process
0014 – Response to Facility IR	11/08/2018	Facility
0016 – Response to CRL	05/17/2019	DP, Biopharm
0018 – Response to Process IR	07/02/2019	Process

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	DLAPI	DLAPI
Drug Product	Pinaki Desai	Robert Berendt
Manufacturing - Process	James Norman	Yubing Tang
Manufacturing – Facility	R01: Laurie Nelson R02: Laurie Nelson R03: James Norman	R01: Juandria Williams R02: Vidya Pai R03: Yubing Tang
Microbiology	R01: Avital Shimanovich	R01: Marla Stevens Riley
Biopharmaceutics	Hansong Chen	Vidula Kolhatkar
Regulatory Business Process Manager	Steven Yang	
Application Technical Lead	Robert Berendt	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESMENT DATA SHEET

IQA ANDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	05/17/2017	
	II			Adequate	12/24/2018	Reviewed by Ying Lin
	III			N/A	N/A	
	IV			Adequate	03/18/2019	Reviewed by Pinaki Desai
	IV			Adequate	03/18/2019	Reviewed by Pinaki Desai

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	NDA 21187	NuvaRing® (Organon)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharm/Tox	Complete	Adequate: (b) (4) (b) (4)	6/21/2018	Saryu Goel
CDRH-ODE	Complete	Inadequate	12/21/2017	Lead: Jason Roberts, CDRH/ODE/DRGUD/OGDB
	Complete	Inadequate	12/18/2018	

	Complete	Adequate	07/02/2019	Biocompatibility: Pushya Potnis, CDRH/ODE/DRGUD/ULDB
CDRH-OC	Complete	ICCR2017-01796: Delay approval and PAI recommended	12/07/2017	Therese Barber, CDRH/OC
	Complete	ICCR2018-02410: Approval recommended	04/23/2018	
	Complete	ICCR2018-02958: PAI 483 responses and EIR reviewed; approval recommended	6/18/2018	
Clinical	Complete	Comparative Analysis performed and found adequate	03/30/2018	Karyn Berry
Other	N/A			

EXECUTIVE SUMMARY (APPROVALS ONLY)

IQA ANDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product during the expiration dating period of 24 months.

- *The applicant has provided acceptable raw material, in-process, and finished product controls.*
- *The applicant has established an adequate in vitro drug release specification (method and acceptance criteria) for routine quality control of the finished product.*
- *The overall facility assessment recommends approval.*
- *The labeling has adequate quality information.*

Therefore, from the quality perspective, this ANDA is recommended for approval.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The basis for the applicant's ANDA is the approved reference listed drug (RLD), NuvaRing® (NDA 21187), listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book).

The drug product has one strength (0.120 mg/0.015 mg per day), and each unit is individually packaged in a sealed, reclosable foil laminate pouch. Three pouches/carton.

At the end of use, the ring should be replaced in the reclosable pouch and discarded in a waste receptacle out of the reach of children and pets. It should not be flushed down the toilet.

Prior to dispensing to the user, store refrigerated 2° to 8°C (36° to 46°F). After dispensing to the user, EluRyng can be stored for up to 4 months at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Avoid storing EluRyng in direct sunlight or at temperatures above 30°C (86°F). For the Dispenser: When EluRyng is dispensed to the user, place an expiration date on the label. The date should not exceed either 4 months from the date of dispensing or the expiration date, whichever comes first.

Final recommended dissolution method/specification acknowledged by Firm?	☒ Yes ☐ No ☐ N/A
Are there comparability protocols provided? If yes, how many?	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	☒ Yes ☐ No *(see comments) ☐ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	☒ Yes ☐ No *(see comments) ☐ N/A

Proposed Indication(s) including Intended Patient Population	EluRyng® is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.
Duration of Treatment	Chronic Each ring is worn continuously for three weeks
Maximum Daily Dose	2.7 mg of Ethinyl Estradiol 11.7 mg/day of Etonogestrel
Alternative Methods of Administration	N/A

B. Quality Assessment Overview (Please note: ATLs should check the most recent policy alert list)

Drug Substance, Drug Product, and Labeling

(b) (4)

The drug product (EluRyng™) is a vaginal ring that is Q1/Q2 with respect to the RLD, NuvaRing®. The drug product is composed of (b) (4) magnesium stearate, 28% vinyl acetate (VA) polyethylene vinyl acetate (PEVA), 2.7 mg ethinyl estradiol (EE), and 11.7 mg etonogestrel (ETO), (b) (4) The ring has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.

(b) (4)

The Type IV DMFs associated with the EVA polymers were assessed and found adequate. (b) (4)

Extractable/leachable studies were provided and adequate to support the suitability of the pouch container closure system with respect to leachable impurities.

The labeling contains adequate quality information.

Process

(b) (4)

Facility

Two pre-approval inspections were recommended to support the review of this ANDA. The applicant has made changes to the proposed (b) (4) (b) (4) . Therefore, there appears to be no significant or outstanding risks to the manufacturing process or final product based on the ANDA-210830-ORIG-1-AMEND-12 process information, individual and composite evaluation of the listed facilities' inspection results, inspectional history, and relevant experience.

Biopharmaceutics

The Applicant developed their own in-house method to conduct in vitro dissolution tests. The method was demonstrated to be discriminatory with respect to thickness of the ring membrane. Overall, the following IVR method and acceptance criteria have been approved:

Method Source	USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Sampling Times	Acceptance criteria
In-house method	Innova® Incubator shaker with ring holder	50	50 mM acetate buffer, pH 4.2	250 mL	Once every 24 hours for 21 days	(b) (4)

Micro
The applicant has met regulatory expectations with regard to the testing that will be performed on this non-sterile, non-aqueous vaginal drug product prior to its release as well as during the stability testing program to support the microbiological quality of the drug product throughout its shelf life.

CDRH-Device
Adequate information (including condom compatibility) was submitted to support the drug-device combination product from a CDRH perspective.

CDRH-Biocompatibility
From a biocompatibility perspective, there are no significant concerns associated with the use of the subject device.

Shelf Life
The 24-month shelf life is supported by 6M ACC (25°C/60%RH) and 24M long-term (5°C) stability results, as well as in-use and photostability studies.

Policy Alerts
No policy alerts were found in the OGD Policy Alert List dated November 25, 2019.

Lifecycle Considerations
We recommend a post-approval inspection for the following reasons:

- If approved, this will be the first generic intravaginal ring in the United States. Enhanced surveillance is recommended because unknown quality problems could occur with this complex dosage form.
- (b) (4)
- Defect controls (100% visual inspection and AQL inspection) were added in review cycle #3. These controls should be evaluated during a post-approval inspection.

Robert Berendt

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FACILITIES

IQA Review Guide Reference

Product Background: *Amneal Pharmaceuticals LLC is submitting this abbreviated new drug application (ANDA) for the Etonogestrel/Ethinyl Estradiol Vaginal Ring which is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy. The RLD is NuvaRing® , (N021187).*

NDA/ANDA: *ANDA-210830-ORIG-1-AMEND-16*

Drug Product Name / Strength: *Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day*

Route of Administration: *Vaginal*

Applicant Name: *Amneal Pharmaceuticals LLC*

Review Recommendation: ***Adequate***

Theme (ANDA only): **N/A**

Justification (ANDA only): ***N/A***

Review Summary: (b) (4) *Therefore, there appears to be no significant or outstanding risks to the manufacturing process or final product based on the ANDA-210830-ORIG-1-AMEND-12 process information, individual and composite evaluation of the listed facilities' inspection results, inspectional history, and relevant experience.*

Original Review Summary: (b) (4) *There appears to be significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined unacceptable to support approval of ANDA210830.*

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Seq0002	25Aug2017
Seq0009	28Feb2018

Seq0010	06Apr2018
Seq0015	12/10/2018
Seq0016	05/17/2019

Highlight Key Outstanding Issues from Last Cycle: *NA*

ANDA-210830-ORIG-1-AMEND-12: Pending resolution of preapproval inspectional deficiencies.

Concise Description Outstanding Issues Remaining: *After review of the EIR supporting the inspection of Amneal, the inspectional observations made during the inspection documented on FDA form 483 and taking the firm's responses into account it has been determined the facility is not ready for commercial manufacturing and the manufacturing process,* (b) (4)

ANDA-210830-ORIG-1-AMEND-12: None.

List Number of Comparability Protocols (ANDA only): *NA*

3.2.S.2 Manufacture

Summary of Facility Information:

(b) (4)

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PROCESS

IQA Review Guide Reference

Product Background:

ANDA:	210830
Drug Product Name / Strength:	Etonogestrel/Ethinyl Estradiol Vaginal Ring 0.120 mg/0.015 mg per day
Route of Administration:	Vaginal
Applicant Name:	Amneal Pharmaceuticals LLC

Review Recommendation: **Adequate**
Theme (ANDA only): Choose an item.
Justification (ANDA only): Choose an item.

Review Summary:

(b) (4)

Update 06/07/2019: We have a minor deficiency related to defect controls.
Update 07/22/2019: The deficiency about defect controls was adequately resolved.

List Submissions being reviewed (table):

Submission	Date
Resubmission after CR (SD#12)	10/19/18
Response to OPQ IR (SD#13)	11/02/18
Resubmission after CR (SD#16)	05/17/19
Response to OPQ IR (SD #18)	07/02/19

Highlight Key Outstanding Issues from Last Cycle:
The cycle #1 process review is included below.

A210830 Process R01.docx

(b) (4)

(b) (4)

Summary of Process Validation Studies Conducted

Reviewer's Assessment: Adequate

This was adequate in the previous review cycle, and no relevant changes were made.

Assessment of Microbiological Controls

Reviewer's Assessment: Adequate

This was adequate in the previous review cycle, and no relevant changes were made.

Comparability Protocols

Reviewer's Assessment: N/A

Lifecycle Management Considerations

(b) (4)

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List of Deficiencies: N/A

Primary Process Reviewer Name and Date: James J. Norman 10/31/2018, 11/05/18, 06/13/2019, 07/22/2019

Secondary Reviewer Name and Date (and Secondary Summary, as needed):, 11/31/2018, 11/05/2018; 06/13/2019, 07/22/2019

James Norman

Digitally signed by James Norman
Date: 7/22/2019 01:24:01PM
GUID: 54d1401f0008405d17dd845b922ef0b9

Yubing Tang

Digitally signed by Yubing Tang
Date: 7/22/2019 01:28:28PM
GUID: 508da7210002a024fb160a84a176e3c7

Recommendation: Complete Response - Major

ANDA 210830
Review # 2

Drug Name/Dosage Form	Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day
Strength	0.120 mg/0.015 mg per day
Route of Administration	Vaginal
Rx/OTC Dispensed	Rx
Applicant	Amneal Pharmaceuticals LLC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0012 - Response to CRL	*10/19/2018*	*All*
0013 - Response to Process IR	*11/02/2018*	*DP, Process*
0014 - Response to Facility IR	*11/08/2018*	*Facility*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	DMF TM	DMF TM
Drug Product	Pinaki Desai	Robert Berendt
Process	James Norman	Yubing Tang
Microbiology	R01: Avital Shimanovich	R01: Marla Stevens Riley
Facility	Laurie Nelson	Juandria Williams
Biopharmaceutics	Hansong Chen	Vidula Kolhatkar
Application Technical Lead	Robert Berendt	N/A
RBPM	Steven Yang	N/A
Laboratory (OTR)	N/A	N/A
ORA Lead	Michael Tollon	N/A
Environmental	N/A	N/A

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	05/17/2017	
	II			Adequate	12/24/2018	Reviewed by Ying Lin
	III			N/A	N/A	
	IV			Adequate	03/18/2019	Reviewed by Pinaki Desai
	IV			Adequate	03/18/2019	Reviewed by Pinaki Desai

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 21187	NuvaRing® (Organon)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH-ODE	Complete	Inadequate	12/18/2018	Jason Roberts, CDRH/ODE/ DRGUD/OGDB

Abbreviated Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – **Major**.

II. Quality Assessment Overview

A. Drug Substance, Drug Product, and Labeling: Inadequate-Major

(b) (4)

The drug product (Eluryng™) is a vaginal ring that is Q1/Q2 with respect to the RLD, NuvaRing®. The Type IV DMFs associated with the EVA polymers were assessed and found adequate. (b) (4) A major deficiency is associated with the CDRH device consult, which identified a deficiency with biocompatibility.

No labeling issue was found.

B. Process: Adequate

(b) (4)

C. Facility: Adequate

Two pre-approval inspections were recommended to support the assessment of this ANDA. The applicant has made changes to the proposed (b) (4) (b) (4) Therefore, there appears to be no significant or outstanding risks to the manufacturing process or final product, individual and composite evaluation of the listed facilities' inspection results, inspectional history, and relevant experience. The Amneal Pharmaceuticals LLC facility (FEI: 3008861605) is determined unacceptable to support approval of ANDA210830.

D. Biopharmaceutics: Inadequate-Minor

The applicant developed an in-house method for in-vitro drug release test (IVR). The IVR method has been assessed and was found acceptable. However, the proposed acceptance criteria are inadequate.

E. Microbiology: Adequate The applicant has met regulatory expectations regarding the test that will be performed on this non-sterile, non-aqueous vaginal drug product prior to its release and the microbiological quality of the product throughout its shelf life.

List of Deficiencies for Complete Response

I. Drug Substance Deficiencies – Ethinyl Estradiol

None

II. Drug Substance Deficiencies – Etonogestrel

None

III. Drug Product Deficiencies

1) (b) (4)

IV. Drug Product – CDRH Device Evaluation Deficiencies

1) **Major deficiency:** The drug product deficiencies have been classified as MAJOR because of insufficient data to support drug/device compatibility and sustainability for the proposed product as noted in Appendix A, Section A(2)(n) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This information is required to ensure proper patient in-use of the product. Upon receipt, in FDA's judgement, the assessment of this information will require thorough evaluation and potentially affects other aspects of the application and the related conclusions.

   You have provided the 90-days study test reports (# 17-00131-G12 and 17-00891-G1) in your submission dated October 19, 2018. Per the test reports, the test ring (Amneal) and Amneal's placebo ring (Sponsor Control) were dipped (b) (4) (b) (4) prior to being implanted in the animals. We are concerned that this process might remove potentially harmful extractive leachable substances and affect the overall leachable profile of the test article extract, which could result in false negative results. Since your subject device [test ring (Amneal)] is provided

as non-sterile, finished product, biocompatibility testing should be done on the representative test article without (b) (4) Please provide justification as to how the test article dipped (b) (4) prior to testing, represents your final, device that is intended to be inserted vaginally without such treatment.

V. Process Deficiencies

None

VI. Facilities Deficiencies

None

VII. Biopharmaceutics Deficiencies

1) Per our current thinking and understanding for vaginal rings, we recommend the following in-vitro release (IVR) acceptance criteria for the proposed drug product:

Etonogestrel	Ethinyl Estradiol
(b) (4)	

We request that you acknowledge your acceptance of the recommended IVR acceptance criteria for your drug product and update the drug product specifications accordingly.

The response to the complete response letter (submission dated October 19, 2018) showed that you have stability data for Day 14 for all exhibit batches. Please submit all available individual unit stability data for Day 5 and Day 14 to the Agency for assessment. In addition, please be advised that all exhibit batches in your stability program are expected to meet the revised IVR acceptance criteria through your proposed expiry period.

Application Technical Lead Name and Date: Robert Berendt, 03/27/2019

Robert Berendt

Digitally signed by Robert Berendt
Date: 3/27/2019 03:27:52PM
GUID: 508da7380002b309c612f7e27bdf5995

FACILITIES

IQA Review Guide Reference

Product Background: *Amneal Pharmaceuticals LLC is submitting this abbreviated new drug application (ANDA) for the Etonogestrel/Ethinyl Estradiol Vaginal Ring which is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy. The RLD is NuvaRing® , (N021187).*

NDA/ANDA: *ANDA-210830-ORIG-1-AMEND-12*

Drug Product Name / Strength: *Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day*

Route of Administration: *Vaginal*

Applicant Name: *Amneal Pharmaceuticals LLC*

Review Recommendation: ***Adequate (Amend 12 submitted 10 December 2018)***

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary: (b) (4) *Therefore, there appears to be no significant or outstanding risks to the manufacturing process or final product based on the ANDA-210830-ORIG-1-AMEND-12 process information, individual and composite evaluation of the listed facilities' inspection results, inspectional history, and relevant experience.*

Original Review Summary: (b) (4) *There appears to be significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined unacceptable to support approval of ANDA210830.*

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Seq0002	25Aug2017
Seq0009	28Feb2018

Seq0010	06Apr2018
Seq0015	12/10/2018

Highlight Key Outstanding Issues from Last Cycle: *NA*

ANDA-210830-ORIG-1-AMEND-12: Pending resolution of preapproval inspectional deficiencies.

Concise Description Outstanding Issues Remaining: *After review of the EIR supporting the inspection of Amneal, the inspectional observations made during the inspection documented on FDA form 483 and taking the firm's responses into account it has been determined the facility is not ready for commercial manufacturing and the manufacturing process,* (b) (4) .

ANDA-210830-ORIG-1-AMEND-12: None.

List Number of Comparability Protocols (ANDA only): *NA*

3.2.S.2 Manufacture

Summary of Facility Information:

(b) (4)

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NA

List of Deficiencies:

January 2019: No deficiencies

Previous June 19, 2018 deficiencies: There is lack of conformance to the application (b) (4) *Also reference Process Review Deficiency #2.*

Primary Facilities Reviewer Name and Date: *Laurie Nelson, June 19, 2018*
Amend-12: Laurie Nelson, January 9, 2019

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Krishna Ghosh, Ph.D./OPF/DIA/B3; 6/19/2018

Amend-12: Vidya Pai, OPF/DIA/B3, 18 March 2019

Vidya Pai

Digitally signed by Vidya Pai
Date: 3/18/2019 09:02:15AM
GUID: 53b581d20000464509a65e37ec9ad4a2

Laurie Nelson

Digitally signed by Laurie Nelson
Date: 3/18/2019 09:10:33AM
GUID: 5922f76e00c40bfb158ba986788152c0

QUALITY ASSESSMENT

PROCESS

IQA Review Guide Reference

Product Background:

ANDA:	210830
Drug Product Name / Strength:	Etonogestrel/Ethinyl Estradiol Vaginal Ring 0.120 mg/0.015 mg per day
Route of Administration:	Vaginal
Applicant Name:	Amneal Pharmaceuticals LLC

Review Recommendation: **Adequate**
Theme (ANDA only): Choose an item.
Justification (ANDA only): Choose an item.

Review Summary:

(b) (4)

(b) (4) The application appears approvable from the process perspective.

List Submissions being reviewed (table):

Submission	Date
Resubmission after CR (SD#12)	10/19/18
Response to OPQ IR (SD#13)	11/02/18

Highlight Key Outstanding Issues from Last Cycle:
The process review from the previous cycle is included below.

A210830 Process R01.docx

(b) (4)

Concise Description Outstanding Issues Remaining: None
List Number of Comparability Protocols (ANDA only): None

APPEARS THIS WAY ON ORIGINAL

Reviewer's Assessment: Adequate
This was adequate in the previous review cycle, and no relevant changes were made.

Assessment of Microbiological Controls

Reviewer's Assessment: Adequate
This was adequate in the previous review cycle, and no relevant changes were made.

Comparability Protocols

Reviewer's Assessment: N/A

Lifecycle Management Considerations

(b) (4)

List of Deficiencies: N/A

Primary Process Reviewer Name and Date: James J. Norman 10/31/2018, 11/05/18

Secondary Reviewer Name and Date (and Secondary Summary, as needed):,
11/31/2018, 11/05/2018

APPEARS THIS WAY ON ORIGINAL

James Norman

Digitally signed by James Norman
Date: 11/05/2018 04:22:43PM
GUID: 54d1401f0008405d17dd845b922ef0b9

Yubing Tang

Digitally signed by Yubing Tang
Date: 11/05/2018 04:34:21PM
GUID: 508da7210002a024fb160a84a176e3c7

Recommendation: Complete Response - Major

Drug Product - Major

Theme (ANDA only): **Due to Consult**

Justification (ANDA only): Submission of additional information is needed. Upon receipt, this information will require thorough evaluation and will potentially affects other aspects of the application and the related conclusions

Facilities - Major

Theme (ANDA only): **Inadequate Facility - PAI Withhold**

Justification (ANDA only): Facility deficiencies require substantial expenditure of FDA resources to re-evaluate the facilities and potentially trigger additional inspections

ANDA 210830
Review # 1

Drug Name/Dosage Form	Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day
Strength	0.120 mg/0.015 mg per day
Route of Administration	Vaginal
Rx/OTC Dispensed	Rx
Applicant	Amneal Pharmaceuticals LLC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
New ANDA	*8/25/17*	*All*
Quality/Response to Sample Request	*10/16/17*	*DP, Process*
Quality/Response to IR	*11/29/17*	*All*
Quality/Response to IR	*2/16/18*	*Facilities*
Quality/Response to IR	*4/6/18*	*All*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER

Drug Master File/Drug Substance	DMF TM	DMF TM
Drug Product	Pinaki Desai	Robert Berendt
Process	James Norman	Yubing Tang
Microbiology	Avital Shimanovich	Marla Stevens Riley
Facility	Laurie Nelson	Juandria Williams
Biopharmaceutics	Hansong Chen	Vidula Kolhatkar
Application Technical Lead	Robert Berendt	N/A
RBPM	Steven Yang	N/A
Laboratory (OTR)	N/A	N/A
ORA Lead	Michael Tollon	N/A
Environmental	N/A	N/A

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)		Adequate	05/17/2017	
	II			Inadequate	03/28/2018	First review cycle: CR sent 04/04/2018
	III			N/A	N/A	
	IV			Inadequate	05/25/2018	Reviewed by Pinaki Desai
	IV			Inadequate	05/25/2018	Reviewed by Pinaki Desai

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
RLD	NDA 21187	NuvaRing® (Organon)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharm/Tox	Complete	Adequate: The applicant's control limit for (b) (4) originating from the raw EVA material is acceptable.	6/21/2018	Saryu Goel
CDRH-ODE	Complete	Inadequate	12/21/2017	Jason Roberts, CDRH/ODE/DRGUD/OGDB
CDRH-OC	Complete	• ICCR2017-01796: Delay approval and PAI recommended 12/07/2017	6/18/2018	Therese Barber, CDRH/OC

		• ICCR2018-02410: Approval recommended 04/23/2018 • ICCR2018-02958: PAI 483 responses and EIR reviewed; approval recommended		
Clinical (non-consult)	Complete	Comparative Analysis performed and found adequate	03/30/2018	Karyn Berry
Other	N/A			

Abbreviated Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – **Major**.

II. Quality Assessment Overview

A. Drug Substance, Drug Product, and Labeling: Inadequate-Major

(b) (4)

The drug product is a vaginal ring that is Q1/Q2 with respect to the RLD, NuvaRing®. The Type IV DMFs associated with the EVA polymers were reviewed and found inadequate. In addition, minor deficiencies were identified in the specifications and post-approval stability protocol, and additional stability data is being requested. A major deficiency is associated with the CDRH device consult, which identified deficiencies with biocompatibility, performance testing (at release and during stability), and device compatibility.

No labeling issue was found.

B. Process: Inadequate-Minor

(b) (4)

C. **Facility**: Inadequate-Major

(b) (4)

D. **Biopharmaceutics:** Inadequate-Minor
The applicant developed an in-house method for in vitro drug release testing (IVRT). The IVRT method has been reviewed and was found acceptable. However, the proposed specifications were not appropriate based on the data submitted.

E. **Microbiology**: Adequate The applicant has met regulatory expectations regarding the test that will be performed on this non-sterile, non-aqueous vaginal drug product prior to its release and the microbiological quality of the product throughout its shelf life.

Robert Berendt

Digitally signed by Robert Berendt
Date: 6/21/2018 12:53:36PM
GUID: 508da7380002b309c612f7e27bdf5995

FACILITIES

IQA Review Guide Reference

Product Background: *Amneal Pharmaceuticals LLC is submitting this abbreviated new drug application (ANDA) for the Etonogestrel/Ethinyl Estradiol Vaginal Ring which is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy. The RLD is NuvaRing® , (N021187).*

NDA/ANDA: *ANDA-210830*

Drug Product Name / Strength: *Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day*

Route of Administration: *Vaginal*

Applicant Name: *Amneal Pharmaceuticals LLC*

Review Recommendation: **Inadequate - Major**

Theme (ANDA only): **Inadequate Facility - PAI Withhold**

Justification (ANDA only): Facility deficiencies require substantial expenditure of FDA resources to re-evaluate the facilities and potentially trigger additional inspections

Review Summary: (b) (4) *. There appears to be outstanding risks to the manufacturing process of the final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The Amneal Facility FEI: 3008861605 is determined unacceptable to support the approval of ANDA 210830 due to lack of conformance to the application;* (b) (4) *required for commercial manufacturing is deemed unacceptable.*

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Seq0002	25Aug2017
Seq0009	28Feb2018
Seq0010	06Apr2018

Highlight Key Outstanding Issues from Last Cycle: *NA*

Concise Description Outstanding Issues Remaining: *After review of the EIR supporting the inspection of Amneal, the inspectional obserations made during the inspection documented on FDA form 483 and taking the firm's responses into account it has been determined the facility is not ready for commercial manufacturing and the manufacturing process,* (b) (4)

List Number of Comparability Protocols (ANDA only): *NA*

3.2.S.2 Manufacture

Summary of Facility Information:

(b) (4)

Reviewer's Assessment: ***Adequate***

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: *NA*

Lifecycle Management Considerations

NA

List of Deficiencies:

There is a lack of conformance to the application due to the (b) (4) *required for commercial manufacturing at your Drug Product manufacturing facility, Amneal Pharmaceuticals LLC (FEI: 3008861605), as stated in your application. Also reference Process Review Deficiency #2.*

Primary Facilities Reviewer Name and Date: *Laurie Nelson, June 19, 2018*

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Krishna Ghosh, Ph.D./OPF/DIA/B3; 6/19/2018

Laurie Nelson

Digitally signed by Laurie Nelson
Date: 6/19/2018 02:03:33PM
GUID: 5922f76e00c40bfb158ba986788152c0

Krishna Ghosh

Digitally signed by Krishna Ghosh
Date: 6/19/2018 01:57:36PM
GUID: 508da7470002bf919f64f7a697b2e6b7

LABELING

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.) Yes

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A

If "No," explain.

For OTC Drugs and Controlled Substances: N/A

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

None

List of Deficiencies: none

Primary Drug Product Reviewer Name and Date: ***Pinaki Desai, 04-FEB-2018***

Secondary Drug Product Reviewer Name and Date: ***Robert Berendt, 25-MAY-2018***

Pinaki Desai

Digitally signed by Pinaki Desai
Date: 5/25/2018 06:08:12PM
GUID: 52260ff900012d0b26101dd96ed2276f

Robert Berendt

Digitally signed by Robert Berendt
Date: 5/25/2018 01:53:03PM
GUID: 508da7380002b309c612f7e27bdf5995

PROCESS

IQA Review Guide Reference

Product Background:	
ANDA:	210830
Drug Product Name / Strength:	Etonogestrel and ethinyl estradiol vaginal system 120 micrograms/day and 15 micrograms/day
Route of Administration:	Intravaginal
Applicant Name:	Amneal

Review Recommendation: **Inadequate - Minor**
Theme (ANDA only): Choose an item.
Justification (ANDA only): Choose an item.

Review Summary: (b) (4)

List Submissions being reviewed (table):

Document(s) Reviewed (SD-#)	Date Received
Original submission SD#1	08/25/17
IR response for OPQ SD#5	11/29/17
IR response for OPQ SD #10	04/06/18

Highlight Key Outstanding Issues from Last Cycle: N/A
Concise Description Outstanding Issues Remaining:

- (b) (4)
-

List Number of Comparability Protocols (ANDA only): None

(b) (4)

Primary Process Reviewer Name and Date:
Mid-cycle: James J. Norman 01/16/2018; 01/31/2018
CR#1: James J. Norman 04/27/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Yubing Tang, 01/28/2018; 01/31/2018; 04/30/2018

James Norman

Digitally signed by James Norman
Date: 5/01/2018 02:12:05PM
GUID: 54d1401f0008405d17dd845b922ef0b9

Yubing Tang

Digitally signed by Yubing Tang
Date: 5/01/2018 09:23:20AM
GUID: 508da7210002a024fb160a84a176e3c7

QUALITY ASSESSMENT

MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA/ANDA: A210830

Drug Product Name / Strength: Etonogestrel and ethinyl estradiol vaginal ring, 0.12 mg/0.015 mg per day

Route of Administration: vaginal

Applicant Name: Amneal Pharmaceuticals LLC

Manufacturing Site:
(b) (4)

Method of Sterilization: Non-sterile drug product

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): **N/A**

Review Summary: Vaginal ring is a non-sterile, non-aqueous product.

List Submissions Being Reviewed: 08/25/2017 and 11/29/2017 (Quality IR response)

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None.

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

The drug substance is not reviewed in this application as the final drug product is a non-sterile product.

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** Smooth, round, and translucent vaginal ring. (b) (4) Below is a picture of the drug product copied from Section P.1.

(b) (4)

- **Drug product composition –**

Ingredient	Function	Quantity/Ring
Etonogestrel	API	11.700 mg
Ethinyl Estradiol	API	2.700 mg
Ethylene Vinyl Acetate Copolymer (28% Vinyl Acetate)	Polymer	(b) (4)
Ethylene Vinyl Acetate Copolymer (9% Vinyl Acetate)	Polymer	
(b) (4)	(b) (4)	
Magnesium Stearate, NF		

- **Description of container closure system –** Rings are packaged individually into resealable aluminum pouches (four layers, outside to inside: PET, LDPE, aluminum foil, LLDPE).

Reviewer's Assessment: ***Adequate***

The applicant provides the drug product and container closure information.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

Pouches were tested for pouch burst strength, which was established at (b) (4) (b) (4)

Reviewer's Assessment: ***Adequate***

The applicant used the burst test to test the integrity of the pouch seal.

Antimicrobial Effectiveness Testing

N/A. Although the drug product is multiple-dose, it is a non-sterile, non-aqueous dosage form.

Reviewer's Assessment: N/A. Multiple dose, non-aqueous drug products are not required to be subjected to USP <51>.

P.3 Manufacture
P.3.1 Manufacturers

(b) (4)

Reviewer's Assessment: ***Adequate***

The applicant provides the manufacturing address.

P. 3.3 Description of the Manufacturing Process and Process Controls
Overall Manufacturing Operation

(b) (4)

Reviewer's Assessment: ***Adequate***

The applicant provides the manufacturing process.

Terminal Sterilization Process – N/A
Aseptic Fill Manufacturing Process – N/A
Sterilization/Depyrogenation of containers, closures, equipment – N/A
Environmental Monitoring– N/A

P. 3.5 Process Validation and/or Evaluation – N/A

P.5 Control of Drug Product

P. 5.1 Specification

Microbiological tests in the release specification are described as:

Test	Test Method	Acceptance criteria
TAMC	USP <61>	(b) (4)
TYMC	USP <61>	
Absence of: *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Candida albicans*	USP <62>	
Pouch integrity	Burst pressure Bubble emission	

Batches PW-ST-16052A, PW-ST-16055A, and PW-ST16056A adhered to release specifications.

Reviewer's Assessment: ***Adequate***

The applicant has met regulatory expectations with regard to the test that will be performed on this non-sterile, non-aqueous vaginal drug product prior to its release.

Acceptance criteria for USP <61> provided in USP <1111> are TAMC NMT 100 CFU/g and TYMC NMT 10 CFU/g. The applicant provided acceptance criteria that are per unit and not per g. The applicant states that each unit is (b) (4) (Section P.3.1). To account for USP acceptance criteria, the number of CFU/unit is converted below to CFU/g. For TAMC, (b) (4) For TYMC (b) (4) CFU/g. The acceptance criteria meet the recommendations in USP <1111> for a vaginal product.

P.5.2 Analytical Procedures

Microbiological testing for TAMC and TYMC will be performed per USP <61> and for absence of specified organisms will be performed per USP <62>.

Reviewer's Assessment: ***Adequate***

The applicant has met regulatory expectations with the test methods and acceptance criteria.

P.5.3 Validation of Analytical Procedures – N/A

P.7 Container Closure – N/A

P.8 Stability

P. 8.1 Stability Summary and Conclusion

Section P.5.1 contains the release specification. The microbiologically relevant tests are the same as those provided in the release specification.

Vaginal rings are stored under long-term conditions at 5°C for microbiological testing at 0, 3, 6, 9, 12, 18, and 24 months, and accelerated conditions at 25±2°C/60±5%RH for microbiological testing at 0, 3, and 6 months.

Reviewer's Assessment: ***Adequate***

The applicant has met regulatory expectations with regard to the design of the stability testing program to support the microbiological quality of the drug product throughout its shelf life.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant will place the first three commercial batches on stability and then one lot annually will be placed on stability.

The proposed shelf-life is 24 months. Vaginal rings are stored under long-term conditions at 5°C for microbiological testing at 0, 3, 6, 9, 12, 18, and 24 months.

Reviewer's Assessment: ***Adequate***

The applicant has met regulatory expectations with regard to the microbiological quality of the drug product throughout its shelf life.

P.8.3 Stability Data

Under long-term storage conditions at 5°C, at 0, 3, 6, and 9 month rings adhered to release specification. Under accelerated conditions, at 0, 3, and 6 month rings also adhered to release specification.

Reviewer's Assessment: ***Adequate***

The stability data the applicant has provided to date supports the microbiological quality of the subject drug product.

A **Appendices** - N/A
R **Regional Information** –N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1
2.A. Package Insert

(b) (4)

Reviewer's Assessment: ***Adequate***

The user is provided with acceptable user instructions.

List of Deficiencies:
Primary Microbiology Reviewer Name and Date: *Avital Shimanovich, Ph.D., 04/27/2018*
Secondary Reviewer Name and Date (and Secondary Summary, as needed): *Marla Steven-Riley, Ph.D., 04/27/2018*

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210830

PHARMACOLOGY/TOXICOLOGY REVIEWS

PHARMACOLOGY-TOXICOLOGY CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

Etonogestrel: Ethinyl Estradiol Vaginal Ring; 0.12 mg/24hr: 0.015 mg/24hr

Drug Product:	EluRyng™, Etonogestrel: Ethinyl Estradiol Vaginal Ring; 0.12 mg/24hr: 0.015 mg/24hr
Referenced ANDA: **Applicant:**	210830 Amneal Pharmaceuticals LLC.
RLD#/Approval Date: **Sponsor:**	NuvaRing®, NDA 021187, Etonogestrel: Ethinyl Estradiol Vaginal Ring; 0.12 mg/24hr: 0.015 mg/24hr, approved 10/03/2001 Organon USA Inc., a subsidiary of Merck & Co. Inc.
Pharmacology-Toxicology Primary Reviewer:	Saryu Goel, DVM, PhD, DABT Pharmacologist
Pharmacology-Toxicology Secondary Reviewer:	Richard Houghtling, PhD Lead Pharmacologist
Tertiary Reviewer:	Mark Ritter, MD Associate Director
To:	Pinaki Desai, DMRP/OLDP/OPQ
Reason for Consult:	To evaluate the toxicity and acceptability of maximum exposure to (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) from generic EluRyng™. (b) (4) controlled at specification limit of not-more-than (b) (4) in the two-ethylene vinyl acetate (EVA) copolymers that contain either 9% or 28% vinyl acetate (VA). EVA copolymers are used to manufacture the generic EluRyng™.
Date of Submission:	08/25/2017 & 11/29/2017
Date Consult Received:	03/20/2018
Date of Completion:	06/21/2018
Conclusion:	From a Pharmacology/Toxicology perspective, a maximum exposure to (b) (4) (b) (4) from proposed generic EluRyng™ is acceptable. See Section 2 for Internal Recommendations. There is no comment in Section 3 to convey to the applicant.
Deficiency Classification:	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

1 Executive Summary

This Pharmacology/Toxicology review addresses a consult request from the Division of Modified Release Products (DMRP) in the Office of Pharmaceutical Quality (OPQ) to evaluate the toxicity and acceptability (b) (4) present in the generic etonogestrel: ethinyl estradiol vaginal ring (0.12 mg/24hr: 0.015 mg/24hr).[1] The above generic is submitted under ANDA 210830 for EluRyng™ by Amneal Pharmaceuticals LLC. (b) (4) (b) (4) (b) (4) (b) (4) in the two-ethylene vinyl acetate (EVA) copolymers containing either 9% (b) (4) or 28% (b) (4) vinyl acetate (VA). The EVA copolymers are used to manufacture the generic etonogestrel: ethinyl estradiol vaginal ring.

The reference listed drug (RLD) is NuvaRing®, an etonogestrel: ethinyl estradiol vaginal ring (0.12 mg/24hr: 0.015 mg/24hr). NuvaRing® was developed by Organon USA Inc a subsidiary of Merck & Co. Inc. under NDA 021187 and was approved on 10/03/2001. NuvaRing® is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy. One NuvaRing® is inserted in the vagina and must remain in place continuously for three weeks. One-week ring free interval is allowed before placement of another vaginal ring.[2]

[NOT FOR Release under FOIA; APPLICABLE TO THE ENTIRE PARAGRAPHS BELOW]

(b) (4)

[redacted]

[1] EluRyng™ (etonogestrel: ethinyl estradiol vaginal ring), ANDA 210830, GDRP DMRP, OPQ Pharm-Tox Consult, 03/16/2018. http://panorama.fda.gov/task/view?ID=5aabe1d80002aa0d579e68071ef2a3f3

[2] NuvaRing® (etonogestrel: ethinyl estradiol vaginal ring; 0.12 mg/24hr: 0.015 mg/24hr), NDA 021187, label, 02/12/2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021187s031lbl.pdf

[3] ANDA 207577, etonogestrel: ethinyl estradiol vaginal ring; 0.12 mg/24 hr: 0.015 mg/24 hr, Pharmacology/Toxicology Consult Review, 06/12/2018. http://panorama.fda.gov/document/view?ID=5b1fc400008bb93e4469e430dd4a8ce3

(b) (4)

2 Internal Recommendation

The Pharmacology/Toxicology review determined that the maximum exposure to (b) (4) (b) (4) from generic etonogestrel: ethinyl estradiol vaginal ring (EluRyng™, ANDA 210830) is acceptable.

3 No comment to convey to the ANDA applicant

4 Regulatory Background

The reference listed drug (RLD) is NuvaRing®, an etonogestrel: ethinyl estradiol vaginal ring (0.12 mg/24hr: 0.015 mg/24hr). NuvaRing® was developed by Organon USA Inc., under NDA 021187 and was approved on 10/03/2001. The ANDA 210830 for generic EluRyng™ (etonogestrel: ethinyl estradiol vaginal ring) is for same strength as the RLD. The ANDA 210830 was submitted by Amneal Pharmaceuticals LLC. and was accepted for filling on 08/25/2017.[4] The applicant used EVA copolymers with 9% vinyl acetate and 28% vinyl acetate to manufacture generic vaginal ring. (b) (4) (b) (4) (b) (4) The applicant provided justification to support the safety from exposure to (b) (4) This review evaluates the acceptability of proposed level of (b) (4) in generic etonogestrel: ethinyl estradiol vaginal ring, ANDA 210830.

4.1 Orange Book Information

The RLD, NuvaRing® (NDA 021187), is the only marketed prescription entry in the Orange Book for etonogestrel: ethinyl estradiol vaginal ring, 0.12 mg/24hr: 0.015 mg/24hr. NuvaRing®

[4] EluRyng™ (etonogestrel: ethinyl estradiol vaginal ring), ANDA 210830, GDRP Filing Review, 10/6/2017. http://panorama.fda.gov/document/view?versionID=59d7b80100239a516c276b9f190d234b

was approved on 10/03/2001 and is marketed by Organon USA Inc a subsidiary of Merck & Co. Inc.[5]

4.2 RLD Formulation (Not for release under FOIA)

(b) (4)

Table 2. Composition of NuvaRing® (NDA 021187) with the levels of EVA with 9% VA and EVA with 28% VA are in red box.[6]

Ingredient	Formulation (mg/ring)
(b) (4)	
• Ethylene vinyl acetate copolymer, 28% m/m vinyl acetate[1]	(b) (4)
• Etonogestrel	11.7
• Ethinyl estradiol	2.7
• Magnesium stearate	(b) (4)
(b) (4)	
• Ethylene vinyl acetate copolymer, 9% m/m vinyl acetate	(b) (4)
(b) (4)	
(b) (4)	

4.3 Proposed Generic Formulation

The proposed generic formulation was obtained from Section 3.2.P.1 in the application submission dated 08/25/2017.[10] The generic contains (b) (4) of EVA copolymer with 9%

[5] Orange Book search for ethinyl estradiol: etonogestrel on 05/26/2018

[6] NuvaRing® (etonogestrel: ethinyl estradiol vaginal ring; 0.12 mg/24 hr: 0.015 mg/24 hr), NDA 021187, EDR 3.2.P.8.1 Stability Data, page 4, 11/25/2013, \\cdsesub1\evsprod\nda021187\0026\m3\32-body-data\32p-drug-prod\nuvaring-vaginal-ring\32p8-stab\p84i-longterm-accel-study-454424001.pdf

[7] NuvaRing® (etonogestrel: ethinyl estradiol vaginal ring; 0.12 mg/24 hr: 0.015 mg/24 hr), NDA 021187, DAARTS, KRISHAN L. RAHEJA, FRM-ADMIN-01 (Memorandum to File), 02/14/2005, https://darrts fda.gov//darrts/faces/ViewDocument?documentId=090140af8016f658&_afrRedirect=2151530067974691

[8] (b) (4) Ethylene-Vinyl Acetate Copolymers, (b) (4) COA, paper submission dated 02/03/2006.

[9] Ethylene-Vinyl Acetate Copolymers, REV-QUALITY-13 (MF General Review) 02/15/2005.

[10] EluRyng™ (etonogestrel: ethinyl estradiol vaginal ring), ANDA 210830, EDR 3.2.P.1. Description and Composition, 08/25/2017. \\cdsesub1\evsprod\anda210830\0001\m3\32-body-data\32p-drug-prod\etonogestrel-ethinyl-estradiol-vaginal-ring-0-120-mg-0-015-mg\32p1-desc-comp\32p1-description-and-composition.pdf

vinyl acetate (b) (4) and (b) (4) of EVA copolymer with 28% vinyl acetate (b) (4) (b) (4) (Table 3).[11] (b) (4) (b) (4)

Table 3. Composition of generic vaginal ring (ANDA 210830) with the levels of EVA with 9% VA and EVA with 28% VA are in red box.

Ingredient	Function	mg/Unit
Etonogestrel (b) (4)	Active	11.70
Ethinyl Estradiol, USP (b) (4)	Active	2.700
EVA Copolymer, 28% VA (VitalDose® K2569.X01)[1]	(b) (4)	
Magnesium Stearate, NF		
EVA Copolymer, 9% VA (VitalDose® K2568.X01)[1]		
(b) (4)		
Total		(b) (4)

(b) (4)

5 Labeling

The current product label for NuvaRing®, NDA 021187, etonogestrel: ethinyl estradiol (0.12 mg/24 hr: 0.015 mg/24 hr) vaginal ring was approved on 02/12/2018. There is a black box warning about smoking and serious cardiovascular events.[14]

5.1 Indications

NuvaRing® is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.

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[11] EluRyng™ (etonogestrel: ethinyl estradiol vaginal ring), ANDA 210830, EDR 1.4.2 Statement of Right of Reference, Appendices 4 (b) (4) 08/25/2017. \\cdsesub1\evsprod\anda210830\0001\m1\us\1-4-2-statement-of-right-of-reference.pdf

[12] EluRyng™ (etonogestrel: ethinyl estradiol vaginal ring), ANDA 210830, EDR 3.2.P.4.1 EVA with 9%VA specification, 11/29/2017. \\cdsesub1\evsprod\anda210830\0005\m3\32-body-data\32p-drug-prod\etonogestrel-ethinyl-estradiol-vaginal-ring-0-120-mg-0-015-mg\32p4-contr-excip\excipients\32p41-eva-copolymer-9-spec.pdf

[13] EluRyng™ (etonogestrel: ethinyl estradiol vaginal ring), ANDA 210830, EDR 3.2.P.4.1 EVA with 28%VA specification, 11/29/2017\\cdsesub1\evsprod\anda210830\0005\m3\32-body-data\32p-drug-prod\etonogestrel-ethinyl-estradiol-vaginal-ring-0-120-mg-0-015-mg\32p4-contr-excip\excipients\32p41-eva-copolymer-28-spec.pdf

[14] NuvaRing®, NDA 021187, Etonogestrel: ethinyl estradiol; 0.12 mg/24 hr: 0.015 mg/24 hr, label, 02/12/2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021187s031lbl.pdf

5.2 Dosage and Administration

NuvaRing® is a polymeric vaginal ring containing 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol, which releases on average 0.12 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol. One NuvaRing® is inserted in the vagina and must remain in place continuously for three weeks. One-week ring free interval is allowed before placement of another vaginal ring.

5.3 Applicant's Justification

The applicant justified the safety of maximum exposure to (b) (4) (b) (4) (b) (4) The applicant estimated a permissible daily exposure (PDE) of 11.29 mg/day (as per calculation shown below) and considered the exposure to (b) (4) over a period of 21 days acceptable.

$$\text{PDE} = \frac{\text{NOAEL, NOEL, etc.} \times \text{Weight adjustment}}{F1 \times F2 \times F3 \times F4 \times F5}$$

$$\text{PDE} = \frac{500 \text{ mg/kg/day} \times 70 \text{ kg}}{6.2 \times 10 \times 10 \times 1 \times 5} = 11.29 \text{ mg/day}$$

Where:
Toxic Dose$_{Low}$ (TD_{LO}) of 500 mg/kg from repeat dose rat skin study was used for NOAEL, NOEL, etc.
Weight adjustment = 70 kg (average weight of an adult human)
F1 = A factor to account for extrapolation between species = 6.2 (Use of rat data)
F2 = A factor to account for variability between individuals = 10
F3 = A factor to account for toxicity studies of short-term exposure = 10 (A rodent study under 3-month duration)
F4 = A factor that may be applied in cases of severe toxicity = 1 (neither genotoxic or carcinogenic)
F5 = A factor that may be applied if the no-effect level was not established = 5 (For use of a repeat dose TD_{LO})

In addition, the applicant conducted nonclinical studies for testing the biocompatibility of the vaginal ring drug product. The results of these studies are reviewed by CDRH.[16]

[15] Etonogestrel: ethinyl estradiol vaginal ring, ANDA 210830, EDR 3.2.P.5.6 Justification, 08/25/2017 \\cdsesub1\evsprod\anda210830\0001\m3\32-body-data\32p-drug-prod\etonogestrel-ethinyl-estradiol-vaginal-ring-0-120-mg-0-015-mg\32p5-contr-drug-prod\32p56-justif-spec\32p56-fp-justification.pdf

[16] ANDA 210830, GDRP, P Potnis, CDRH review of toxicology studies, 12/21/2017; http://panorama fda.gov/document/preview?versionID=5a3bc8e1000e610a1d944b4032b1759e&ID=5a3bc8e1000e61095ffe4a2c762002db

28-Day Systemic Toxicity in Rats
- Systemic Injection Test - ISO
- Salmonella Typhimurium and Escherichia Colireverse Mutation Assay - With Confirmation - ISO
- L929 MTT Test 1 Concentration -ISO - 17-00131-G13
L929 MTT TEST (1 CONCENTRATION) - ISO - 17-00131-G2
Intracutaneous Injection Test - ISO
Kligman Maximization Test - ISO
Rodent Blood Micronucleus Assay
Mouse Lymphoma Mutagenesis Assay With Confirmation - ISO
Intramuscular Implantation Test - ISO 4 Week Implantation
Primary Vaginal Irritation - Repeat Exposure - ISO
Rabbit Pyrogen Test Material Mediated -ISO
L929 MTT Test 1 Concentration - ISO - 17-00-142-G1
L929 MTT Test 1 Concentration - ISO - 17-00418-G1
28-Day Systemic Toxicity in Female Rats

5.4 Toxicology

This Pharmacology/Toxicology review evaluated the toxicity of maximum exposure to (b) (4) (b) (4) requested in a consult from DMRP in OPQ. (b) (4) used in the formulation of the generic EluRyng™ (ethinyl estradiol: etonogestrel vaginal ring; 0.12 mg/24 hr: 0.015 mg/24 hr, ANDA 210830).

The acceptability of the levels of (b) (4) in proposed generic EluRyng™ were determined taking into consideration the presence of this solvent in the RLD, NuvaRing®. The applicant provided a justification based on an estimated PDE using a TD_{LO} of 500 mg/kg from repeat dose rat skin study with (b) (4) The PDE estimated by the applicant was not acceptable because the source of information was cited as (b) (4) (b) (4) The information in the above toxicity study could not be independently verified for accuracy and suitability to current vaginal route of exposure. The additional studies provided by the applicant were conducted with the drug product and were not suitable to identify the potential toxicity solely due to (b) (4) The acceptability of (b) (4) is reviewed in context to the levels in the RLD and the toxicology information in publicly available literature.

5.4.1 *Chemical and physical and characteristics of* (b) (4)

(b) (4)

(b) (4)

5.4.2 (b) (4) *levels in proposed generic VeraRing™ and RLD, NuvaRing®*

The maximum exposure to (b) (4) from proposed generic EluRyng™ is lower than (b) (4) with RLD, NuvaRing® (see Table 1) (Not for Release under FIOA). Therefore, the levels of (b) (4) in generic EluRyng™ may not pose an increased toxicity risk compared to RLD, NuvaRing®.

5.4.3 *Evaluation of Genetic Toxicity, Acute and Chronic General Toxicity, Dermal Toxicity and Ocular Toxicity of* (b) (4)

The toxicity of (b) (4) is evaluated by reviewing the information in the literature for (b) (4) The toxicology information on (b) (4) (b) (4) (b) (4) are used in this assessment. The review of genetic toxicity, acute and chronic general toxicity, dermal toxicity, and ocular toxicity studies indicate that (b) (4) poses a low risk of toxicity at (b) (4) from the use of proposed generic EluRyng™. A previous pharmacology/toxicology review reached a similar conclusion based on a toxicity assessment for a higher level of exposure to (b) (4) in RLD.[7]

(b) (4) are reported non-mutagenic in bacterial assays (*Salmonella* strains TA98, TA 100, TA1535, TA1537, and TA1538 at levels up to (b) (4) (b) (4) and non-clastogenic in mouse micronucleus assay when dosed intraperitoneally with 25 mL/kg (b) (4) (b) (4)

(b) (4) applied as a 50% preparation in petrolatum under semi-occlusion was reported to produce no sensitization, phototoxicity or

(b) (4)

photosensitization in over 100 human subjects. (b) (4) cause defatting of skin and are irritating to skin if unable to evaporate because of closed or semi-occluded conditions. The oral rat LD_{50} was 10 g/kg and dermal rabbit LD_{50} was 3.2 g/kg of similar (b) (4) (b) (4) and produced only slight dermal irritation in rabbits. Additionally, a 0.1 mL of (b) (4) dose instilled in rabbit's eyes produced only slight conjunctival irritation with no corneal lesions. The Draize score in the above assays out of 110 was up to 6 at 1 hr, 1 at 4 hr, and 0 for remainder of test period.[17]

(b) (4) was non-teratogenic in Sprague-Dawley CD® rats exposed via inhalation route at 0, 300 or 900 ppm for 6 hr per day on Days 6-15 of gestation. (b) (4) was determined to be neither fetotoxic nor teratogenic to rats at concentrations up to 900 ppm in air. Subacute exposures to 654 ppm (4.2 mg/L) (b) (4) (b) (4) for 6 hr/day, 3 days /week for a total of 13 exposures in four rhesus monkeys caused no mortality. (b) (4) caused slight lymphocytopenia and neutrophilia in the differential leukocyte count at the mid-point and end of the study. Chronic inhalation exposures to 0 or 6500 mg/L (b) (4) for 8 hr/day for 5 days/week for up to 16 months in rats (Sprague-Dawley, 24 males/group) caused albuminuria and presence of hyaline droplets in the proximal tubules in the kidneys of rat exposed for 12 months or 16 months. The renal changes are considered specific to rodents that is attributed to reversible binding of hydrocarbon to $\alpha_{2\mu}$-globulin. Humans do not synthesize $\alpha_{2\mu}$-globulin, hence not effected by the (b) (4) toxicity.[17] (b) (4) can cause severe injury and death upon aspiration into lungs. Such lethal effect is due to physical obstruction and interference with respiration, and not expected at low exposures.[18]

5.4.4 *Risk Assessment*

The levels of (b) (4) in generic EluRyng™ do not present an increased toxicity risk and is considered acceptable because potentially higher exposure occurs with the RLD, NuvaRing®. The applicant provided a PDE for (b) (4) from a study via dermal application. This PDE cannot be confirmed because no specific study or article was provided. Therefore, a search of literature was done and an article by (b) (4) (b) (4) (b) (4) genotoxicity risk. The (b) (4) show slight dermal and ocular irritation in rabbits. A local dermal treatment under semi-occluded condition with 50% preparation in 100 human subjects was free of sensitization, phototoxicity or photosensitization. The above study provided a 100-fold safety margin for dermal toxicity over the levels in proposed generic (b) (4) ppm). The chronic exposure to (b) (4) is known to cause renal toxicity in rodent. The mechanism of toxicity is reported to be dependent on reversible binding of hydrocarbon to $\alpha_{2\mu}$-globulin; however, this is not a concern in humans because humans do not express $\alpha_{2\mu}$-globulin. Furthermore, (b) (4) is nonteratogenic in rats. Considering the totality of data, the low level of exposure to (b) (4) from generic EluRyng™ is acceptable.

6 Conclusion

The Pharmacology/Toxicology review determined (b) (4) has low risk for genotoxicity, dermal toxicity, general toxicity, and teratogenicity at the proposed level of exposure.

Furthermore, the maximum exposure to [redacted] (b) (4) from generic EluRyng™ (etonogestrel: ethinyl estradiol vaginal ring, ANDA 210830) is acceptable because the exposures to [redacted] (b) (4) is higher with RLD, NuvaRing®.

Saryu Goel

Digitally signed by Saryu Goel
Date: 6/21/2018 11:51:23AM
GUID: 537f884000027a73e376707605e2dc5f

Richard Houghtling

Digitally signed by Richard Houghtling
Date: 6/21/2018 11:59:34AM
GUID: 508da6e7000271ba077f3f44d91a4ab1

Mark Ritter

Digitally signed by Mark Ritter
Date: 6/21/2018 11:52:26AM
GUID: 508da6e80002732e6afdd41c9bb5d417

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210830

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	210830
Drug Product Name	Etonogestrel/Ethinyl Estradiol Vaginal Ring
Strength(s)	0.120 mg/0.015 mg per day
Applicant Name	Amneal Pharmaceuticals LLC
Applicant Address	50 Horseblock Road Brookhaven, NY 11719
US Contact Name and US Mailing Address	Candis Edwards, Senior Vice President, Regulatory Affairs 50 Horseblock Road Brookhaven, NY 11719
US Contact Telephone Number	631-974-7949
US Contact Fax Number	631-527-3523
Original Submission Date(s)	08/25/2017
Submission Date(s) of Amendment(s) Under Review	11/28/2017- response to BE IR
Primary Reviewer	Diana Vivian, Ph.D.
Secondary Reviewer	Dongmei Lu, Ph.D.
Study Number(s)	BE/16/373
Study Type(s)	In vivo PK
Strength(s)	0.120 mg/0.015 mg per day
Clinical Site #1	Raptim Research Ltd.
Clinical Site #1 Address	Clinical Pharmacology Unit (A-226), T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai – 400701, India.
Clinical Site #2	Sai Snehdeep Hospital
Clinical Site #2 Address	Plot No. 12/13, Sector No-20, Kopar Khairane, Navi Mumbai-400 709, India
Analytical Site	(b) (4)
Analytical Site Address	
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending**
	Post October 1, 2014 ANDAs ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection**

	☐ Complete ☐ N/A (Waiver/Deem Bioequivalent) [1]	☒ Complete ☐ N/A (Waiver/Deem Bioequivalent) [1]	
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☐ Not granted ☒ N/A		
QC Dissolution	☒ Pending ☐ Adequate ☐ Inadequate		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☐ Major ☐ Minor/IR ☒ N/A (Review is Adequate)		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☒ Adequate ☐ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	*Reminder: Check PSG in development spreadsheet on V:drive (if PSG is under development, wait for PSG to post to finalize the review)* ☒ Recommended/Latest Revision Date: April 2013 RLD Number: 21187 ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1,4	**Fasting**	**0.120 mg/0.015 mg per day**	☒ Adequate ☐ Inadequate

1 EXECUTIVE SUMMARY

This application contains the results of an in vivo bioequivalence (BE) study comparing Amneal Pharmaceuticals LLC's Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day, to the corresponding reference listed product, Organon USA Inc.'s NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring), 0.12 mg/24 hr; 0.015 mg/24 hr. The BE study was designed as a single-dose, two-way crossover study in healthy female subjects.

The subjects were dosed in four groups for period 1 and eight subgroups for period 2. Subjects were recruited from the same enrollment pool, have similar demographics, and used the same clinical sites. Groups differed only in dosing date and were assigned based

[1] Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

on menstrual cycle start date. The reviewer considered the dosing groups as one group for statistical analysis[2] and obtained the following results:

Ethinyl Estradiol

Ethinyl Estradiol and Etonogestrel Vaginal Ring 1× 0.015 mg/24 Hr and 0.12 mg/ 24 Hr Bioequivalence Study No. BE/16/373, N=64 Females Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	10248.59	11135.96	0.92	88.69	95.50
AUC∞ (pg·hr/mL)	10301.83	11251.33	0.92	88.12	95.14
Cmax (pg/mL)	26.10	27.70	0.94	89.90	98.75

Etonogestrel

Ethinyl Estradiol and Etonogestrel Vaginal Ring 1× 0.015 mg/24 Hr and 0.12 mg/ 24 Hr Bioequivalence Study No. BE/16/373, N=58 Females Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	1374156	1422311	0.97	92.92	100.45
AUC∞ (pg·hr/mL)	1404207	1454280	0.97	92.78	100.49
Cmax (pg/mL)	3040.35	3142.06	0.97	92.98	100.70

The dissolution data will be reviewed separately. The firm did not request any waivers of in vivo BE study requirements.

Per GDRP, OSIS recommends accepting data without on-site inspections for the Sai Snehdeep Hospital clinical site[3] (b) (4) Additionally, per the EIR, the inspection at the Raptim Research clinical site is classified as No Action Indicated (NAI).[5] In addition, the study submitted in the current ANDA does not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer. The OSIS inspection status of the current ANDA is complete.

The application is acceptable with no deficiencies.

[2] v:\firmsnz (b) (4) controls\98-392a.doc.
[3] http://panorama.fda.gov/task/view?ID=59a9b58b0047fb3a33ce9991d064b98c
[4] http://panorama.fda.gov/task/view?ID=595fb90c014c5bfd908341fe01e022f8
[5] http://panorama.fda.gov/task/view?ID=5931b62e007cfb6ef5151a0403abade9

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Drug Product and Strength	Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.12 mg/24 hr; 0.015 mg/24 hr
Reference Standard (RS) and Strength	NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring), 0.12 mg/24 hr; 0.015 mg/24 hr
RS Holder; NDA/ANDA Number; Approval Date[6]	Organon USA Inc., NDA 021187, approved on 10/2/2001
Reference Listed Drug (RLD) and Strength	Same as RS
RLD Holder; NDA/ANDA Number; Approval Date[7]	Same as RS

3.2 PK/PD Information

Most recent RLD label (provide embedded document)[8] Please check if an NG/G/J tube study is needed.	Label approved 08/09/2017 label.pdf
Indication	NuvaRing is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.
Boxed warning	**WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS** Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, CHCs, including NuvaRing, should not be used by women who are over 35 years of age and smoke.
Bioavailability	The bioavailability of etonogestrel after vaginal administration is approximately 100%. The bioavailability of ethinyl estradiol after vaginal administration is approximately 56%, which is comparable to that with oral administration of ethinyl estradiol.
Food Effect	N/A

[6] Per Orange Book. Last accessed: 11/13/2017. https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021187
[7] Per Orange Book
[8] Click insert tab and go to object and select create from file then choose display as icon. Then browse the file you want to add and insert and OK

Tmax	Etonogestrel: 200.3 hr Ethinyl estradiol: 59.3 hr
Metabolism	*In vitro* data shows that both etonogestrel and ethinyl estradiol are metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme. Ethinyl estradiol is primarily metabolized by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as sulfate and glucuronide conjugates. The hydroxylated ethinyl estradiol metabolites have weak estrogenic activity. The biological activity of etonogestrel metabolites is unknown.
Excretion	Etonogestrel and ethinyl estradiol are primarily eliminated in urine, bile and feces.
Half-life	Etonogestrel: 29.3 hr Ethinyl estradiol: 44.7 hr
Maximum Daily Dose	0.15 mg/24 hr EE; 0.12 mg/24 hr ETO for 21 days

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	Product-specific draft guidance (recommended April 2013): PSG.pdf	
Summary of OGD or DB History	Approved ANDAs:	None
	Pending ANDAs:	Yes (204305, 207577, and (b) (4)
	Controls:	The Q1/Q2 sameness of the test and reference products was confirmed in CC#42491.[9] The firm also submitted several CCs regarding chemistry requirements (batch size, sample retention, multiple lot requirement for excipients, and whether they can submit an ANDA (b) (4) RLD label; CC #45810, #8914721, #50893, #549549, and #14417557)

[9] GDRP; Project #42491, Q1Q2 Formulation Review (OGD # C13-0561), Primary Review, #42491.doc, 12/9/2014.

	Protocols:[10]	No protocol from the current applicant.
	Pending Citizen Petitions and other legal and regulatory issues:[11] If yes, please comment.	☐ Yes ☒ No

3.4 Pre-Study Bioanalytical Method Validation

Ethinyl Estradiol

Information Requested	Data	
Bioanalytical method validation report location	**5314-bioanalyt-analyt-met,16-5-2-method-validation-report: Page no. 1 to 239**	
Analyte	Ethinyl Estradiol	
Internal standard (IS)	Estradiol D3	
Method description	Liquid-Liquid Extraction procedure & Analysis by LC/MS/MS Method	
Limit of quantitation	0.89 pg/mL	
Average recovery of drug (%)	69.79% LQC: 63.56% MQC: 70.30% HQC: 75.51%	
Average recovery of IS (%)	68.52%	
Standard curve concentrations (pg/mL)	STD A	0.89
	STD B	1.79
	STD C	3.58
	STD D	7.15
	STD E	14.31
	STD F	28.61
	STD G	47.68
	STD H	70.12

[10] OGD-DB Protocols Tracking Database: http://fdswv04385/seltrack/Protocols.ASP and GDRP search. Last accessed 11/13/2017.
[11] Please check DLRS policy updates in the link http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx

Information Requested	Data	
	STD I	100.18
QC concentrations (pg/mL)	LLOQ QC	0.91
	LQC	2.67
	LMQC	10.08
	MQC	50.41
	HQC	81.30
QC Intra-batch precision range (%)	LLOQ QC	4.93 to 13.89
	LQC	1.85 to 15.00
	LMQC	2.63 to 12.73
	MQC	1.23 to 8.93
	HQC	1.48 to 10.71
QC Intra-batch accuracy range (%)	LLOQ QC	82.42 to 116.48
	LQC	94.38 to 113.48
	LMQC	107.74 to 114.78
	MQC	88.49 to 110.22
	HQC	100.33 to 114.54
QC Inter-batch precision range (%)	LLOQ QC	13.91
	LQC	9.47
	LMQC	7.96
	MQC	7.17
	HQC	7.46
QC Inter-batch accuracy range (%)	LLOQ QC	101.10
	LQC	107.49
	LMQC	110.52
	MQC	103.61
	HQC	109.82

Information Requested	Data
Bench-top stability (hrs)	64 hours and 33 minutes @ ambient temperature
Stock stability (days)	07 days @ -20ºC for Analyte and Internal Standard
Processed Stability (Hrs)	54 hours and 02 minutes @ 2 to 8ºC (Wet Extract Stability)
	48 hours and 27 minutes @ 2 to 8ºC (Dry Extract Stability)
	86 hours and 04 minutes @ 5ºC (Auto sampler Stability)
Freeze-thaw stability (cycles)	6th cycles @ - 20ºC
Long-term storage stability (days)	111 days @ -20ºC
Dilution integrity	813.03 pg/mL diluted to 10-fold and 162.61 pg/mL diluted to 2-fold
Selectivity	Interference observed at the retention time of Analyte was within the acceptance criteria and No Interference was observed at the retention time of Internal Standard in blank samples

Etonogestrel

Information Requested	Data	
Bioanalytical method validation report location	**5314-bioanalyt-analyt-met,16-5-2-method-validation-report: Page no. 1 to 239**	
Analyte	Etonogestrel	
Internal standard (IS)	Etonogestrel D6	
Method description	Liquid-Liquid Extraction procedure & Analysis by LC/MS/MS Method	
Limit of quantitation	38.52 pg/mL	
Average recovery of drug (%)	69.54% LQC: 65.71 MQC: 68.29 HQC: 74.63	
Average recovery of IS (%)	70.83%	
Standard curve concentrations (pg/mL)	STD A	38.52

Information Requested	Data	
	STD B	77.04
	STD C	154.08
	STD D	308.15
	STD E	616.31
	STD F	1232.62
	STD G	2054.36
	STD H	3021.12
	STD I	4315.88
QC concentrations (pg/mL)	LLOQ QC	39.52
	LQC	115.56
	LMQC	436.08
	MQC	2180.38
	HQC	3516.74
QC Intra-batch precision range (%)	LLOQ QC	3.40 to 11.62
	LQC	1.86 to 9.15
	LMQC	2.21 to 13.28
	MQC	0.69 to 2.81
	HQC	1.13 to 8.99
QC Intra-batch accuracy range (%)	LLOQ QC	86.26 to 105.59
	LQC	91.10 to 104.37
	LMQC	88.27 to 106.69
	MQC	93.09 to 106.69
	HQC	94.62 to 109.31
QC Inter-batch precision range (%)	LLOQ QC	8.62
	LQC	6.38
	LMQC	8.05

Information Requested	Data	
	MQC	4.50
	HQC	6.82
QC Inter-batch accuracy range (%)	LLOQ QC	95.52
	LQC	99.15
	LMQC	98.87
	MQC	96.98
	HQC	100.13
Bench-top stability (hrs)	64 hours and 33 minutes @ ambient temperature	
Stock stability (days)	07 days @ -20ºC for Analyte and Internal Standard	
Processed Stability (Hrs)	54 hours and 02 minutes @ 2 to 8ºC (Wet Extract Stability)	
	48 hours and 27 minutes @ 2 to 8ºC (Dry Extract Stability)	
	86 hours and 04 minutes @ 5ºC (Auto sampler Stability)	
Freeze-thaw stability (cycles)	6th cycles @ - 20ºC	
Long-term storage stability (days)	111 days @ -20ºC	
Dilution integrity	35167.35 pg/mL diluted to 10-fold and 7033.47 pg/mL diluted to 2-fold	
Selectivity	Interference observed at the retention time of Analyte was within the acceptance criteria and No Interference was observed at the retention time of Internal Standard in blank samples	

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? **If not, was cross validation study conducted?**	☒ Yes ☐ No K_3EDTA
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No Long term storage stability covered a period of 111 days at -20ºC. Samples were stored for a maximum of 95 days at -20ºC.

Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

Comments on the Pre-Study Method Validation: Adequate

QCs were prepared with both ethinyl estradiol and etonogestrel, along with their internal standards. Selectivity and lack of interference between analytes was demonstrated.

3.5 In Vivo Studies

Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean(Range)	Arithmetic Mean Parameters (+/-SD) (% CV)							Study Report Location
					C_{max} (pg/mL)	*T_{max} (hr)	AUC_{0-t} (hr*pg/mL)	AUC_{0-inf} (hr*pg/mL)	$t_{½}$ (hr)	K_{el} (1/hr)	AUC Extrapolated (%)	
Analyte: Ethinyl Estradiol												
BE/16/373	Bioequivalence study of Ethinyl Estradiol and Etonogestrel Vaginal Ring 0.015 mg/24 Hr and 0.12 mg/ 24 Hr in normal, healthy, adult, human, non-pregnant female subjects with childbearing potential.	An open-label, balanced, randomized, two-treatment, two-sequence, two-period, single dose, two-way crossover design.	**Test Product (T):** Ethinyl Estradiol and Etonogestrel Vaginal Ring 0.015 mg/24 Hr and 0.12 mg/24 Hr (1 X 0.015 mg/0.12 mg per day Per Vaginal) [Batch No. PW-ST-16056A]	N = 69 (69F/0M) Healthy non-pregnant female subjects 31.39 (22.00-39.00)	27.61 ± 10.33 (37.39)	72.00 (6.00 - 649.07)	10902.45 ± 4556.83 (41.80)	11130.85 ± 4499.47 (40.42)#	36.08 ± 56.56 (156.76)#	0.03 ± 0.01 (43.33)#	1.69 ± 3.94 (232.68)#	**Module 5.3.1.2**
			Reference Product (R): Ethinyl Estradiol and Etonogestrel Vaginal Ring 0.015 mg/24 Hr and 0.12 mg/24 Hr (1 X 0.015 mg/0.12 mg per day Per Vaginal) [Lot No. 0000571248 M036725]		29.03 ± 8.75 (30.15)	72.00 (6.00 - 433.02)	11739.14 ± 3944.50 (33.60)	11942.99 ± 4067.09 (34.05)	35.64 ± 51.02 (143.16)	0.03 ± 0.02 (45.85)	1.50 ± 3.07 (204.49)	

*Median (Range) is provided; #N = 67

Note: No value of K_{el}, $t_{1/2}$, AUC_{0-inf} and AUC Extrapolated were reported Subject number (b)(6) Test T) in period II and Subject number (b)(6) (Test T) in period I as they did not exhibit a terminal log linear phase in the concentrations versus time profile

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Arithmetic Mean Parameters (+/-SD) (% CV)							Study Report Location
					C_{max} (pg/mL)	*T_{max} (hr)	AUC_{0-t} (hr*pg/mL)	AUC_{0-inf} (hr*pg/mL)	$t_{½}$ (hr)	K_{el} (1/hr)	AUC Extrapolated (%)	
Analyte: Etonogestrel												
BE/16/373	Bioequivalence study of Ethinyl Estradiol and Etonogestrel Vaginal Ring 0.015 mg/24 Hr and 0.12 mg/ 24 Hr in normal, healthy, adult, human, non-pregnant female subjects with childbearing potential.	An open-label, balanced, randomized, two-treatment, two-sequence, two-period, single dose, two-way crossover design.	**Test Product (T):** Ethinyl Estradiol and Etonogestrel Vaginal Ring 0.015 mg/24 Hr and 0.12 mg/24 Hr (1 X 0.015 mg/0.12 mg per day Per Vaginal) [Batch No. PW-ST-16056A]	N = 69 (69F/0M) Healthy non-pregnant female subjects 31.39 (22.00-39.00)	3215.05 ± 1024.81 (31.88)	290.33 (120.02 - 504.00)	1457635.30 ± 461477.36 (31.66)	1495280.89 ± 473842.65 (31.69)	48.31 ± 21.90 (45.32)	0.02 ± 0.01 (39.26)	2.43 ± 3.79 (155.66)	**Module 5.3.1.2**
			Reference Product (R): Ethinyl Estradiol and Etonogestrel Vaginal Ring 0.015 mg/24 Hr and 0.12 mg/24 Hr (1 X 0.015 mg/0.12 mg per day Per Vaginal) [Lot No. 0000571248 M036725]		3277.56 ± 887.51 (27.08)	336.72 (36.00 - 528.00)	1491363.56 ± 422076.86 (28.30)	1530039.36 ± 451386.82 (29.50)	48.28 ± 17.19 (35.61)	0.02 ± 0.01 (39.59)	2.21 ± 3.12 (140.86)	

*Median (Range) is provided.

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information

Study Number	BE/16/373			
Study Title	Bioequivalence study of Ethinyl Estradiol and Etonogestrel Vaginal Ring 0.015 mg/24 Hr and 0.12 mg/ 24 Hr in normal, healthy, adult, human, non-pregnant female subjects with childbearing potential.			
Study Type	☒ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other (specify)
Submission Location:				
Study Report	**Module 5.3.1.2**			
Validation Report	**Module 5.3.1.4**			
Bioanalytical Report	**Module 5.3.1.4**			
Clinical Site (Name, Address, Phone #, Fax#)	Raptim Research Ltd., Clinical Pharmacology Unit (A-226), T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai – 400701, India. Tel. No.: +91-22-27781889 Ext no. 158; Fax No.: +91-22-27781884 And Sai Snehdeep Hospital, Plot No. 12/13, Sector No-20, Kopar Khairane, Navi Mumbai-400 709, India Tel. No.: +91 22 39205600/700, 27544051-55; Fax No.: +91-22-27544052			
Principal Clinical Investigator (Name , Email)	Dr. Jay Rane, jay rane@raptimresearch.com			
Dosing dates	Group 1: 23/2/17-21/4/17; group 2: 1/3/17-27/4/17; group 3: 3/3/17-29/4/17; group 4: 3/5/17-29/4/17			
Analytical Site (Name, Address, Phone #, Fax#)	(b) (4)			
Principal Analytical Investigator (Name, email)	(b) (4)			
Analysis dates:	29/4-26/5/17			

Storage Period of Biostudy Samples **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range**	95 days -20°C
Long-Term Storage Stability Coverage (no. days@temp°C)	111 days @ -20°C for Ethinyl Estradiol 111 days @ -20°C for Etonogestrel
LTSS Data Location	**5314-bioanalyt-analyt-met, 16-5-2-method-validation-report: supplement-to-method-validation-report-** (b) (4) (b) (4) **Page no. 192 to 195 of 239**

4.1.1.1.2 Product (Bio-batch) Information

Product	Test	Reference
Treatment ID	**T**	**R**
Product Name	Etonogestrel/Ethinyl Estradiol Vaginal Ring delivers 0.120 mg/0.015mg per day	NuvaRing® (etonogestrel + ethinyl estradiol vaginal ring) delivers 0.120 mg/0.015mg per day
Manufacturer	Amneal Pharmaceuticals	N.V Organon, OSS, The Netherland, a subsidiary of Merck & CO., INC., Whitehouse Station, NJ 08889, USA Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of Merck & CO., INC., Whitehouse Station, NJ 08889, USA
Batch No./Lot No.	Batch No :PW-ST-16056A	Lot No: M036725
Manufacturing Date	27/07/2016	Not Applicable
Expiration Date	N/A	08/2019
Strength	Ethinyl Estradiol 0.015 mg/24 Hr and Etonogestrel 0.12 mg/24 Hr	Ethinyl Estradiol 0.015 mg/24 Hr and Etonogestrel 0.12 mg/24 Hr
Dosage Form	Vaginal Ring	Vaginal Ring
Bio-batch Size	(b) (4)	Not Applicable

Production Batch Size	(b) (4)				Not Applicable			
Potency	Etonogestrel: 99.4% Ethinyl Estradiol: 97.5%				Etonogestrel: 97.1% Ethinyl Estradiol: 97.4%			
Content Uniformity	Etonogestrel		Ethinyl Estradiol		Etonogestrel		Ethinyl Estradiol	
	No of Units	N = 10	No of Units	N = 10	No of Units	N = 10	No of Units	N = 10
	Min	98.9%	Min	98.9%	Min	97.7%	Min	98.1%
	Max	101.7%	Max	101.7%	Max	98.3%	Max	99.1%
	Mean	100.4%	Mean	100.4%	Mean	98.0%	Mean	98.4%
	AV	1.8	AV	1.8	AV	0.8	AV	0.8
Dose Administered	1 x 0.015 mg/0.120 mg per day				1 x 0.015 mg/0.120 mg per day			
Route of Administration	Per Vaginal				Per Vaginal			

Are the test and reference products expired at the time of study? **If Yes, please comment.**	☐ Yes ☒ No
Is same bio-batch used in the dissolution and all BE studies? **If No, please comment.**	☒ Yes ☐ No
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? **If No, please comment.**	☐ Yes ☐ No ☒ N/A This is not a solid oral dosage form, but the bio-batch size is greater than 10% of the production batch size.
Is difference of the potency values for the Test and RLD within 5%? **If No, please comment.**	☒ Yes ☐ No

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 72 Dosed: 72 in period I, 70 in period II Completed: 69 Samples Analyzed: 69 Statistically Analyzed: 69
No. of Sequences	2
No. of Periods	2
No. of Treatments	2

No. of Groups	4 in period I(Group 1: Subjects 01-15; Group 2: Subjects 16-43; Group 3: Subjects 44-65; Group IV: Subjects 66-72). The study was conducted in 8 sub-groups based on menstrual cycle start date for period II.
Washout Period	The washout period varied depending on the subject/group. A ring free period was kept between period 01 ring removal (day 21) till onset of subsequent menstrual cycle.
Randomization	☒ Yes ☐ No
Blood Sampling Times	Pre-dose (within 05 minutes prior to insertion of vaginal ring), and at 06.00, 12.00, 18.00, 24.00, 30.00, 36.00, 48.00 (Day 02), 60.00 (Day 02), 72.00 (Day 03), 96.00 (Day 04), 120.00 (Day 05), 144.00 (Day 06), 168.00 (Day 07) 192.00 (Day 08), 216.00 (Day 09), 240.00 (Day 10), 288.00 (Day 12), 336.00 (Day 14), 384.00 (Day 16) and 432.00 (Day 18) hours post ring insertion and blood samples were collected at 504.00 hours (05 minutes before ring removal) and at 12.00 (Day 21), 24.00 (Day 22), 48.00 (Day 23), 96.00 (Day 25), 120.00 (Day 26) and 144.00 (Day 27) hours after ring removal in K_3EDTA containing pre-labeled vacutainers in each study period.
IRB Approval	☒ Yes Date: 01/11/2017 ☐ No
Informed Consent	☒ Yes Date: 01/11/2017 ☐ No
Length of Fasting	At least 10 hours prior to ring insertion and 4 hours post ring insertion.
Length of Confinement	Subjects were checked in after OC pill free period or onset of menstrual cycle to ensure fasting of at least 10.00 hours prior to insertion of vaginal ring in each study period and confined in the clinical pharmacology unit (CPU) till 72.00 hours post insertion during each study period. Subjects were re-housed at 492.00 hours on day 20 for removal of ring at 504.00 hours on day 21. After ring removal, subjects were housed until the collection of the 24 h sample on day 22.
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☒ Yes ☐ No ☐ N/A
Safety Monitoring	☒ Yes ☐ No

Comments on Study Design: Adequate/Inadequate

1. Post-screening, subjects received combined oral contraceptive (COC) containing desogestrel 150µg/ethinyl estradiol 30µg followed by oral contraceptive free period for that menstrual cycle before participation in the study. Subjects started oral contraceptive treatment on their normal menstrual cycle day 01 to 10 for required synchronization during the study. Case report forms document the dates of oral contraceptive use. For example, subject (b) (6) started oral contraceptives on (b) (6) and ended on (b) (6) Subject (b) (6) period I ring was inserted on (b) (6) Subject (b) (6) started oral contraceptives on (b) (6) and ended on (b) (6) Subject (b) (6) period I ring was inserted on (b) (6) The reviewer

checked the MicroMedex database, the RLD label, and PubMed, and no known drug interactions were found between desogestrel and ethinyl estradiol or etonogestrel. Since the COC contained ethinyl estradiol, the reviewer examined the period I pre-dose concentrations of ethinyl estradiol. Only subject (b) (6) had a period 1 pre-dose ethinyl estradiol concentration of >5% of Cmax and this subject was excluded from analysis (see details in section 4.1.1.5 of this review). Therefore, the COC use during the run-in period for menstrual cycle synchronization is unlikely to have influenced study results.

2. As per the study Protocol 72 subjects were to be enrolled in this study. In period I, the study was conducted in four groups. For subject menstrual cycle synchronization, 15 subjects were enrolled in group - I on 23/02/17, 28 subjects were enrolled in group - II on 01/03/17, 22 subjects were enrolled in group - III on 03/03/17 and 7 subjects were enrolled in group IV on 05/03/17.

3. In period II, the study was conducted in total eight sub-groups, as per synchronization of subjects menstrual cycle (ring insertion was performed after day-2 or day-3 of menstruation), 08 subjects were enrolled in group-I (Part-A) on 22/03/17, 07 subjects were enrolled in group-I (Part-B) on 24/03/17, 15 subjects were enrolled in group-II (Part-A) on 27/03/17, 11 subjects were enrolled in group-II (Part-B) on 30/03/17, 18 subjects were enrolled in group-III (Part-A) on 31/03/17, 04 subjects were enrolled in group-III (Part-B) on 01/04/17 and 01 subject was enrolled in group-IV (Part-A) on 31/03/17, 06 subjects were enrolled in group-IV (Part-B) on 01/04/17.

Study Details	Study Period	Groups			
		Group I	Group II	Group III	Group IV
Subject Numbers	I	(b) (6)			
Check-in					
Ring Insertion					
Check-out (72.00 hrs)					
Check-in (Ring removal)					
Ring Removal					
Check-out					

		Group I		Group II		Group III		Group IV	
		PART-A	PART-B	PART-A	PART_B	PART-A	PART-B	PART-A	PART-B
Subject Numbers	II	(b) (6)							
Check-in									
Ring Insertion									
Check-out (72.00 hrs)									
Check-in (Ring removal)									
Ring Removal									
Check-out									

Note: Subject number (b) (6) did not report to the facility for check-in of Period II due to personal reason hence considered as dropped out. Subject number (b) (6) withdrawn from study due to personal reason.

4. Within day 1-3 after the onset of menstrual cycle, vaginal rings were inserted as per randomization.

5. The dose insertion activity was carried out under the supervision of Investigator/trained study personnel including the Quality Assurance personnel.

6. Subjects were asked to remain in supine posture for at least 04.00 hours after insertion of investigational product unless clinically indicated. Thereafter, subjects were allowed to engage in normal activities while avoiding severe physical exertion.

7. As per study protocol, if a subject's menstrual cycle started during the ring-free period, then samples were collected until the 2nd period ring insertion. Hence in a few subjects, blood samples were not collected due to period II ring insertion. These blood samples were reported as Missing samples. The study protocol did not follow the 7 day ring-free period recommended in the drug labeling. The reviewer excluded all subjects with pre-dose concentrations >5% of Cmax from statistical analysis (see Section 4.1.1.4 of this review for further detail).

8. While conduction of clinical phase groups were separated into subgroups for period-II, for computation of Pharmacokinetic and statistical analysis period and group for each subject was reassigned by the applicant i.e. Group-A, Group-B and Group-C; Period-I, -II, -III and – IV (Period is denoted as period_PK) and that is presented in the below table. The reviewer used the actual periods (i.e. period I and period II only) for statistical analysis.

Pharmacokinetic and statistical analysis period and group for each subject was reassigned (Period is denoted as period_PK)

Groups	Subject no.	Period used for PK and Statistical analysis	Ring insert date
Group A	(b) (6)	(Period-I)	(b) (6)
		(Period-II)	
		(Period-III)	
Group B		(Period-I)	
		(Period-II)	
		(Period-III)	
Group C		(Period-I)	
	(b) (6)	(Period-II)	(b) (6)
		(Period-III)	
		(Period-IV)	

9. Although there were two clinical sites, subjects were not split into groups by clinical site. The activities conducted at the two clinical sites for all subjects were as follows:

Company Name/ Address	Functions
Raptim Research Ltd., Clinical Pharmacology Unit (A-226) (b) (4)	Clinical BA/BE Testing Services (Screening activity, subject verification, allocation of subject number, Investigational Product acceptance, dispensing, reconciliation, and sample retention) and (b) (4)
Sai Snehdeep Hospital, Plot No. 12/13, Sector No-20, Kopar Khairane, Navi Mumbai-400 709, India.	Clinical BA/BE Testing Services (Subject's housing during the study, subject check-in, subject check-out, ring insertion (dosing activity), ring removal, blood sample collection and processing for plasma)

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Study No. BE/16/373			
Parameter		**Treatment Groups**	
		Test Product (T) N = 69	**Reference Product (R) N = 69**
Age (years)	Mean ± SD	31.39 ±3.38	31.39 ±3.38
	Range	(22.00-39.00)	(22.00-39.00)
Age Groups	< 18	00 (0.00%)	00 (0.00%)
	18 – 40	69 (100.00%)	69 (100.00%)
	41 – 64	00 (0.00%)	00 (0.00%)
	65 – 75	00 (0.00%)	00 (0.00%)
	> 75	00 (0.00%)	00 (0.00%)
Sex	Male	00 (0.00%)	00 (0.00%)
	Female	69 (100.00%)	69 (100.00%)
Race	Asian	69 (100.00%)	69 (100.00%)
	Black	None (0.00%)	None (0.00%)
	Caucasian	None (0.00%)	None (0.00%)
	Hispanic	None (0.00%)	None (0.00%)
	Other	None (0.00%)	None (0.00%)
BMI(Kg/m²)	Mean ± SD	23.99 ±2.33	23.99 ±2.33
	Range	(18.86-28.79)	(18.86-28.79)
Height(cm)	Mean ± SD	157.24 ±5.78	157.24 ±5.78
	Range	(143.00-172.00)	(143.00-172.00)
Weight(Kg)	Mean ± SD	59.33 ±6.61	59.33 ±6.61
	Range	(50.10-74.00)	(50.10-74.00)

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.1.2.2 Dropout Information

Study No. BE/16/373				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced**	**Replaced with**
(b) (6)	Subject did not report to the facility for check- in of Period II due to personal reason hence considered as dropout.	II	NO	Not applicable
	Subject did not report to the facility for check- in of Period II due to personal reason hence considered as dropout.	II	NO	Not applicable
	Subject withdrew from the study on day 25 ambulatory sample collection in period-II due to personal reasons.	II	NO	Not applicable

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

4.1.1.2.3 Study Adverse Events

Body System / Adverse Event	**Reported Incidence by Treatment Groups**	
	Fasted Bioequivalence Study Study No. BE/16/373	
	Test Product (T) (N= 70)	**Reference Product (R) (N = 72)**
Gastrointestinal Disorders		
Nausea	02 (2.86%)	01 (1.39%)
Epigastric pain	01 (1.43%)	-
Abdominal Pain	01(1.43%)	-
vomiting	01(1.43%)	01(1.39%)
General disorders and administration site conditions		
Foreign body sensation	02 (2.86%)	01(1.39%)
Nervous system disorders		
Headache	02 (2.86%)	-
Musculoskeletal and connective tissue disorders		
Backache	-	01(1.39%)
Skin and subcutaneous tissue disorders		

Rash on hands and feet	-	01(1.39%)
Itching on hands and feet.	-	01(1.39%)
Rash on hands	01(1.43%)	-
Total	**10 (14.26%)**	**06 (8.33%)**

Were subjects who experienced vomiting included in statistical analysis?	☒ Yes ☐ No ☐ N/A
If yes, does the time of emesis exceed two times the median Tmax value (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A This is not an orally administered product; therefore, the subjects who experienced emesis should still be included. Subjects (b) (6) experienced emesis in period II (T product) and period I (R product), respectively. These subjects were appropriately included in analysis.
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.1.2.4 Protocol Deviations

Study No. BE/16/373		
Type	**Test Product (T)**	**Reference Product (R)**
Blood sample collections	(b) (6)	
As per the protocol, meal was scheduled at 53.00 and 57.00 hours however it was provided one hour earlier i.e at 52.00 and 56.00 hour after the ring insertion of period-I during their stay in facility for subject numbers (b) (6) of group-II on subject's request.		
Post study safety evaluation	As per section 8.8.8 of the protocol, post study safety evaluation was to be performed after last sample	

	collection of last period or in case of subject withdrawal/termination or dropout however, post study safety evaluation was not performed for subject number (b) (6) as she did not report to the clinical facility for post study safety evaluation due to personal reason. Subject confirmed telephonically that she did not have any health problem.
Identification in biometric system	As per protocol, subjects were to be identified in biometric system prior to pre-enrollment activity and ambulatory sample collection. However, during pre-enrollment activity and ambulatory sample collection subjects were identified on the basis of signature and identity card instead of biometric system. As the study was conducted at Sai Snehdeep Hospital, there was some technical problem for the connectivity of software in the facility.
Subjects sample analysis	As per study protocol, samples from each subject for all time periods to be assayed at the same time; however, analytical method for quantification of Ethinyl estradiol and Etonogestrel having analytical run time is about 12.5 minutes, hence to save analytical time, period wise subject sample analysis of was performed.
As per study protocol, Bioanalysis to be carried out for subject completing both the study periods, sample from subjects who do not complete both the periods not to be analyzed. Subject number (b) (6) were dropped out for period-II, but their period-I samples were analyzed due to oversight.	Subject numbers: (b) (6) administered with reference product in period I.

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Details of Concomitant Medication:

Sub No.	Adverse Event	Period	Concomitant medication	Frequency	Start Date	End Date
(b) (6)	Nausea with epigastric pain	II	Tablet Rantac (Ranitidine Hydrochloride) 150 mg	Stat	(b) (6)	

Details of Missing Samples:

Period-I:

Subject	Day	TIME (hr)	Reason
(b) (6)	16	384.00	Subjects did not report for ambulatory sample due to personal reason
	27	144.00	
	27	144.00	Period II ring insertion
	27	144.00	
	26	120.00	Subjects did not report for ambulatory sample due to personal reason
	27	144.00	Period II ring insertion
	27	144.00	
	27	144.00	
	27	144.00	
	18	432.00	Subjects did not report for ambulatory sample due to personal reason
	27	144.00	Period II ring insertion
	27	144.00	
	8	192.00	Subjects did not report for ambulatory sample due to personal reason
	26	120.00	

Subject	Day	TIME (hr)	Reason
(b) (6)	27	144.00	Period II ring insertion
	26	120.00	
	27	144.00	
	25	96.00	Subjects did not report for ambulatory sample due to personal reason
	26	120.00	Period II ring insertion
	27	144.00	
	26	120.00	
	27	144.00	
	26	120.00	
	27	144.00	
	26	120.00	
	27	144.00	
	26	120.00	
	27	144.00	Period II ring insertion
	26	120.00	
	27	144.00	
	12	288.00	Subjects did not report for ambulatory sample due to personal reason
	14	336.00	
	16	384.00	
	26	120.00	Period II ring insertion
	27	144.00	
	26	120.00	
	27	144.00	
	26	120.00	
	27	144.00	
	9	216.00	Subjects did not report for ambulatory sample due to personal reason
	18	432.00	
	26	120.00	Period II ring insertion
	27	144.00	
	14	336.00	Subjects did not report for ambulatory sample due to personal reason
	26	120.00	Period II ring insertion

Subject	Day	TIME (hr)	Reason
(b) (6)	27	144.00	
	26	120.00	
	27	144.00	
	26	120.00	Subjects did not report for ambulatory sample due to personal reason
	26	120.00	
	26	120.00	Period II ring insertion
	27	144.00	
	10	240.00	Subjects did not report for ambulatory sample due to personal reason
	12	288.00	
	14	336.00	
	9	216.00	
	10	240.00	
	27	144.00	Due to spillage during sample separation
	12	288.00	Subjects did not report for ambulatory sample due to personal reason
	4	96.00	
	26	120.00	Period II ring insertion
	27	144.00	
	27	144.00	
	27	144.00	
	23	48.00	Subjects did not report for ambulatory sample due to personal reason
	27	144.00	Period II ring insertion
	25	96.00	Subjects did not report for ambulatory sample due to personal reason
	27	144.00	Period II ring insertion
	27	144.00	
	6	144.00	Subjects did not report for ambulatory sample due to personal reason
	27	144.00	Period II ring insertion

Period-II:

Subject	Day	Sampling hours	Reason
(b) (6)	18	432	Subjects did not report for ambulatory sample due to personal reason
	14	336	
	9	216	
	10	240	
	4	96	
	8	192	
	14	336	
	14	336	
	16	384	
	9	216	
	8	192	
	7	168	
	10	240	
	8	192	
	12	288	
	25	96	
	26	120	

Missing samples are reported as "MIS" and was not included for PK and statistical analysis.

Comments on Clinical Results: Adequate

1. As per study protocol, samples from each subject for all time periods were to be assayed at the same time; however, the analytical method for quantification of ethinyl estradiol and etonogestrel had a run time of about 12.5 minutes. Hence, to save analytical time, period wise subject sample analysis was performed. The reviewer notes that multiple subjects of the same period were analyzed at one time (e.g. period I of subjects (b) (6) were run in a single batch).

   A comparison of the reviewer-calculated PK parameters in period I vs. period 2 is as follows:

		T			R		
		AUCt	AUCi	Cmax	AUCt	AUCi	Cmax
Period 1	Mean	10825.68	10858.98	26.55778	11720.59	12038.9	29.23406
	Min	5058.96	5097.74	14.56	5703.81	5736.71	20.44
	Max	26091.84	26131	61.68	27477.21	27611.69	63.16
Period 2	Mean	11379.38	11473.2	29.17387	11806.75	11918.95	28.65
	Min	6566.67	6676.3	15.1	5597.58	5634.1	14.75
	Max	29101.08	29383.58	63.31	21368.82	22553.76	49.7

There is no consistent trend of an increase or decrease in PK parameters between periods 1 and 2. Additionally, the PK results were not marginal (see section 4.1.1.4 for further detail). Because of this, the applicant will not be required to repeat bioanalysis for this study. The applicant will be advised for future studies to analyze all study samples from a subject in a single run.

2. Enrolled subjects followed restrictions regarding medications (including herbal drugs and vitamin supplements) or OTC products prior to ring insertion in Period-I as mentioned in the exclusion criteria. Each subject received COC containing desogestrel 150µg/ethinylestradiol 30µg pills after screening procedure. Oral contraceptive pills treatment was started on subject's normal menstrual cycle in between day 01 to day 10 for indication of systemic contraceptives. Subject (b) (6) was given ranitidine as a part of management of AE (Nausea with epigastric pain). Ranitidine was checked against the RLD label, the MicroMedex Database, and PubMed, and no known interactions with ethinyl estradiol or etonogestrel were found. The applicant validated the lack of effect of ranitidine on analyte analysis during method validation.

3. Three subjects voluntarily withdrew from the study. Period I of subjects (b) (6) were bio-analyzed as a protocol violation. No samples from Subject (b) (6) were bio-analyzed. Since subjects (b) (6) only had period I data, the reviewer and the firm both did not include these subjects in statistical analysis.

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Standard Operating Procedure for Repeat Analysis
		Standard Operating Procedure for Subject Sample Analysis

Reviewer Note: The applicant modified their sample analysis SOP on (b) (4) after the completion of study sample analysis, and made the following changes:

Version No.	Section No.	Page No.	Reason for Revision
15	V	12	Section 4.2.11 Exclusion criteria changed for LLOQ and ULOQ
16	V	5	% of HQC changed
	V	10	Minimum number of Dilution QCs changed from two to four.
	V	14	Criteria for failing consecutive Quality Control Samples is modified.
	V	16	Form of Analytical batch acceptance included.
	All	All	Periodic Revision

Several samples in the current study were repeated due to failure of consecutive QC samples. The criteria for failing consecutive QC samples in the updated SOP is the following: *If 3 or more consecutive QCs fail in an analytical batch i.e. are outside the acceptance criteria of 85.00% to 115.00% of their respective nominal concentration values, then all samples from the last passing QC sample to next passing QC sample should be repeated as per "SOP for Repeat Analysis"*. It is unknown what was changed from the previous version. However, this criterion is listed in the repeat analysis SOP (b) (4) which was effective at the time of sample analysis. Therefore, this is acceptable.

All necessary SOPs submitted?	☒ Yes ☐ No

4.1.1.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. BE/16/373 Analyte Name: Ethinyl Estradiol									
Parameter	**Standard Curve Samples**								
Concentration (pg/mL)	0.90	1.81	3.61	7.23	14.46	28.91	48.19	70.87	98.43
Inter day Precision (% CV)	4.12	7.98	7.19	5.98	4.42	4.25	3.52	4.00	3.94
Inter day Accuracy (% Actual)	101.11	98.34	99.17	99.86	100.55	101.28	98.42	101.04	100.06
Linearity	0.9946 to 0.9999								
Linearity range (pg/mL)	0.90 to 98.43 pg/mL								
Sensitivity/LOQ (pg/mL)	0.90 pg/mL								

Bioequivalence Study No. BE/16/373 Analyte Name: Ethinyl Estradiol				
Parameter	**Quality Control Samples**			
	LQC	LMQC	MQC	HQC
Concentration (pg/mL)	2.70	9.85	49.24	79.42
Inter day Precision (% CV)	7.08	6.48	6.95	7.30
Inter day Accuracy (% Actual)	101.11	100.10	100.26	98.19

Bioequivalence Study No. BE/16/373 Analyte Name: Etonogestrel									
Parameter	**Standard Curve Samples**								
Concentration (pg/mL)	39.04	78.08	156.16	312.32	624.64	1249.28	2082.13	3061.95	4252.71
Inter day Precision (% CV)	3.35	7.47	6.05	6.26	4.54	4.85	3.98	3.97	3.93
Inter day Accuracy (% Actual)	100.82	100.58	95.56	99.94	99.93	100.52	100.48	100.71	101.40
Linearity	0.9945 to 0.9999								
Linearity range (pg/mL)	39.04 to 4252.71 pg/mL								
Sensitivity/LOQ (pg/mL)	39.04 pg/mL								

Bioequivalence Study No. BE/16/373 Analyte Name: Etonogestrel				
Parameter	**Quality Control Samples**			
	LQC	LMQC	MQC	HQC
Concentration (pg/mL)	116.71	425.94	2129.69	3434.99
Inter day Precision (% CV)	8.44	7.37	6.78	7.78
Inter day Accuracy (% Actual)	100.54	103.29	103.34	101.10

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly The applicant included chromatograms for all subjects.
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.1.3.3 Reanalysis of Study Samples

Study No. BE/16/373 Analyte Name: Ethinyl Estradiol Additional information in 5314-bioanalyt-analyt-met, be-16-373, 16-5-bio-analytical-report, Pages. 163 to 193 of 229								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	00	00	0.00	0.00	00	00	0.00	0.00
Pre-Dose Concentration Samples Category	02	04	0.11	0.21	02	04	0.11	0.21
Internal Standard Variation Category	70	56	3.71	2.87	68	54	3.61	2.77
Zero or BLQ Value Between Two Quantifiable Values Category	00	03	0.00	0.15	00	03	0.00	0.15
Chromatography Related Issues Category	03	06	0.16	0.31	03	06	0.16	0.31
Three Consecutive QC Failure	27	26	1.43	1.33	27	24	1.43	1.23
Equipment Related Issue Category	02	00	0.11	0.00	02	00	0.11	0.00
Total	104	95	5.51	4.88	102	91	5.41	4.67

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."
Total Number of Test Samples : 1886
Total Number of Reference Samples : 1948

Study No. BE/16/373 Analyte Name: Etonogestrel Additional information in 5314-bioanalyt-analyt-met, be-16-373, 16-5-bio-analytical-report, Pages. 163 to 193 of 229								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	00	00	0.00	0.00	00	00	0.00	0.00

Above Upper Limit of Quantification (AULOQ) Category	73	68	3.87	3.49	73	68	3.87	3.49
Pre-Dose Concentration Samples Category	35	35	1.86	1.80	27	31	1.43	1.59
Internal Standard Variation Category	21	51	1.11	2.62	18	49	0.95	2.52
Chromatography Related Issues Category	05	02	0.27	0.10	05	02	0.27	0.10
3 Consecutive QC Failure	07	20	0.37	1.03	07	19	0.37	0.98
Equipment Related Issue Category	01	00	0.05	0.00	01	00	0.05	0.00
Total	142	176	7.53	9.03	131	169	6.95	8.68

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."
Total Number of Test Samples : 1886
Total Number of Reference Samples : 1948

Details of Samples repeated due to pre-dose concentration:
Ethinyl Estradiol:

Sr. No.	Sample ID	Original Batch ID	Repeat Batch ID	Original Concentration (pg/mL)	Repeat Concentration (pg/mL)		Mean of Duplicate Analysis (pg/mL)	Accepted Concentration (pg/mL)
					Concentration 1	Concentration 2		
1.	53101	(b) (6)	200517REP22(IRS04)-02R1-01	2.27	0.00	0.00	0.00	0.00
2.	05201			27.58	0.00	0.00	0.00	0.00
3.	07201			1.34	0.00	0.00	0.00	0.00
4.	08201			1.70	0.00	0.00	0.00	0.00
5.	17201		240517REP24(IRS06)R4	1.66	0.69 (BLQ)	0.59 (BLQ)	NA	BLQ
6.	27201			5.86	2.26	2.93	2.60	2.60

Etonogestrel:

Sr. No.	Sample ID	Original Batch ID	Repeat Batch ID	Original Concentration (pg/mL)	Repeat Concentration (pg/mL)		Mean of Duplicate Analysis (pg/mL)	Accepted Concentration (pg/mL)
					Concentration 1	Concentration 2		
1.	01101	(b) (6)	200517REP21(IRS03)	156.88	0.00	0.00	0.00	0.00
2.	02101			103.74	0.00	0.00	0.00	0.00
3.	03101			185.78	51.76	0.00	NA	51.76
4.	04101			164.25	0.00	0.00	0.00	0.00
5.	13101			176.83	0.00	0.00	0.00	0.00
6.	14101			74.17	0.00	0.00	0.00	0.00
7.	16101			88.09	0.00	0.00	0.00	0.00
8.	17101			81.61	0.00	0.00	0.00	0.00
9.	18101			46.44	0.00	0.00	0.00	0.00
10.	19101			102.92	0.00	0.00	0.00	0.00
11.	20101			171.40	0.00	0.00	0.00	0.00
12.	21101		240517REP24(IRS06)R4	53.68	0.00	0.00	0.00	0.00
13.	22101		200517REP21(IRS03)	418.65	63.45	44.98	NA	As test for validity failed, hence the sample was further Identified in predose sample category
14.	23101			264.02	48.16	0.00	NA	48.16
15.	24101			188.05	0.00	0.00	0.00	0.00
16.	29101			66.57	0.00	0.00	0.00	0.00
17.	30101			216.73	91.46	70.69	81.08	81.08
18.	33101			113.86	0.00	0.00	0.00	0.00
19.	34101			728.87	84.81	79.33	82.07	82.07
20.	35101			197.01	0.00	0.00	0.00	0.00
21.	36101			39.13	0.00	0.00	0.00	0.00
22.	37101			143.17	0.00	0.00	0.00	0.00
23.	38101			211.32	0.00	0.00	0.00	0.00

Sr. No.	Sample ID	Original Batch ID	Repeat Batch ID	Original Concentration (pg/mL)	Repeat Concentration (pg/mL)		Mean of Duplicate Analysis (pg/mL)	Accepted Concentration (pg/mL)
					Concentration 1	Concentration 2		
24.	44101	(b) (6)		150.08	0.00	0.00	0.00	0.00
25.	65101			73.26	0.00	0.00	0.00	0.00
26.	67101			42.85	0.00	0.00	0.00	0.00
27.	68101			93.27	0.00	0.00	0.00	0.00
28.	02201			63.13	64.01	56.90	60.40	63.13
29.	09201		200517REP 21(IRS03)	85.82	71.89	54.59	63.24	63.24
30.	10201			42.20	0.00	39.53	NA	42.20
31.	13201			55.73	53.50	57.48	55.49	55.73
32.	22201			209.23	54.48	69.59	62.04	62.04
33.	23201			111.69	62.88	37.03 (BLQ)	NA	62.88
34.	24201			143.33	21.92	18.56	20.24	20.24
35.	25201			129.56	83.61	82.97	83.29	83.29
36.	27201		240517REP 24(IRS06)R4	156.59	49.85	72.53	NA	As test for validity failed, hence the sample was further Identified in predose sample category
37.	28201			119.70	0.00	75.75 (Repeat 01)	NA	
38.	30201			78.79	43.89	0.00	NA	43.89
39.	31201			49.30	0.00	0.00	0.00	0.00
40.	32201			52.25	0.00	0.00	0.00	0.00
41.	33201			90.90	0.00	46.01	NA	46.01
42.	37201		200517REP 21(IRS03)	42.79	0.00	43.51	NA	42.79
43.	38201			43.78	0.00	47.02	NA	43.78
44.	42201			51.01	45.86	18.38 (BLQ)	NA	51.01
45.	44201			46.10	0.00	0.00	0.00	0.00
46.	46201			103.60	0.00	7.84 (BLQ)	NA	7.84 (BLQ)
47.	53201			40.19	17.78 (BLQ)	0.00	NA	17.78 (BLQ)
48.	54201			84.96	0.00	13.80 (BLQ)	NA	13.80 (BLQ)
49.	58201			41.05	52.57	0.00	NA	52.57

Sr. No.	Sample ID	Original Batch ID	Repeat Batch ID	Original Concentration (pg/mL)	Repeat Concentration (pg/mL)		Mean of Duplicate Analysis (pg/mL)	Accepted Concentration (pg/mL)
					Concentration 1	Concentration 2		
50.	60201	(b) (6)	200517REP21 (IRS03)	45.69	0.00	0.00	0.00	0.00
51.	63201			61.58	0.00	0.00	0.00	0.00
52.	05101			97.57	44.41	41.96	43.19	43.19
53.	07101			77.38	0.00	0.00	0.00	0.00
54.	08101			118.65	158.02	158.65	158.34	158.34
55.	09101			96.45	34.30 (BLQ)	61.48	NA	61.48
56.	12101			54.37	0.00	0.00	0.00	0.00
57.	25101			52.02	0.00	0.00	0.00	0.00
58.	27101			158.81	81.84	49.48	NA	As test for validity failed, hence the sample was further Identified in predose sample category
59.	28101			97.01	37.78 (BLQ)	60.01	NA	60.01
60.	48101			118.65	0.00	0.00	0.00	0.00
61.	67201			51.82	0.00	0.00	NA	Further Identified in Internal Standard Variation category
62.	68201			52.92	0.00	40.95	NA	40.95
63.	71201			230.86	145.35	282.46	NA	As test for validity failed, hence the sample was further Identified in predose sample category

Note: Sample 67201 was repeated in duplicate due to pre-dose concentration. Both repeated samples (i.e. 67201-01 AND 67201-02) had IS variation and were further repeated under the internal standard variation category. The reviewer used the original value for analysis for this sample, since pre-dose concentration repeats are considered PK repeats.

Sr. No.	Sample ID	Original Batch ID	Repeat Batch ID	Original Concentration (pg/mL)	Repeat Concentration (pg/mL)		Mean of Duplicate Analysis (pg/mL)	Accepted Concentration (pg/mL)
					Concentration 1	Concentration 2		
64.	17201	(b) (6)	240517REP 24(IRS06)R4	41.47	26.79 (BLQ)	19.72 (BLQ)	NA	BLQ
65.	01201			54.30 (Repeat 01)	0.00	13.12 (BLQ)	NA	BLQ
66.	22101			418.65 (Repeat 01)	28.62 (BLQ)	40.16	NA	40.16
67.	28201			119.70 (Repeat 01)	59.84	54.65	57.25	57.25
68.	71201			230.86 (Repeat 01)	79.27	82.65	80.96	80.96
69.	27101			158.81 (Repeat 01)	47.78	51.68	49.73	49.73
70.	27201		260517REP 25(IRS07)	156.59 (Repeat 01)	61.56	62.07	61.82	61.82

- NA: % Difference not calculated as BLQ or 0.00 pg/mL concentration observed.

Details of Samples Repeated due to 'Zero or BLQ value between two quantifiable values' (ethinyl estradiol only):

Sr. No	Sample ID	Original Batch ID	Repeat Batch ID	Original Concentration (pg/mL)	Repeat Concentration (pg/mL)		Mean of Duplicate Analysis (pg/mL)	Accepted Concentration (pg/mL)
					Concentration 1	Concentration 2		
1.	18123	(b) (6)	240517REP24 (IRS06)R4	0.00	5.58	5.18	5.38	5.38
2.	46126			0.42 (BLQ)	1.16	0.59	NA	1.16
3.	46127			0.06 (BLQ)	5.41	5.25	5.33	5.33

Details of Samples Repeated due to Chromatography Related Issues:
Ethinyl Estradiol:

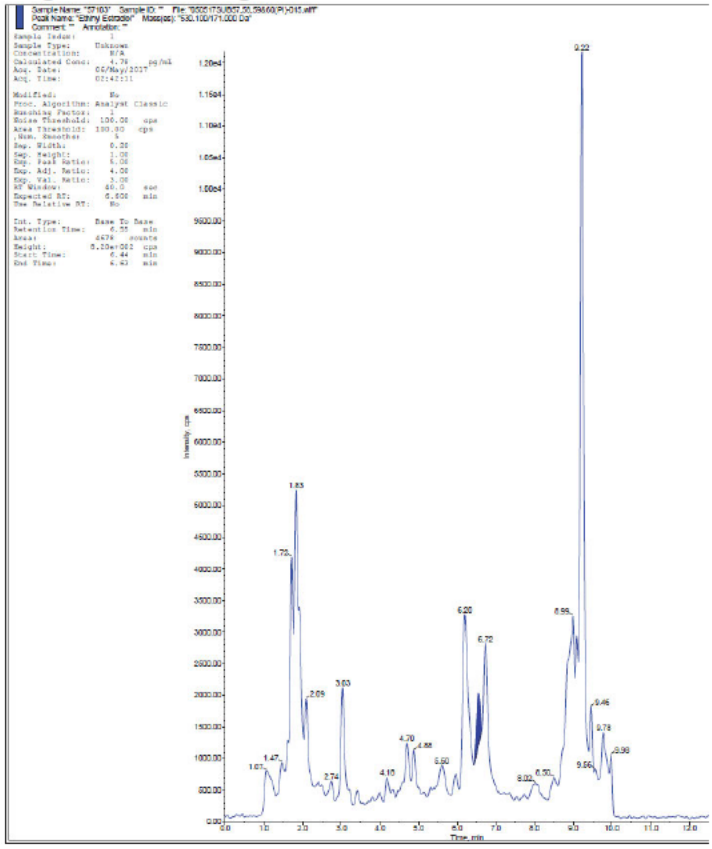
Sr. No.	Sample ID	Original Batch ID	Repeat Batch ID	Original Concentration (pg/mL)	Repeat Concentration (pg/mL)	Accepted Concentration (pg/mL)
1.	20118	(b) (6)	200517REP22 (IRS04)-02R1-01	12.28	10.54	10.54
2.	41119			2.46	24.57	24.57
3.	41125			1.87	0.86	0.86
4.	41128		200517REP22 (IRS04)-02R1-01	3.47	0.00	0.00
5.	42111			1.17	21.15	21.15
6.	43104			0.59	21.28	21.28
7.	43105			4715.99	23.35	23.35
8.	57103			4.78	13.69	13.69
9.	58128			0.00	0.00	0.00

Note: -

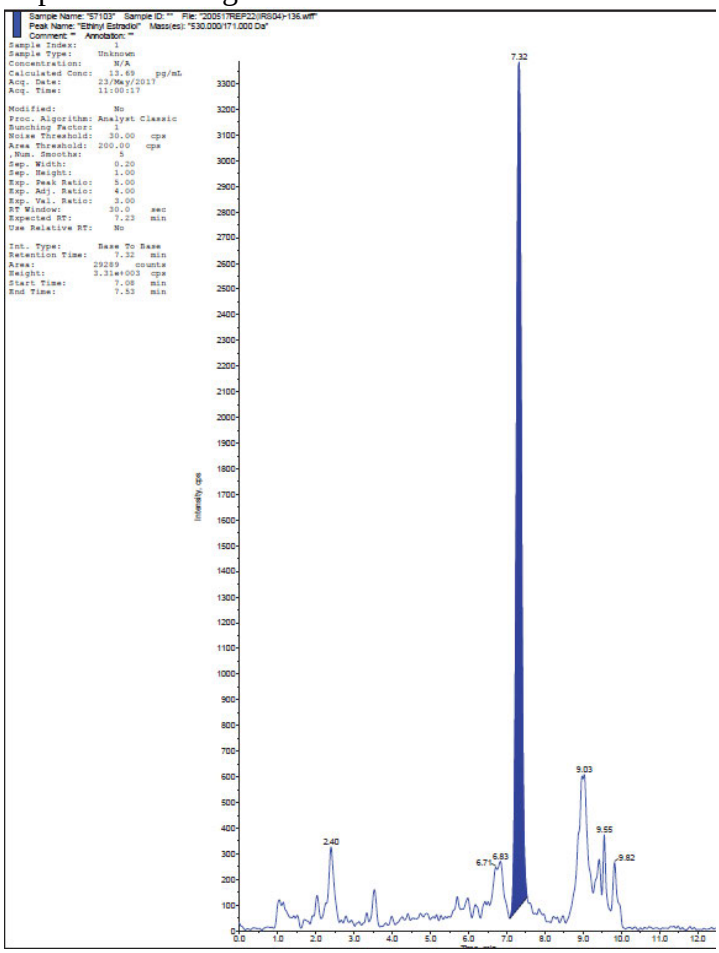
- In Sample ID's 20118, 41119, 41125 and 41128 were showing peak splitting.
- In Sample ID's 42111, 43104 and 57103 - Analyte peak was not integrated.
- In Sample ID's 43105 and 58128- IS peak was not integrated.

Details of Sample 57103:

Original Chromatogram:

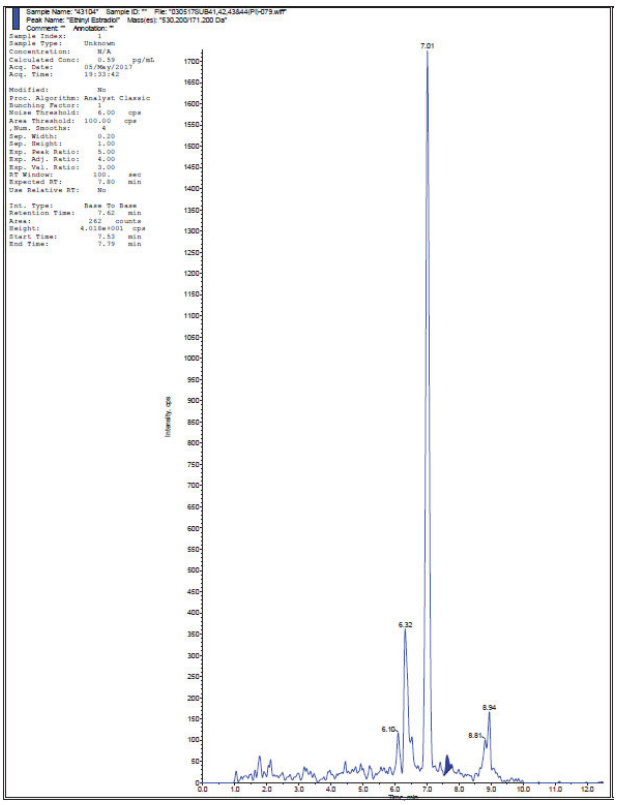


Repeat Chromatogram:

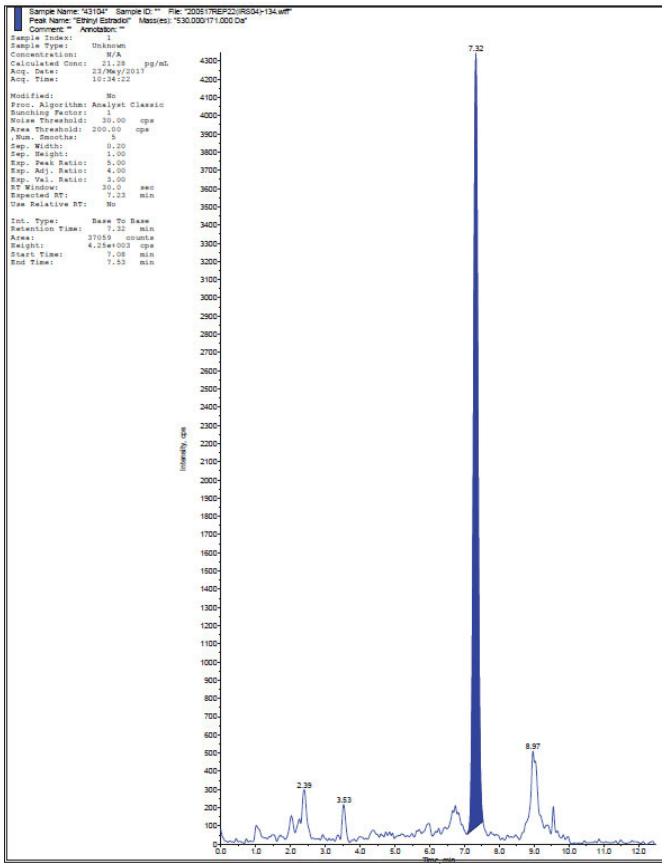


Example additional sample repeated because the analyte peak was not integrated (sample 43104)

Original Chromatogram:



Repeat Chromatogram:



Etonogestrel:

Sr. No	Sample ID	Original Batch ID	Repeat Batch ID	Original Concentration (pg/mL)	Repeat Concentration (pg/mL)	Accepted Concentration (pg/mL)
1.	11215	(b) (6)	200517IRS02 (REP20)	382412.38	1983.94	1983.94
2.	11217			465687.16	2545.89	2545.89
3.	42109			17.28	1083.10	1083.10
4.	44102			13.61	358.68	358.68
5.	72107			24.36	686.58	686.58
6.	72120			20.06	1981.13	1981.13
7.	07220*		200517REP19 (IRS01)	8.10	5548.04	5548.04

Note: -

- In Sample ID's 42109, 44102, 72107, 72120 and 07220- Analyte peak was not integrated.
- In Sample ID's 11215 and 11217- IS peak was not integrated.
- "*"-In analytical Batch ID (b) (6) (PII), sample ID 07220 was having poor chromatography for Etonogestrel, However, as the adjacent samples with IDs i.e. 07219 and 07221 were having AULOQ concentrations in original analysis, sample ID 07220 was repeated with dilution.

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☐ Yes ☒ No There were seven reasons for repeat analysis during the study: above upper limit of quantification, pre-dose concentration samples, internal standard variation, zero or BLQ value between two quantifiable values, chromatography-related issues, 3 consecutive QC failure, and equipment related issue. Samples above the upper limit of quantification were diluted 2-fold before reanalysis. Method validation covered a 2-fold and 10-fold dilution; therefore, these repeats are acceptable. Internal standard variation was objectively defined in the repeat analysis protocol as beyond 50-150% of the mean of the internal standard area observed for the acceptable CC and QC samples for non-labeled IS and beyond 20-185% for labeled IS. Both internal standards in this case were labeled, so the criterion of beyond 20-185% was used. The firm submitted pdf files of Excel sheets to show their internal standard variation calculations. Therefore, repeated samples due to internal standard variation are acceptable. 3 consecutive QC failure repeat analysis was objectively defined in the repeat analysis protocol. If 3 or more

	consecutive QCs failed (i.e. outside 85-115% of their nominal values), all samples from the last passing QC sample to the next passing QC sample were repeated. Details of samples repeated due to chromatography-related issues are shown above. The firm supplied the original and repeated chromatograms for these samples in Module 5.3.1.4. (Subject chromatograms). The reviewer examined the provided chromatograms and agrees with the firm's repeat of these samples, except for the repeat of sample 57103. This sample was repeated because the analyte peak (ethinyl estradiol) was not integrated. However, in the original chromatogram, there is no obvious peak at the expected retention time of the analyte. Therefore, the reviewer used the original value for this sample in PK analysis. For the samples repeated due to equipment-related issue, not peak was observed in the original samples for the analyte and the internal standard because of autosampler vial insert breakage. These are analytical repeats and are acceptable. The reviewer considers samples repeated due to pre-dose concentration and Zero or BLQ Value Between Two Quantifiable Values Category to be PK repeats. Reviewer statistical analysis was conducted with the original values for these samples. Details of original and repeated values for these samples are shown above.
If no, is recalculation of PK parameters necessary?	☒ Yes ☐ No ☐ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☒ No ☐ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☒ Yes ☐ No ☐ N/A

Details of Rejected Batches:

Batch ID	Reason for Failure		Observations
	Ethinyl Estradiol	Etonogestrel	
(b) (6)	Significant interference observed in Blank and Blank + IS sample at the RT of Analytes		• Significant Interference in Blank and Blank +IS for both the analytes might be due to some solution contamination during sample processing of the batch. Additionally, RT shifting was observed in many samples for Ethinyl Estradiol and hence the analyte peak was not integrated appropriately.
	Significant interference observed in Blank +IS sample at the RT of Ethinyl Estradiol	03 out of 09 Calibration curve standards failed to meet the acceptance criteria of % Nominal.	• Predose and Blank samples of Ethinyl Estradiol were not having any interference indicating sample specific contamination for Blank +IS sample. • For Etonogestrel, no assignable cause was identified for the failure of CC standards.
	09 out of 16 Quality Control Samples failed to meet the acceptance criteria of % Accuracy.	Significant interference observed in carryover Blank sample at the RT of Etonogestrel	• For Ethinyl Estradiol, as the QC samples were within acceptance for Etonogestrel, any sample processing error was ruled out for the failure of QC samples. • For Etonogestrel the autosampler carryover experiment in method validation did not show any significant carryover and also none of the other batches showed significant response in Carryover Blank sample
	Batch was within acceptance criteria for Ethinyl Estradiol	Significant interference observed in Blank +IS sample at the RT of Etonogestrel	• Any solution contamination was ruled out as the Blank sample was free from interference and also the IS spiking solution used for this batch was also used for batch ID Id (b) (6) which was free from any interference. Additionally, the CC standards and QC samples were within the acceptance and also the batch was within acceptance for Ethinyl Estradiol. Based on these observations significant interference might be sample specific.

Batch ID	Reason for Failure		Observations
	Ethinyl Estradiol	Etonogestrel	
(b) (6)	Significant interference observed in carryover Blank sample at the RT of Ethinyl Estradiol	Significant interference observed in Blank and Blank + IS sample at the RT of Etonogestrel	• For Ethinyl Estradiol, the autosampler carryover experiment in method validation did not show any carryover and also none of the other batches showed significant response in Carryover Blank sample. • For Etonogestrel, all the possible aspects were reviewed and no assignable cause was identified for the failure
	Significant interference observed in Blank +IS sample at the RT of Ethinyl Estradiol	Batch was within acceptance criteria for Etonogestrel	• Any solution contamination was ruled out as the Blank sample was free from interference and Predose samples of Ethinyl Estradiol were not having any interference. • In addition, STD A was showing abnormal concentration due to which all the other CC standards were failing. However, the batch was within acceptance criteria for Etonogestrel which ruled out the possibility of processing error. Based on these observations, no assignable cause was identified for the failure
	failed to meet the batch acceptance criteria at higher calibration curve standard (STD I)	Batch was within acceptance criteria for Etonogestrel	• STD I failing for Ethinyl Estradiol, however, the batch was within acceptance criteria for Etonogestrel which ruled out the possibility of sample processing error. • In addition, the chromatography and the IS response of the failed CC standards were found to be appropriate.
	03 out of 09 Calibration curve standards failed to meet the acceptance criteria of % Nominal.		• On review of these analytical batches, it was observed that as the CC standards were failing for only one analyte and the other analyte was passing and hence, any sample processing error was ruled out. Also, the IS response and the chromatography of the failed CC standards were found to be appropriate. Hence, no assignable cause was identified for the failure.
	Batch was within acceptance criteria for Ethinyl Estradiol.	03 out of 09 Calibration curve standards failed to meet the acceptance criteria of % Nominal.	

Batch ID	Reason for Failure		Observations
	Ethinyl Estradiol	Etonogestrel	
(b) (6)	13 out of 16 Quality Control Samples failed to meet the acceptance criteria of % Accuracy	Batch was within acceptance criteria for Etonogestrel	• The consolidated data of these batches due to failure of QC acceptance criteria was reviewed and it was observed that though the batches were failing for one analyte, for other analyte, the batch was within acceptance and hence any error in sample processing was ruled out. • Furthermore, in all the batches no significant interference was observed for Blank and Blank+IS samples. • The chromatography and the IS response was observed for the failed QC samples and was found to be appropriate. • Hence, no assignable cause could be identified for the failure of these batches
	10 out of 16 Quality Control Samples failed to meet the acceptance criteria of % Accuracy		
	13 out of 16 Quality Control Samples failed to meet the acceptance criteria of % Accuracy		
	06 out of 16 Quality Control Samples failed to meet the acceptance criteria of % Accuracy		
	11 out of 16 Quality Control Samples failed to meet the acceptance criteria of % Accuracy		
	13 out of 16 Quality Control Samples failed to meet the acceptance criteria of % Accuracy		
	03 HQC samples failed to meet the acceptance criteria of % Accuracy hence batch was stopped manually after completion of sample Id 35113.	Batch was only repeated for Ethinyl Estradiol	
	09 out of 16 Quality Control Samples failed to meet the acceptance criteria of % Accuracy	03 out of 04 LQC samples failed to meet the acceptance criteria of % Accuracy	• The batch was reviewed for all the possible aspects but no assignable cause was identified for the failure

Comments on Bioanalytical Results: Adequate

1. 3834 subject samples were analyzed in 64 runs (including sample reanalysis and incurred sample reproducibility), 18 of which were rejected for at least one analyte (28% of total batches, details shown above). Batches were rejected per the applicant's protocol. The applicant reviewed the consolidated data of the failed batches did not observe any trend for rejection. All sample re-injections were due to analytical reasons/equipment issues (details are shown on pages 142-148 of the Bioanalytical Study Report). When one analyte met acceptance criteria and the other analyte failed, the original data for the passing analyte was used.

2. 448 samples (11.7% of total fasting study samples) were re-analyzed for incurred sample reanalysis (ISR). 67.41% of ISR samples were within ±20% of original values for ethinyl estradiol and 68.97% of ISR samples were within ±20% of original values for etonogestrel. At least 2 samples per subject per period were selected for ISR, at least one at or near the Cmax level and at least one in the elimination phase (approximately $\geq$ 3x the LLOQ concentration). Both analytes met the acceptance criteria for ISR of at least 67.00% within ±20% of original values.

3. Subject sample analysis was started after completion of the clinical portion of the study:

Study dates	*Phase*	*Initiation*	*Completion*
	Clinical		
	Group I (subject numbers: (b) (6)	(b) (6)	
	Group II (subject numbers: (b) (6)		
	Group III (subject numbers:		
	Group IV (subject numbers:		
	Bioanalysis (Subject sample analysis)		
	Pharmacokinetic and Statistics		

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters, Reviewer-Calculated

Ethinyl Estradiol

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	11081.87	40.59	5058.96	29101.08	11764.97	33.40	5597.58	27477.21	0.94
AUCI	pg hr/mL	11140.79	40.71	5097.74	29383.58	11968.60	33.87	5634.10	27611.69	0.93
CMAX	pg/mL	27.768	37.57	14.56	63.31	28.933	29.84	14.75	63.16	0.96
TMAX	hr	72.000	.	6.00	600.00	72.000	.	6.00	432.00	1.00
KE	hr-1	0.034	34.95	0.01	0.06	0.035	41.11	0.00	0.07	0.97
THALF	hr	24.776	63.58	11.28	102.93	32.862	217.56	10.48	590.24	0.75

*** Tmax values are presented as median, range.**

Etonogestrel

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	1462225	32.06	638830.1	2923308	1508069	27.96	799932.5	2788620	0.97
AUCI	pg hr/mL	1495553	32.29	643261.7	3122322	1546117	29.24	809319.3	2975786	0.97
CMAX	pg/mL	3230.965	32.43	1602.03	6158.85	3318.962	26.46	2035.80	6183.86	0.97
TMAX	hr	288.000	.	120.00	504.00	336.000	.	36.00	528.00	0.86
KE	hr-1	0.017	33.75	0.01	0.04	0.016	29.13	0.00	0.03	1.05
THALF	hr	47.093	40.53	17.72	108.38	47.870	36.90	22.71	147.53	0.98

*** Tmax values are presented as median, range.**

4.1.1.4.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Ethinyl Estradiol and Etonogestrel Vaginal Ring (No of completed subjects; N = 69) Dose (1× 0.015 mg/24 Hr and 0.12 mg/ 24 Hr) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Bioequivalence Study						
Parameter	**Test (A)**	**N**	**Ref (B)**	**N**	**Ratio(T/R) %**	**90% Confidence Interval**
Ethinyl Estradiol						
AUC_{0-t} (pg*hr/mL)	10178.03	69	11301.16	69	90.06	85.79 – 94.54
AUC_{0-inf} (pg*hr/mL)	10635.74	67*	11584.12	69	91.81	88.39 – 95.36
C_{max} (pg/mL)	26.52	69	28.65	69	92.57	88.37 – 96.97
Etonogestrel						
AUC_{0-t} (pg*hr/mL)	1415225.03	69	1456389.67	69	97.17	93.48 - 101.02
AUC_{0-inf} (pg*hr/mL)	1453913.40	69	1493909.92	69	97.32	93.39 - 101.42
C_{max} (pg/mL)	3119.31	69	3211.35	69	97.13	93.29 - 101.14

*The applicant did not include Subject (b) (6) period 2 (T) and Subject (b) (6) period 1 (T) in the determination of AUCi for ethinyl estradiol because a reliable ke estimate could not be obtained for these subjects.

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Ethinyl Estradiol and Etonogestrel Vaginal Ring 1× 0.015 mg/24 Hr and 0.12 mg/ 24 Hr Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. BE/16/373 Ethinyl Estradiol							
Parameter (units)	**Test**	**N***	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	10248.59	64	11135.96	64	0.92	88.69	95.50
AUC∞ (hr *pg/ml)	10301.83	64	11251.33	64	0.92	88.12	95.14
Cmax (pg/ml)	26.10	64	27.70	64	0.94	89.90	98.75

*The reviewer excluded periods from 5 subjects due to pre-dose concentrations greater than 5% of Cmax. Therefore, these subjects were not included in geometric mean analysis (see details in comments section,

below). The two subjects which the applicant excluded from AUCi determination only (Subject (b) (6) period 2 and Subject (b) (6) period 1) were excluded by the reviewer because of high pre-dose values in one of the periods for these subjects.

Ethinyl Estradiol and Etonogestrel Vaginal Ring 1× 0.015 mg/24 Hr and 0.12 mg/ 24 Hr Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. BE/16/373 Etonogestrel							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	1374156	58	1422311	58	0.97	92.92	100.45
AUC∞ (hr *pg/ml)	1404207	58	1454280	58	0.97	92.78	100.49
Cmax (pg/ml)	3040.35	58	3142.06	58	0.97	92.98	100.70

*The reviewer excluded periods from 11 subjects due to pre-dose concentrations greater than 5% of Cmax. Therefore, these subjects were not included in geometric mean analysis (see details in comments section, below).

4.1.1.4.4 Additional Information for the Study

Root Mean Square Error	Ethinyl Estradiol AUCt: 0.1251 AUCi: 0.1295 Cmax: 0.1587 Etonogestrel AUCt: 0.1254 AUCi: 0.1285 Cmax: 0.1285
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).**	☐ Yes ☒ No The median Tmax T/R ratio for ethinyl estradiol was 1. The median Tmax T/R ratio for etonogestrel was 0.86.
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☒ Yes ☐ No See comment, below.
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☒ Yes ☐ No See comments section, below.
Are there first measurable drug concentration as Cmax? **If yes, please comment.**	☒ Yes ☐ No Ethinyl estradiol only (see comment in next row)
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☒ Yes ☐ No For ethinyl estradiol only, the following

	subjects had Cmax as the first measurable drug concentration and first timepoint: Subject (b)(6) period 1 and 2 Subject period 1 Subject period 1 Subject period 1 Subject period 1 Subject period 1 This drug product is designed to release drug continuously over a period of 21 days. The majority of subjects had a first measurable timepoint near to Cmax for ethinyl estradiol, and the plasma concentration profile (see mean plot, below) stays fairly stable for the 21 day ring insertion period. Therefore, a first timepoint Cmax for ethinyl estradiol for this drug product is not likely to impact PK results and the reviewer and the firm included these subjects in analysis.

Ratio of AUC0-t/AUC∞[12] : Ethinyl Estradiol				
Treatment	**N**	**Mean**	**Minimum**	**Maximum**
Test	66	0.99	0.86	1.00
Reference	66	0.99	0.66	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	Subject (b)(6) (R treatment) had an AUC ratio of 0.66. All other subjects had AUC ratios greater than 0.8. The reviewer examined the plot for this subject; the concentration-time curve properly covers the absorption, distribution, and elimination phases.			

Ratio of AUC0-t/AUC∞[13] : Etonogestrel				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	62	0.98	0.80	1.00
Reference	64	0.98	0.74	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	Subject (b)(6) (R treatment) had an AUC ratio of 0.74. All other subjects had AUC ratios greater than 0.8. The reviewer examined the plot for this subject; the concentration-time curve properly covers the absorption, distribution, and elimination phases.			

Comments on PK results: Adequate

1. The in vivo BE study was dosed in four groups in the first period; each group was divided into two groups in the second period. The groups were separated by

[12] See individual test to reference ratios of PK Parameters in SAS Output
[13] See individual test to reference ratios of PK Parameters in SAS Output

dosing day. Each subgroup had differing washout periods. Groups were assigned based on the start of each subject's menstrual cycle. The subjects were recruited from the same enrollment pool, have similar demographics, and were dosed at the same site. Therefore, these were not considered as two separate groups for this analysis.[14] For both ethinyl estradiol and etonogestrel, PK results were not marginal; group effect is not expected to influence the BE results.

2. The 90% confidence intervals for Cmax, AUCt, and AUCi of ethinyl estradiol and etonogestrel met BE requirements.

Ethinyl Estradiol:

3. Six samples were repeated due to due to pre-dose values and 3 samples were repeated due to "Zero or BLQ Value Between Two Quantifiable Values". The reviewer used original values for these samples, as they are considered PK repeats. Observed pre-dose values and percent of individual Cmax are shown below. The five periods highlighted in red were excluded from the reviewer's PK analysis because of pre-dose concentrations greater than 5% of Cmax. The majority (83%) of pre-dose concentrations for ethinyl estradiol occurred in period 2 of the study.

Subject	Period	Treatment*	Pre-dose Conc. (pg/mL)	Cmax (pg/mL)	% of Cmax
(b) (6)	2	1	27.58	20.04	137.62
	2	1	1.34	24.77	5.41
	2	2	1.7	48.95	3.47
	2	2	1.66	21.18	7.84
	2	2	5.86	46.19	12.69
	1	2	2.27	26.37	8.61

*Treatment 1=T and 2=R

Etonogestrel:

4. 64 subject samples were repeated due to pre-dose concentrations observed (and 6 were repeated an additional time because of inconsistency of duplicate repeat results). The reviewer used all original values for these samples, since they are considered PK repeats. Observed pre-dose values and percent of individual Cmax are shown below. The LOQ for etonogestrel in the fasting study was 38.52 pg/mL; several observations were near this LOQ. The twelve periods highlighted in red (covering 11 subjects) were excluded from the reviewer's PK analysis because of pre-dose concentrations greater than 5% of Cmax. Of the pre-dose concentrations observed, 36 (56%) occurred in period I and 28 (44%) occurred in period II. Since the observations were approximately evenly split between periods, it is unlikely the high number of pre-dose concentrations was due to carryover from period I.

[14] v:\firmsnz\(b) (4)controls\98-392a.doc.

Subject	Period	Treatment*	Pre-dose Conc. (pg/mL)	Cmax (pg/mL)	% Cmax
(b) (6)	1	1	156.88	2080.13	7.54
	2	2	54.3	2125.33	2.55
	1	2	103.74	4442.17	2.34
	2	1	63.13	4550.45	1.39
	1	1	185.78	3060.23	6.07
	1	2	164.25	3306.81	4.97
	1	2	97.57	1474.82	6.62
	1	2	77.38	4097.37	1.89
	1	1	118.65	6077.86	1.95
	1	1	96.45	3923.04	2.46
	2	2	85.82	4052.78	2.12
	2	1	42.2	3259.31	1.29
	1	2	54.37	3286.7	1.65
	1	2	176.83	4222.37	4.19
	2	1	55.73	4245.62	1.31
	1	1	74.17	2376.7	3.12
	1	1	88.09	3231.28	2.73
	1	1	81.61	2231.64	3.66
	2	2	41.47	2506.77	1.65
	1	2	46.44	2836.79	1.64
	1	2	102.92	3275.58	3.14
	1	1	171.4	2666.71	6.43
	1	2	53.68	2082.38	2.58
	1	1	418.65	3658.84	11.44
	2	2	209.23	3638.49	5.75
	1	1	264.02	3836.65	6.88
	2	2	111.69	3486.39	3.20
	1	2	188.05	3580.55	5.25
	1	1	52.02	2690.55	1.93
	2	2	129.56	3340.35	3.88
	1	1	158.81	5401.27	2.94
	2	2	156.59	6183.86	2.53
	1	2	97.01	4046.44	2.40
	2	1	119.7	3712.08	3.22
	1	2	66.57	2037.35	3.27
	1	1	216.73	4459.88	4.86
	2	2	78.79	4666.16	1.69
	2	1	49.3	3688.76	1.34
	2	2	52.25	2863.91	1.82
	1	1	113.86	2686.71	4.24

(b) (6)					
	2	2	90.9	2773.98	3.28
	1	2	728.87	2880.42	25.30
	1	1	197.01	4214.32	4.67
	1	2	39.13	4484.11	0.87
	1	2	143.17	2163.86	6.62
	2	1	42.79	3085.59	1.39
	1	1	211.32	4159.23	5.08
	2	2	43.78	3749.43	1.17
	2	2	51.01	2478.68	2.06
	1	1	150.08	2057.07	7.30
	2	2	46.1	3594.69	1.28
	2	1	103.6	4133.72	2.51
	1	1	118.65	3392.7	3.50
	2	1	40.19	3604.82	1.11
	2	2	84.96	3666.66	2.32
	2	2	41.05	2520	1.63
	2	1	45.69	4195.98	1.09
	2	2	61.58	3022.88	2.04
	1	2	73.26	2514.3	2.91
	1	1	42.85	2524.56	1.70
	2	2	51.82	3837.01	1.35
	1	2	93.27	2544.12	3.67
	2	1	52.92	3340.29	1.58
	2	1	230.86	6158.85	3.75

*Treatment 1=T and 2=R

4.1.1.5 Overall Comment

Was the fasting bioequivalence study acceptable? Acceptable

Mean Plasma Concentrations, Single-Dose Bioequivalence Study

Ethinyl Estradiol

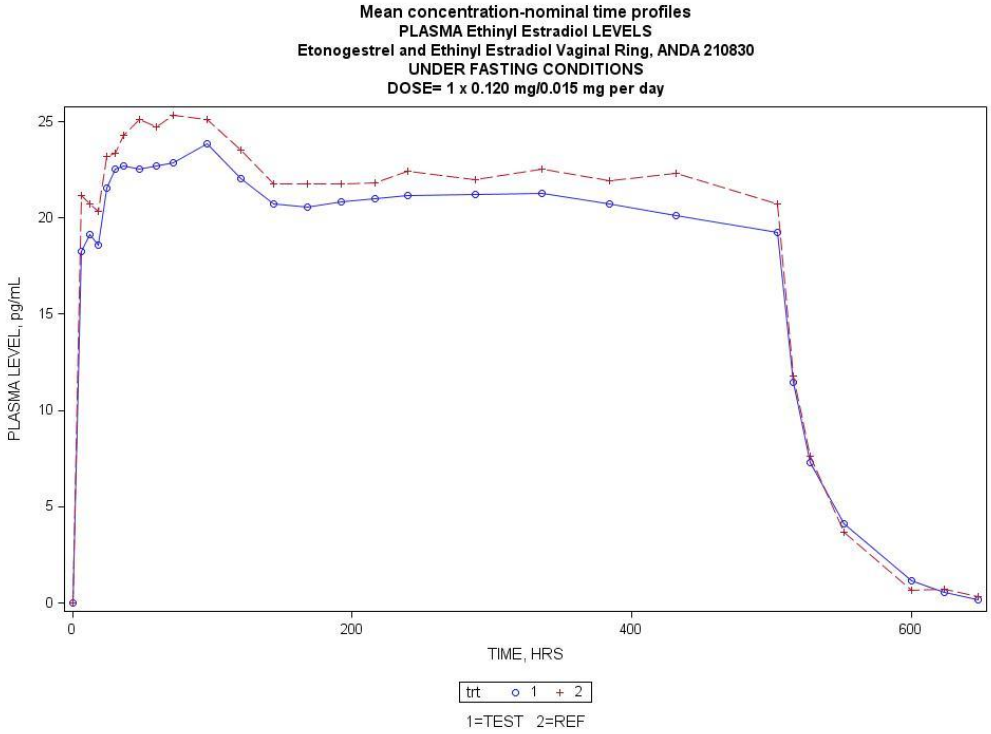
	Test (n=67)		Reference (n=66)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.03	812.40	0.00
6.00	18.23	30.22	21.19	26.16	0.86
12.00	19.12	29.45	20.72	26.21	0.92
18.00	18.59	31.35	20.32	25.96	0.91
24.00	21.56	33.74	23.18	28.49	0.93
30.00	22.53	34.71	23.37	27.70	0.96
36.00	22.70	35.48	24.26	28.77	0.94
48.00	22.54	32.08	25.09	31.28	0.90
60.00	22.69	37.94	24.75	34.89	0.92
72.00	22.85	36.62	25.34	34.46	0.90
96.00	23.86	39.64	25.14	36.62	0.95
120.00	22.02	41.63	23.50	38.17	0.94
144.00	20.72	42.04	21.76	35.84	0.95
168.00	20.56	45.77	21.75	35.07	0.95
192.00	20.85	44.01	21.76	37.45	0.96
216.00	21.02	44.50	21.82	34.97	0.96
240.00	21.17	41.47	22.42	34.04	0.94
288.00	21.20	45.19	21.97	32.76	0.97
336.00	21.26	44.43	22.51	36.63	0.94
384.00	20.74	42.40	21.95	35.89	0.94
432.00	20.15	41.26	22.31	37.53	0.90
504.00	19.26	45.23	20.72	38.23	0.93
516.00	11.48	57.07	11.79	47.22	0.97
528.00	7.30	60.51	7.62	56.88	0.96
552.00	4.13	131.35	3.68	101.95	1.12
600.00	1.15	388.27	0.67	235.93	1.73
624.00	0.57	331.90	0.73	384.25	0.78
648.00	0.19	489.81	0.34	388.81	0.55

Etonogestrel

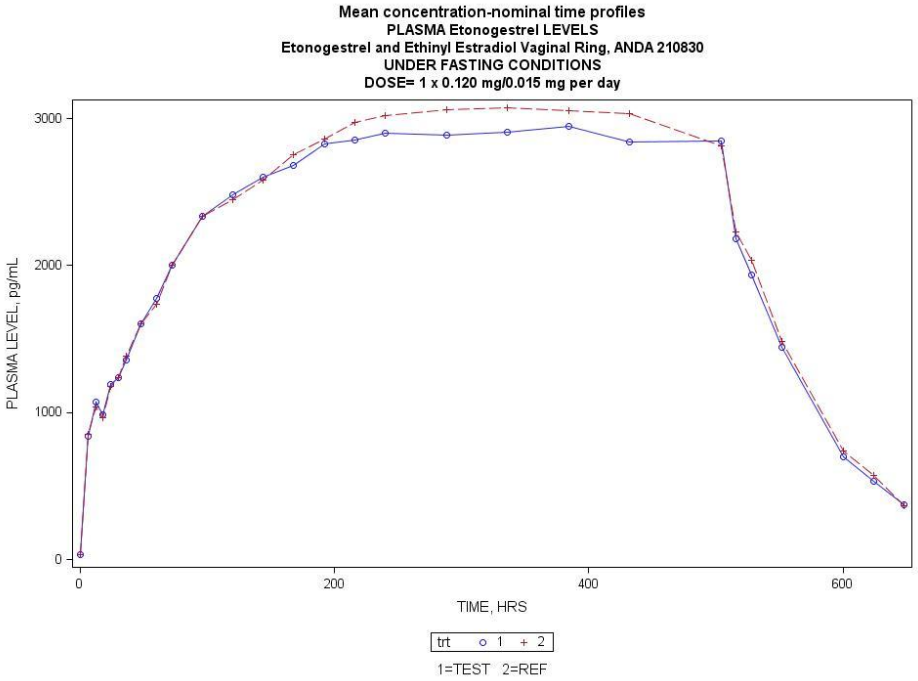
	Test (n=62)		Reference (n=64)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	35.56	163.19	36.41	130.93	0.98
6.00	837.11	48.91	849.78	41.29	0.99
12.00	1071.77	65.49	1041.59	54.80	1.03
18.00	988.55	46.49	963.68	43.32	1.03
24.00	1191.64	45.24	1178.95	39.83	1.01
30.00	1237.80	43.84	1238.08	41.61	1.00
36.00	1358.55	40.31	1381.39	40.98	0.98
48.00	1604.72	40.15	1602.38	35.22	1.00
60.00	1774.67	40.65	1734.53	37.36	1.02
72.00	2001.44	38.20	2004.37	35.17	1.00
96.00	2334.97	35.95	2338.42	29.08	1.00
120.00	2481.76	33.41	2448.48	29.82	1.01
144.00	2602.94	31.84	2579.07	26.51	1.01
168.00	2683.40	32.33	2756.42	26.33	0.97
192.00	2828.30	30.68	2863.15	27.17	0.99
216.00	2856.42	29.47	2973.12	26.42	0.96
240.00	2900.25	31.90	3023.29	26.69	0.96
288.00	2887.13	30.53	3063.99	26.75	0.94
336.00	2906.85	32.81	3075.00	27.61	0.95
384.00	2950.79	34.12	3056.80	29.93	0.97
432.00	2838.29	32.12	3032.80	30.55	0.94
504.00	2847.47	36.70	2812.08	30.63	1.01
516.00	2182.60	42.17	2229.98	39.53	0.98
528.00	1936.74	37.88	2033.48	40.96	0.95
552.00	1444.36	43.02	1481.54	46.79	0.97
600.00	697.25	62.02	740.02	56.44	0.94
624.00	533.71	74.92	575.08	84.29	0.93
648.00	374.68	81.82	369.63	72.22	1.01

Mean Plasma Concentrations, Single-Dose Bioequivalence Study

Ethinyl Estradiol



Etonogestrel



4.2 Formulation Data

4.2.1 Test Formulation

Ingredients	mg/Unit	% w/w
Ethinyl Estradiol, USP (b) (4)	2.700	(b) (4)
Etonogestrel (b) (4)	11.700	
Ethylene Vinylacetate Copolymer, 28% Vinylacetate (b) (4)	(b) (4)	
Ethylene Vinylacetate Copolymer, 9% Vinylacetate (b) (4)		
Magnesium Stearate, NF		
(b) (4)	N/A*	
Total	(b) (4)	**100.0**

(b) (4)

Reference Product Formulation (not for release under FOIA):[15]

Composition of NuvaRing		
Ingredient	Formulation (mg/ring)	(b) (4)
(b) (4)		
• Ethylene vinylacetate copolymer, 28% m/m vinylacetate • Etonogestrel • Ethinyl estradiol • Magnesium stearate	(b) (4) 11.7 2.7 (b) (4)	
(b) (4)		
• Ethylene vinylacetate copolymer, 9% m/m vinylacetate		
(b) (4)		

The qualitative and quantitative composition of the drug product is provided in the following table[16]:

Name of ingredient	Quantity per unit
(b) (4) (Etonogestrel)	11.7 mg
(b) (4) (Ethinylestradiol)	2.7 mg
Excipients	
Ethylene vinyl acetate copolymer, 28% vinyl acetate	(b) (4)
Ethylene vinyl acetate copolymer, 9% vinyl acetate	
Magnesium stearate	
(b) (4	
(b) (4)	

NuvaRing® has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. The drug product is a contraceptive vaginal ring made of a (b) (4) containing etonogestrel and ethinyl estradiol, and (b) (4) controlling release rate. The (b) (4) (b) (4) consists of ethylene vinyl acetate co-polymer with 28% of vinyl acetate (b) (4)) and the skin polymer is made of the same co-polymer with 9% vinyl acetate (b) (4).[17] The main advantages of the vaginal ring compared to oral contraceptives are the more constant steroid levels built up in comparison with oral formulations, the avoidance of the hepatic first-pass effects and the potential for a better patient compliance.

Similar to the RLD, the test product contains a drug reservoir core and a rate controlling membrane surrounding the core. Two different grades of Ethylene Vinyl Acetate Copolymer (EVA) namely, EVA 28% and EVA 9% have been utilized in the formulation

[15] DARRTS; 06/21/2012, REV-QUALITY-03(General Review), Suarez, Sandra.
[16] RFS: Module 3.2.P.8.3 from Annual Report-13. 11/25/2013.
[17] DARRTS; 12/21/2000, REV-QUALITY-03(General Review), Mitra, Amit K.

to provide drug reservoir matrix and rate controlling membrane, respectively. Ethylene-Vinyl Acetate (EVA), also known as poly (ethylene-vinyl acetate) (PEVA), is the copolymer of ethylene and vinyl acetate. Both Etonogestrel and Ethinyl Estradiol are homogeneously dispersed in EVA 28% reservoir core, and EVA 9% forms the rate controlling outer membrane.

Table 15. Physical Description Comparison between RLD and Amneal's Generic Product			
Parameters		**RLD (Nuvaring®)**	**Amneal's Generic Drug Product**
Description		Flexible, transparent, colorless to almost colorless rings	Flexible, transparent to translucent, colorless to almost colorless rings
Strength		0.120 mg/0.015 mg per day	0.120 mg/0.015 mg per day
Shape		Circular	Circular
Color		Transparent, Colorless to almost Colorless	Transparent to Translucent, Colorless to almost Colorless
Average Weight (mg)			(b) (4)
Ring Outer Diameter Range [N =10]			
Avg. Ring Cross Sectional Diameter [N =10]			
Surface Area (SA)			
Picture (Image)	Top View		(b) (4)
Packaging Configuration		Each NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) is individually packaged in a re-closable aluminum laminate sachet consisting of three layers, from outside to inside: polyester, aluminum foil, and low-density polyethylene.	(b) (4)

Comparison of the Test and Reference Product

Excipient	RLD (mg/ring)	Test (mg/ring)	Difference (%)*
Ethylene Vinylacetate Copolymer 28%	(b) (4)		-0.72
Magnesium Stearate			0.36
Ethylene Vinylacetate Copolymer 9%			-0.56

* Difference = [(Test – RLD) / RLD] * 100

4.2.2 Inactive Ingredients (IIG Table)

(b) (4)

*All excipients except magnesium stearate are present in higher amounts in the reference product than in the test product. The MDI amount shown is a conservative estimate, since drug is released at a continuous rate from a single ring over a period of 21 days and the ring is removed at the end of the dosing interval.

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☐ Yes ☐ No ☒ N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	☒ Yes ☐ No
If no, are they all within IIG (per day) limits?	☐ Yes ☐ No ☒ N/A
If no, are additional data or Pharm/Tox consult necessary?	☐ Yes ☐ No ☒ N/A
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)?	☐ Yes ☐ No ☒ N/A
Are all strengths of the test formulation acceptable?	☒ Yes ☐ No

Comments on Formulation:

The Q1/Q2 sameness of the test and reference products was confirmed in CC#42491.[18] The firm proposes to use the same formulation as that determined to be Q1/Q2 in the CC.

The test product formulation is **adequate**.

[18] GRDP; Project #42491, Q1Q2 Formulation Review (OGD # C13-0561), Primary Review, #42491.doc, 12/9/2014.

4.3 Dissolution Testing

4.3.1 Dissolution Data

Dissolution Conditions	**Apparatus:**	Innova® Incubator Shaker
	Speed of Rotation:	50 RPM
	Medium:	50 mM Acetate Buffer, pH 4.2
	Volume:	250 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site (Name, Address)		(b) (4)

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (Days) µg Dissolved, Etonogestrel											Study Report Location
						1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
469-ds	09/27/16	Etonogestrel/Ethinyl Estradiol Lot # PW-ST-16056A Mfg. Date: 07/27/2016	Vaginal Ring, 0.120 mg/0.015 mg	12	Mean	210	173	159	154	151	145	142	136	134	131	128	**Module 5.3.1.3**
					Range	(b) (4)											
					%CV	2.0	3.3	2.6	2.5	2.6	2.2	2.6	2.3	2.3	2.7	1.8	
						12	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**		
					Mean	129	123	122	120	117	116	115	113	112	111		
					Range	(b) (4)											
					%CV	2.0	2.8	2.1	1.5	2.2	2.1	1.8	2.5	2.1	1.9		

Dissolution Conditions	**Apparatus:**	Innova® Incubator Shaker
	Speed of Rotation:	50 RPM
	Medium:	50 mM Acetate Buffer, pH 4.2
	Volume:	250 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site (Name, Address)		(b) (4)

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (Days) µg Dissolved, Etonogestrel											Study Report Location
						1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
469-ds	09/27/16	Nuvaring® (Etonogestrel/Ethinyl Estradiol) Lot # M036725 Exp Date: 08/2019	Vaginal Ring, 0.120 mg/0.015 mg	12	Mean	211	169	159	155	149	143	141	135	123	132	128	**Module 5.3.1.3**
					Range	(b) (4)											
					%CV	1.0	1.3	2.7	2.8	1.1	1.4	1.4	1.3	1.5	1.0	1.9	
						12	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**		
					Mean	127	123	121	119	117	115	115	113	112	109		
					Range	(b) (4)											
					%CV	2.0	2.0	1.8	1.7	1.4	1.5	1.4	2.6	1.4	2.1		

Dissolution Conditions	**Apparatus:**	Innova® Incubator Shaker
	Speed of Rotation:	50 RPM
	Medium:	50 mM Acetate Buffer, pH 4.2
	Volume:	250 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site (Name, Address)		(b) (4)

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (Days) µg Dissolved, Ethinyl Estradiol**											**Study Report Location**
469-ds	09/27/16	Etonogestrel/Ethinyl Estradiol Lot # PW-ST-16056A Mfg. Date: 07/27/2016	Vaginal Ring, 0.120 mg/0.015 mg	12		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Module 5.3.1.3**
					Mean	25	19	18	18	17	17	17	16	16	16	16	
					Range	(b) (4)											
					%CV	2.1	4.2	3.5	2.9	3.4	2.9	3.9	3.2	2.8	3.1	3.2	
						12	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**		
					Mean	16	15	15	15	15	15	15	14	14	14		
					Range	(b) (4)											
					%CV	2.8	3.8	2.8	1.9	2.6	3.5	3.5	4.7	2.1	3.5		

Dissolution Conditions	**Apparatus:**	Innova® Incubator Shaker
	Speed of Rotation:	50 RPM
	Medium:	50 mM Acetate Buffer, pH 4.2
	Volume:	250 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site (Name, Address)		(b) (4)

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (Days) µg Dissolved, Ethinyl Estradiol**											**Study Report Location**
						1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
469-ds	09/27/16	Nuvaring® (Etonogestrel/Ethinyl Estradiol) Lot # M036725 Exp Date: 08/2019	Vaginal Ring, 0.120 mg/0.015 mg	12	Mean	26	20	19	19	18	18	18	17	15	17	16	**Module 5.3.1.3**
					Range	(b) (4)											
					%CV	1.9	2.3	3.0	3.5	0.0	2.5	2.9	0.0	2.6	2.3	3.1	
						12	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**		
					Mean	17	16	16	16	16	15	15	15	15	14		
					Range	(b) (4)											
					%CV	3.1	2.7	3.1	1.8	3.3	1.9	2.6	3.4	0.0	3.2		

Dissolution Conditions	**Apparatus:**	Innova® Incubator Shaker
	Speed of Rotation:	50 RPM
	Medium:	50 mM (b) (4) pH 4.2
	Volume:	250 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	(b) (4)	
Dissolution Testing Site (Name, Address)	(b) (4)	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (Days) µg Dissolved, Etonogestrel**											**Study Report Location**
						1	2	3	4	5	6	7	8	9	10	11	
469-ds	11/02/16	Etonogestrel/Ethinyl Estradiol Lot # PW-ST-16056A Mfg. Date: 07/27/2016	Vaginal Ring, 0.120 mg/0.015 mg	12	Mean	(b) (4)											**Module 5.3.1.3**
					Range												
					%CV												
					Mean												
					Range												
					%CV												

Dissolution Conditions	**Apparatus:**	Innova® Incubator Shaker
	Speed of Rotation:	50 RPM
	Medium:	50 mM (b) (4) pH 4.2
	Volume:	250 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	(b) (4)	
Dissolution Testing Site (Name, Address)	(b) (4)	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (Days) µg Dissolved, Etonogestrel**											**Study Report Location**
						1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
469-ds	11/02/16	Nuvaring® (Etonogestrel/Ethinyl Estradiol) Lot # M036725 Exp Date: 08/2019	Vaginal Ring, 0.120 mg/0.015 mg	12	Mean	(b) (4)											**Module 5.3.1.3**
					Range												
					%CV												
					Mean												
					Range												
					%CV												

Dissolution Conditions	**Apparatus:**	Innova® Incubator Shaker
	Speed of Rotation:	50 RPM
	Medium:	50 mM (b) (4)
	Volume:	250 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site (Name, Address)		(b) (4)

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (Days) µg Dissolved, Ethinyl Estradiol**											**Study Report Location**
						1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
469-ds	11/02/16	Etonogestrel/Ethinyl Estradiol Lot # PW-ST-16056A Mfg. Date: 07/27/2016	Vaginal Ring, 0.120 mg/0.015 mg	12	Mean	(b) (4)											**Module 5.3.1.3**
					Range												
					%CV												
					Mean												
					Range												
					%CV												

Dissolution Conditions	**Apparatus:**	Innova® Incubator Shaker
	Speed of Rotation:	50 RPM
	Medium:	50 mM (b) (4)
	Volume:	250 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	(b) (4)	
Dissolution Testing Site (Name, Address)	(b) (4)	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (Days) µg Dissolved, Ethinyl Estradiol**										**Study Report Location**
						1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
469-ds	11/02/16	Nuvaring® (Etonogestrel/Ethinyl Estradiol) Lot # M036725 Exp Date: 08/2019	Vaginal Ring, 0.120 mg/0.015 mg	12	(b) (4)												**Module 5.3.1.3**

Dissolution Conditions	**Apparatus:**	Innova® Incubator Shaker
	Speed of Rotation:	50 RPM
	Medium:	(b) (4)
	Volume:	250 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site (Name, Address)		(b) (4)

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (Days) µg Dissolved, Etonogestrel**											**Study Report Location**
						1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
469-ds	11/02/16	Etonogestrel/Ethinyl Estradiol Lot # PW-ST-16056A Mfg. Date: 04/04/2016	Vaginal Ring, 0.120 mg/0.015 mg	12	Mean	(b) (4)											**Module 5.3.1.3**
					Range												
					%CV												
					Mean												
					Range												
					%CV												

Dissolution Conditions	**Apparatus:**	Innova® Incubator Shaker
	Speed of Rotation:	50 RPM
	Medium:	(b) (4)
	Volume:	250 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site (Name, Address)		(b) (4)

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (Days) µg Dissolved, Etonogestrel**											**Study Report Location**
						1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
469-ds	11/02/16	Nuvaring® (Etonogestrel/Ethinyl Estradiol) Lot # M036725 Exp Date: 08/2019	Vaginal Ring, 0.120 mg/0.015 mg	12	Mean	(b) (4)											**Module 5.3.1.3**
					Range												
					%CV												
					Mean												
					Range												
					%CV												

Dissolution Conditions	**Apparatus:**	Innova® Incubator Shaker
	Speed of Rotation:	50 RPM
	Medium:	(b) (4)
	Volume:	250 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site (Name, Address)		(b) (4)

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (Days) µg Dissolved, Ethinyl Estradiol**											**Study Report Location**
						1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
469-ds	11/02/16	Etonogestrel/Ethinyl Estradiol Lot # PW-ST-16056A Mfg. Date: 04/04/2016	Vaginal Ring, 0.120 mg/0.015 mg	12	Mean	(b) (4)											**Module 5.3.1.3**
					Range												
					%CV												
					Mean												
					Range												
					%CV												

Dissolution Conditions	**Apparatus:**	Innova® Incubator Shaker
	Speed of Rotation:	50 RPM
	Medium:	(b) (4)
	Volume:	250 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications		(b) (4)
Dissolution Testing Site (Name, Address)		(b) (4)

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (Days) µg Dissolved, Ethinyl Estradiol											Study Report Location
						1	2	3	4	5	6	7	8	9	10	11	
469-ds	11/02/16	Nuvaring® (Etonogestrel/Ethinyl Estradiol) Lot # M036725 Exp Date: 08/2019	Vaginal Ring, 0.120 mg/0.015 mg	12	Mean	(b) (4)											Module 5.3.1.3
					Range												
					%CV												
					Mean												
					Range												
					%CV												

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(b) (4)

(b) (4)

(b) (4)

Please comment on whether dissolution data are adequate to support requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).	N/A

Overall Comments:

There are no waiver requests in the current application. The dissolution data are adequate from BE standpoint.

The dissolution data will be reviewed separately.

4.4 Attachments

4.4.1 SAS Output

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Ethinyl Estradiol	FastingCONCethinylestradiol_reviewer.xlsx	210830 EE calcke.sas	210830_FASTING_stat_Ethinyl EstradiolACTU	210830_FASTING_table_Ethinyl EstradiolACT FIRMREVIEWERRATIOFASTING.RTF REVIEWERPKFASTING.RTF
Etonogestrel	FastingCONCetonogestrel_reviewer.xlsx	210830 ETO calcke.sas	210830_FASTING_stat_EtonogestrelACTUAL	210830_FASTING_table_EtonogestrelACTUA FIRMREVIEWERRATIOFASTING.RTF REVIEWERPKFASTING.RTF

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 210830

APPLICANT: Amneal Pharmaceuticals LLC

DRUG PRODUCT: Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day

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

Please be advised of the following for any future studies:

As per your study protocol, samples from each subject for all time periods were to be assayed at the same time. Because the analytical method for quantification of ethinyl estradiol and etonogestrel was about 12.5 minutes, multiple periods of each subject were not run together. However, multiple subjects of the same period were analyzed at one time (e.g. period I of subjects (b) (6) were run in a single batch). Please be advised for future studies to analyze all study samples from a subject in a single run in accordance with recommendations in the Guidance for Industry: Bioanalytical Method Validation (Sept. 2013).

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

Sincerely yours,

Ethan M. Stier, Ph.D., R. Ph.
Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

Completed Assignment for 210830 ID: 33390

Reviewer: Vivian, Diana **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day, Amneal

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Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
33390	8/25/2017	BIO	ANDA Original [1]	1	1
33390	8/25/2017	Parallel	Fasting Study (Full template) [1]	1	1
33390	8/25/2017	Parallel	Fasting Study (Full Template - Additional Analyte) [0.25]	0.25	0.25
				Total:	2.25

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210830

BIOPHARMACEUTICAL REVIEWS

BIOPHARMACEUTICS REVIEW for ANDA SUBMISSIONS	
Application No.	ANDA 210830-ORIG-1-AMEND-16
Product Name	Etonogestrel/Ethinyl Estradiol
Applicant	Amneal Pharmaceuticals
Dosage Form/Strengths	Vaginal Ring delivers 0.120 mg/0.015 mg per day
Route of Administration	Vaginal ring
Indication for Use	For use by women to prevent pregnancy
Submission Date	5/17/2019
Review Date	7/26/2019
Primary Reviewer	Hansong Chen, PharmD., Ph.D.
Secondary Reviewer	Vidula Kolhatkar, Ph.D.
Recommendation	**Adequate**

REVIEW SUMMARY:

Background:
The Reference Listed Drug NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) delivers 0.120 mg/0.015 mg per day, developed by Organon USA Inc., was approved by the FDA under NDA 021187 on 10/03/2001.
Amneal Pharmaceuticals proposed the generic version of NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) delivers 0.120 mg/0.015 mg per day and submitted this new ANDA to the Office of Generic Drugs on 8/25/2017.

On 6/22/2018, the Agency issued a Complete Response (CR) letter to ANDA 210830. On 10/19/2018, the Applicant resubmitted ANDA 210830-ORIG-1-AMEND-12 to the Agency. However, another CR was issued to this ANDA amendment on 4/12/2019. On 5/17/2019, the Applicant again submitted ANDA 210830-ORIG-1-AMEND-16 to the Agency.

Submission:
In the resubmission, the Applicant provided the response to the Biopharmaceutics deficiency.

Review's Objective:
Biopharmaceutics review focuses on the Applicant's response to the Biopharmaceutics deficiency in the CR letter.

Reviewer's Assessment:
The Applicant developed their own in-house method to conduct in vitro dissolution tests. The IVR method has been reviewed and was found acceptable during the 1st review cycle. However,

the originally proposed acceptance criteria were not appropriate based on the data submitted. Per our current thinking and understanding for vaginal rings, we recommend the following acceptance criteria for the proposed drug product:

Etonogestrel	Ethinyl Estradiol
	(b) (4)

In this amendment, the Applicant stated that they accepted the recommended IVR acceptance criteria except the Day 21 criteria for Ethinyl Estradiol, for which they proposed to keep the recommended criteria range unchanged but move both lower and upper limits up by 0.6 µg/day. The newly proposed Day 21 criteria for Ethinyl Estradiol have been reviewed and were found acceptable.

Overall, the following IVR method and acceptance criteria have been approved:

Method Source	USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Sampling Times	Acceptance criteria
In-house method	Innova® Incubator shaker with ring holder	50	50 mM acetate buffer, pH 4.2	250 mL	Once every 24 hours for 21 days	(b) (4)

Reviewer's Assessment:

From the Biopharmaceutics perspective, this Reviewer recommends that ANDA 210830-ORIG-1-AMEND-16 for Etonogestrel/Ethinyl Estradiol, Vaginal Ring, delivering 0.120 mg/0.015 mg per day is ADEQUATE for approval.

1. REVIEW:

a) List Submissions being reviewed (table):

8/25/2017	ANDA 210830/Original submission
11/29/2017	eCTD-0005/Response to Biopharmaceutics Information Requests
4/6/2018	eCTD-0010/Response to Biopharmaceutics Information Requests
10/19/2018	eCTD-0012/ANDA 210830 resubmission
5/17/2019	eCTD-0012/ANDA 210830 2nd resubmission

b) Highlight Key Outstanding Issues from Last Review Cycle:

- The Applicant should accept the recommended IVR acceptance criteria.

c) Concise Description of Outstanding Issues:

- None.

d) IVR method and acceptance criteria proposed by the Applicant during this review cycle:

Method Source	USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Sampling Times	Acceptance criteria
In-house method	Innova® Incubator shaker with ring holder	50	50 mM acetate buffer, pH 4.2	250 mL	Once every 24 hours for 21 days	(b) (4)

e) Biopharmaceutics deficiency in the CR letter and the Applicant's response

On 4/12/2019, FDA issued the second CR letter to ANDA 210830-ORIG-1-AMEND-12. On 5/17/2019, the Applicant resubmitted ANDA 210830-ORIG-1-AMEND-16 to the Agency to address the deficiencies. The following are the Biopharmaceutics deficiency, the Applicant's Response, and Reviewer's assessment.

Biopharmaceutics Deficiency

Per our current thinking and understanding for vaginal rings, we recommend you consider the following IVR acceptance criteria for the proposed drug product:

(b) (4)

We request that you acknowledge your acceptance of the recommended IVR acceptance criteria for your drug product and update the drug product specifications accordingly.

The response to the CR letter showed that you have stability data for Day 14 for all exhibit batches. Please submit all available individual unit stability data for Day 5 and Day 14 to the Agency for review. In addition, please be advised that all proposed exhibit batches are expected to meet this revised IVR acceptance criteria in your stability program through your proposed expiry period.

The Applicant's response to the Biopharmaceutics Deficiency

The Applicant stated that they accepted the recommended IVR acceptance criteria except the Day 21 criteria for Ethinyl Estradiol, for which they proposed to keep the recommended criteria range unchanged but move both lower and upper limits up by 0.6 µg/day. The detailed justification for the newly proposed Day 21 criteria for Ethinyl Estradiol can be located by clicking the link below:
\\cdsesub1\evsprod\anda210830\0016\m1\us\1-2-cover-letter-esigned-seq-0016-20190517.pdf

(b) (4)

(b) (4)

[redacted]

The Applicant reported that all the stability data meet the Agency's recommended IVR acceptance criteria except that Day 21 Ethinyl Estradiol release of batch #PW-ST-16055A and #PW-ST-16056A at 9 months and 12 months is slightly higher than the upper limit of the Agency's recommended acceptance criteria. But they can meet the newly proposed Day 21 criteria for Ethinyl Estradiol.

(b) (4)

Sample	[redacted]
9 Month Refrigerated, Batch #PW-ST-16055A	
9 Month Refrigerated, Batch #PW-ST-16056A	
12 Month Refrigerated, Batch #PW-ST-16055A	
12 Month Refrigerated, Batch #PW-ST-16056A	

The Applicant emphasized that they submitted all available individual unit stability data for Day 5 and Day 14 in this Amendment. However, some IVR data at Day 5 and Day 14 are not available for all stability time points because the IVR acceptance criteria have evolved since the submission of this ANDA.

Reviewer's assessment

The newly proposed Day 21 criteria for Ethinyl Estradiol are acceptable due to the following reasons:

- *The proposed vaginal ring is indicated for 3 weeks' use. Day 21 is the last day before the ring is removed and a new ring is inserted in a week.*
- *Moving both lower and upper limits up by 0.6 µg/day still ensures that the ring has expected in vitro release and this is unlikely to have negative clinical impact.*

2. LIST OF BIOPHARMACEUTICS COMMENTS:

None.

CONCLUSION and RECOMMENDATION:

Approved IVR method and acceptance criteria

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
Innova® Incubator shaker with ring holder	50	50 mM acetate buffer, pH 4.2 37 ± 0.5 °C	250 mL	(b) (4)

SIGNATURE BLOCK:

Primary Biopharmaceutics Reviewer:

Name and Date

Hansong Chen, Pharm.D., Ph.D.

Secondary Biopharmaceutics Reviewer

Name and Date

Vidula Kolhatkar, Ph.D.

Hansong Chen

Digitally signed by Hansong Chen
Date: 11/08/2019 09:51:40AM
GUID: 525d7d660003845a197a2e1682433d0d

Vidula Kolhatkar

Digitally signed by Vidula Kolhatkar
Date: 11/08/2019 09:55:28AM
GUID: 5424aeae00c3274f93e50573f7ca407e

BIOPHARMACEUTICS REVIEW for ANDA SUBMISSIONS	
Application No.	ANDA 210830-ORIG-1-AMEND-12
Product Name	Etonogestrel/Ethinyl Estradiol
Applicant	Amneal Pharmaceuticals
Dosage Form/Strengths	Vaginal Ring delivers 0.120 mg/0.015 mg per day
Route of Administration	Vaginal ring
Indication for Use	For use by women to prevent pregnancy
Submission Date	10/19/2018
Review Date	3/7/2019
Primary Reviewer	Hansong Chen, PharmD., Ph.D.
Secondary Reviewer	Vidula Kolhatkar, Ph.D.
Recommendation	**Inadequate**

REVIEW SUMMARY:

Background:
The Reference Listed Drug NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) delivers 0.120 mg/0.015 mg per day, developed by Organon USA Inc., was approved by the FDA under NDA 021187 on 10/03/2001.
Amneal Pharmaceuticals proposed the generic version of NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) delivers 0.120 mg/0.015 mg per day and submitted this new ANDA to the Office of Generic Drugs on 8/25/2017.

On 6/22/2018, the Agency issued a Complete Response (CR) letter to ANDA 210830. The biopharmaceutics deficiency in the CR letter is included under "Highlight Key Outstanding Issues from Last Cycle". On 10/19/2018, the Applicant resubmitted ANDA 210830 to the Agency.

Submission:
In the resubmission, the Applicant provided the response to the Biopharmaceutics deficiency.

Review's Objective:
Biopharmaceutics review focuses on the Applicant's response to the Biopharmaceutics deficiency in the CR letter and In Vitro Release (IVR) acceptance criteria.

Reviewer's Assessment:
The Applicant developed their own in-house method to conduct in vitro dissolution tests. The IVR method has been reviewed and was found acceptable. However, the proposed acceptance

criteria were not appropriate based on the data submitted. Per our current thinking and understanding for vaginal rings, we recommend the acceptance criteria for the proposed drug product:

(b) (4)

Reviewer's Assessment:

From the Biopharmaceutics perspective, this Reviewer recommends that ANDA 210830-ORIG-1-AMEND-12 for Etonogestrel/Ethinyl Estradiol, Vaginal Ring, delivers 0.120 mg/0.015 mg per day is INADEQUATE for approval at this stage.

1. REVIEW:

a) List Submissions being reviewed (table):

8/25/2017	ANDA 210830/Original submission
11/29/2017	eCTD-0005/Response to Biopharmaceutics Information Requests
4/6/2018	eCTD-0010/Response to Biopharmaceutics Information Requests
10/19/2018	eCTD-0012/ANDA 210830 resubmission

b) Highlight Key Outstanding Issues from Last Review Cycle:

- (b) (4)

c) Concise Description of Outstanding Issues:

- The Applicant should accept the in vitro release acceptance criteria as recommended.

d) IVR method and acceptance criteria proposed by the Applicant during the last cycle:

Method Source	USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Sampling Times	Acceptance criteria
In-house method	Innova® Incubator shaker with ring holder	50	50 mM acetate buffer, pH 4.2	250 mL	Once every 24 hours for 21 days	(b) (4)

e) Biopharmaceutics deficiency in the CR letter and the Applicant's response

On 6/22/2018, the FDA issued a CR letter to ANDA 210830. On 10/19/2018, the Applicant resubmitted ANDA 210830 to the Agency to address these deficiencies. The following are the Biopharmaceutics deficiency, the Applicant's Response, and Reviewer's assessment.

Biopharmaceutics Deficiency

(b) (4)

The Applicant's response to the Biopharmaceutics Deficiency

The Applicant stated that they acknowledged the Agency's comment. As requested by the Agency, the in vitro release data obtained for the stability batches is being submitted in **Module 5.3.1.3** of this amendment. The data includes individual, mean, SD, profiles for in vitro release data for all stability batches.

Reviewer's assessment

The Applicant provided the stability data up to 24 months for all three exhibit batches.

IVR acceptance criteria

Per our current thinking and understanding for vaginal rings, we will recommend different acceptance criteria for this proposed drug product. The Acceptance criteria for Day 1 and Day 21 will be set with a range of in vitro drug release instead of NLT or equal to on Day 1 and NMT and equal to on Day 21. For the middle time points, the acceptance criteria will be set as a range of in vitro drug release during a single day instead of several days.

After further analyzing the IVR data of the biobatch, the drug release of the proposed drug product has the following stages: burst release, transition stage, and steady state stage. The early stage includes Day 1 and Day 2, in which the drug starts to be released from the vaginal ring and IVR variability is relatively high. The transition stage includes Day 3 to Day 7, in which the drug release starts to stabilize. The last stage is the steady state stage including from Day 13 to Day 20, in which the drug release is stable and linear.

Day 5 is selected as the second time point, which represents the transition stage. The acceptance criterion is set using mean±3SD principle. Similarly, Day 14 is selected as the third time point,

which represents the steady state stage. Based on the IVR data obtained, the acceptance criterion for Day 14 is set using the same principle. The same principle applies to the acceptance criteria of Day 1 and Day 21 as well. Overall, considering data obtained for the biobatch and exhibit lots and current understanding of the product we recommend the following acceptance criteria:

(b) (4)

Based on the release data of three exhibit batches, Batch 16056A and Batch 16055A are able to meet the above acceptance criteria at Stage 1, and Batch 16052A can meet them at Stage 1 or 2.

2. LIST OF BIOPHARMACEUTICS COMMENTS:

See Appendix for details.

CONCLUSION and RECOMMENDATION:

Final IVR method and acceptance criteria

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
Innova® Incubator shaker with ring holder	50	50 mM acetate buffer, pH 4.2 37 ± 0.5 °C	250 mL	(b) (4)

				(b) (4)

SIGNATURE BLOCK:

Primary Biopharmaceutics Reviewer:

Name and Date

Hansong Chen, PharmD., Ph.D.

Secondary Biopharmaceutics Reviewer

Name and Date

Vidula Kolhatkar, Ph.D.

APPENDIX

Biopharmaceutics Information Requests and Applicant Responses

The following information needs to be conveyed to the Applicant in the CR letter:

Per our current thinking and understanding for vaginal rings, we recommend you consider the following IVR acceptance criteria for the proposed drug product:

(b) (4)

We request that you acknowledge your acceptance of the recommended IVR acceptance criteria for your drug product and update the drug product specifications accordingly.

The response to the CR letter showed that you have stability data for Day 14 for all exhibit batches. Please submit all available individual unit stability data for Day 5 and Day 14 to the Agency for review. In addition, please be advised that all proposed exhibit batches are expected to meet this revised IVR acceptance criteria in your stability program through your proposed expiry period.

Hansong Chen

Digitally signed by Hansong Chen
Date: 3/27/2019 11:11:59AM
GUID: 525d7d660003845a197a2e1682433d0d

Vidula Kolhatkar

Digitally signed by Vidula Kolhatkar
Date: 3/27/2019 11:19:10AM
GUID: 5424aeae00c3274f93e50573f7ca407e

BIOPHARMACEUTICS REVIEW for ANDA SUBMISSIONS	
Application No.	ANDA 210830
Product Name	Etonogestrel/Ethinyl Estradiol
Applicant	Amneal Pharmaceuticals
Dosage Form/Strengths	Vaginal Ring, delivers 0.120 mg/0.015 mg per day
Route of Administration	Vaginal ring
Indication for Use	For use by women to prevent pregnancy
Submission Date	8/25/2017
Review Date	1/5/2018, 5/3/2018
Primary Reviewer	Hansong Chen, PharmD., Ph.D.
Secondary Reviewer	Vidula Kolhatkar, Ph.D.
Recommendation	**Inadequate**

REVIEW SUMMARY:

Background:
The Reference Listed Drug NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) delivers 0.120 mg/0.015 mg per day, developed by Organon USA Inc., was approved by the FDA under NDA 021187 on 10/03/2001.

Submission:
Amneal Pharmaceuticals proposed the generic version of NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) delivers 0.120 mg/0.015 mg per day, and submitted this new ANDA to the Office of Generic Drugs on 8/25/2017.

Review's Objective:
Biopharmaceutics review focuses on the dissolution method and acceptance criteria.

Reviewer's Assessment:
The Applicant developed their own in-house method to conduct in vitro dissolution tests. The dissolution method has been reviewed and was found acceptable. However, the proposed specifications were not appropriate based on the data submitted. The applicant accepted the Agency recommend acceptance criteria for Day 1 and Day 21 but proposed wider acceptance criteria for Day 8-14. The following represents the Applicant's proposed acceptance criteria:

(b) (4)

(b) (4)

The Applicant should provide additional information to justify their proposed acceptance criteria.

In addition, the Applicant was asked to clarify if the all five batches manufactured for the discriminatory power study (b) (4) formulation of the five batches. The Applicant was also requested to clarify if they have manufactured any commercial batches. In the response to the Biopharmaceutics Information Request, the Applicant fully addressed these issues.

From the Biopharmaceutics perspective, this Reviewer recommends that ANDA 210830 for Etonogestrel/Ethinyl Estradiol, Vaginal Ring, delivers 0.120 mg/0.015 mg per day is INADEQUATE for approval at this stage.

The following information needs to be conveyed to the Applicant in the CR letter:

(b) (4)

1. SUBMISSION CONTENT CHECKLIST:

	INFORMATION	YES	NO	N/A
1	Is there a USP dissolution method?	☐	☒	☐
2	Did the Applicant use the USP dissolution method?	☐	☐	☒
3	Is there an FDA-Database dissolution method?	☐	☒	☐
4	Did the Applicant use the FDA-Database dissolution method?	☐	☐	☒
5	Did the Applicant conduct dissolution testing with a proposed in-house dissolution method?	☒	☐	☐
6	Did the Applicant use 12 individual units of the test (proposed) drug product in the dissolution testing?	☒	☐	☐
7	Did the Applicant provide complete dissolution data for the test (proposed) drug product (all raw data, range, mean, % CV, date of dissolution testing)?	☒	☐	☐
8	Was the dissolution/release testing and pivotal bioequivalence study conducted using test drug product within the proposed expiry period?	☒	☐	☐
9	Does the proposed product (any strength) have a functional scoring?	☐	☒	☐
10	If there is a functional scoring, did the Applicant provide complete dissolution data for the whole vs. split tablets?	☐	☐	☒
11	Is there significant change in the dissolution of stability samples?	☐	☒	☐

2. REVIEW:

a) List Submissions being reviewed (table):

8/25/2017	ANDA 210830/Original submission
11/29/2017	eCTD-0005/Response to Biopharmaceutics Information Requests
4/6/2018	eCTD-0010/Response to Biopharmaceutics Information Requests

b) Highlight Key Outstanding Issues from Last Review Cycle:

- The Applicant should clarify if the all five batches manufactured for the discriminatory power have the same (b) (4)
- The Applicant should tighten the dissolution specifications.
- The Applicant should clarify if they have manufactured any commercial batches.

c) Concise Description of Outstanding Issues:

- Additional information is needed to support applicant's proposed acceptance criteria

d) Dissolution method and acceptance criterion/criteria proposed by the Applicant:

Method Source	USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Sampling Times	Acceptance criterion/criteria
In-house method	Innova® Incubator shaker with ring holder	50	50 mM acetate buffer, pH 4.2	250 mL	Once every 24 hours for 21 days	(b) (4)

e) In Vitro Dissolution Data

Table 1. Summary of mean in vitro Etonogestrel dissolution data of the proposed drug product and RLD

Batch number /Time points (h)	Day 1 µg/day	Days 2-9 µg/day	Day 10-20 µg/day	Day 21 µg/day
RLD Batch M036725	(b) (4)			
Test Product Batch 16056A*				
Test Product Batch 16052A				
Test Product Batch 16055A				

* Bioequivalence study was conducted on Batch PW-ST-16056A

Table 2. Summary of mean in vitro Ethinyl Estradiol dissolution data of the proposed drug product and RLD

Batch number /Time points (h)	Day 1 µg/day	Days2-9 µg/day	Day 10-20 µg/day	Day 21 µg/day
RLD Batch M036725	(b) (4)			
Test Product Batch PW-ST-16056A				
Test Product Batch PW-ST-16052A				
Test Product Batch PW-ST-16055A				

Bioequivalence study was conducted on Batch PW-ST-16056A.

Refer to Appendix 1 for the tables of detailed dissolution data.

Figure 1. Etonogestrel dissolution profile comparison of the proposed drug products and RLD

(b) (4)

Figure 2. Ethinyl Estradiol dissolution profile comparison of the proposed drug products and RLD

f) Additional information contained within the submission supporting the proposed dissolution method and acceptance criteria? (i.e. clinical relevance, QbD, etc.)

The Applicant did not conduct any additional studies to demonstrate if the dissolution method and acceptance criteria are clinically relevant.

The Applicant used QbD approach to conduct risk assessment for formulation variables and manufacturing process variables.

The Applicant conducted a 2^3 two-level, full factorial design with two center points DoE study to investigate if the changes in skin processing temperature, water bath temperature, and air gap have an impact on dissolution of the final finished product. The results show that none of them have significant impact on dissolution of Etonogestrel and Ethinyl Estradiol within the studied range. The following ranges are established for exhibit batches:
Skin processing temperature: 135°C (130°C - 140°C)
Airgap: 50mm (40mm – 60 mm)
Water bath temperature: 30°C (28°C - 32°C)

3. REVIEWER'S ASSESSMENT:

Dissolution Method: *The Applicant developed their in-house method to conduct in vitro dissolution method. The dissolution method has been reviewed and was found acceptable. See the details in Appendix II.*

Dissolution Acceptance Criteria: *The Applicant proposed the following dissolution specifications:*

(b) (4)

The Applicant just simply adopted the specifications set for the RLD product for their proposed product. The dissolution data provided show that the proposed specifications are not appropriate. This Reviewer used mean±2SD to set the following specifications and requested the Applicant to accept them. All three batches of test product are able to meet these specifications at Stage 1 or Stage 2.

(b) (4)

It should be noted that for Days 8-14, daily release rate should be used to determine if it meets the above specifications. Acceptance Table 1 of USP <724> should be used to determine whether the acceptance criteria are met at different stages.

In the response to Biopharmaceutics IR, the Applicant proposed slightly different dissolution specifications based on the FDA's recommendations, which was reviewed. Additional information is needed to support these wider acceptance criteria.

Other:

4. LIST OF BIOPHARMACEUTICS COMMENTS:

Additional information is needed to support applicant's proposed acceptance criteria. Refer to Appendix 2 deficiency comments.

CONCLUSION and RECOMMENDATION:

Applicant's proposed dissolution method and acceptance criterion/criteria (acceptance criteria to be finalized after response to deficiency comments)

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criterion (a)
Innova® Incubator shaker with ring holder	50	50 mM acetate buffer, pH 4.2 37 ± 0.5 °C	250 mL	(b) (4)

SIGNATURE BLOCK:

Primary Biopharmaceutics Reviewer:

Name and Date

Hansong Chen, PharmD., Ph.D., 1/10/2018, 1/31/2018, 5/3/2018

Secondary Biopharmaceutics Reviewer

Name and Date

Vidula Kolhatkar, Ph.D., 1/5/2017

APPENDIX 1

Dissolution Data Tables

Dissolution data of test products and RLD

Etonogestrel
RLD Batch M036725

Table 1. Summary of In-Vitro Dissolution – NuvaRing® (Etonogestrel)																						
Product Name: Nuvaring **Lot #** M036725				**Expiry Date:** 08/2019 **Analysis Date** :9/27/2016						**Method** # 469-DS **Apparatus:** Innova® Incubator Shaker **Medium:** 50 mM Acetate buffer, pH 4.2						**Volume:** 250 mL **Speed:** 50 rpm, **Temperature:** 37°C ± 0.5°C						
Unit #	µg Dissolved (ETO)																					
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**Mean***
1	(b) (4)																					
2																						
3																						
4																						
5																						
6																						
7																						
8																						
9																						
10																						
11																						
12																						
Mean	211	169	159	155	149	143	141	135	123	132	128	127	123	121	119	117	115	115	113	112	109	130
Min	(b) (4)																					
Max																						
%RSD	1.0	1.3	2.7	2.8	1.0	1.4	1.4	1.3	1.5	1.0	1.9	2.0	2.0	1.8	1.7	1.4	1.5	1.4	2.6	1.4	2.1	0.9
Reference: Book/Page # KR1540/92																						

Test Product PW-ST-16056A

Table 3. Summary of In-Vitro Dissolution – Amneal's Etonogestrel/Ethinyl Estradiol Vaginal Ring (Etonogestrel)																						
Product Name: Amneal's Etonogestrel/ Ethinyl Estradiol Vaginal Ring **Lot #** PW-ST-16056A							**Mfg Date:** 07/27/2016 **Analysis Date** :9/27/2016					**Method #** 469-DS **Apparatus:** Innova® Incubator Shaker **Medium:** 50 mM Acetate buffer, pH 4.2							**Volume:** 250 mL **Speed:** 50 rpm, **Temperature:** 37°C ± 0.5°C			
Unit #	µg Dissolved (ETO)																					
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**Mean***
1	(b) (4)																					
2																						
3																						
4																						
5																						
6																						
7																						
8																						
9																						
10																						
11																						
12																						
Mean	210	173	159	154	151	145	142	136	134	131	128	129	123	122	120	117	116	115	113	112	111	131
Min	(b) (4)																					
Max																						
%RSD	2.0	3.3	2.6	2.5	2.6	2.2	2.6	2.3	2.3	2.7	1.8	2.0	2.8	2.1	1.5	2.2	2.1	1.8	2.5	2.1	1.9	1.9
Reference: Book/Page # KR1540/86																						

*Mean (Day 2- day 21)

Test Product PW-ST-16052A

Table 1. Summary of In-Vitro Dissolution – Amneal's Etonogestrel/Ethinyl Estradiol Vaginal Ring (Etonogestrel)																						
Product Name: Amneal's Etonogestrel/ Ethinyl Estradiol Vaginal Ring **Lot #** PW-ST-16052A							**Mfg Date:** 07/14/2016 **Analysis Date** :9/27/2016					**Method #** 469-DS **Apparatus:** Innova® Incubator Shaker **Medium:** 50 mM Acetate buffer, pH 4.2							**Volume:** 250 mL **Speed:** 50 rpm **Temperature:** 37°C ± 0.5°C			
Unit #	µg Dissolved (ETO)																					
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	***Mean**
1	(b) (4)																					
2																						
3																						
4																						
5																						
6																						
7																						
8																						
9																						
10																						
11																						
12																						
Mean	192	156	146	143	139	135	132	126	133	123	119	119	116	114	113	110	109	107	106	106	103	123
Min	(b) (4)																					
Max																						
%RSD	1.9	3.9	3.7	2.0	2.5	3.3	2.5	2.0	2.1	2.8	2.6	1.9	2.2	3.4	3.0	2.6	2.2	2.3	2.5	2.2	1.7	2.1
Reference: Book/Page # KR1540/139																						

* Mean (Day 2- day 21)

Test Product PW-ST-16055A

Table 3. Summary of In-Vitro Dissolution – Amneal's Etonogestrel/Ethinyl Estradiol Vaginal Ring (Etonogestrel)																						
Product Name: Amneal's Etonogestrel/ Ethinyl Estradiol Vaginal Ring **Lot #** PW-ST-16055A					**Mfg Date:** 07/21/2016 **Analysis Date :**9/27/2016						**Method #** 469-DS **Apparatus:** Innova® Incubator Shaker **Medium:** 50 mM Acetate buffer, pH 4.2						**Volume:** 250 mL **Speed:** 50 rpm **Temperature:** 37°C ± 0.5°C						
Unit #	**µg Dissolved (ETO)**																					
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	***Mean**
1	(b) (4)																					
2																						
3																						
4																						
5																						
6																						
7																						
8																						
9																						
10																						
11																						
12																						
Mean	208	168	156	152	148	142	140	136	132	130	127	127	123	120	118	116	115	113	111	111	108	130
Min	(b) (4)																					
Max																						
%RSD	1.3	1.2	1.9	1.8	1.4	2.0	1.5	1.0	2.3	2.0	1.9	1.4	2.0	2.0	1.7	1.4	1.3	1.4	1.9	2.1	1.1	1.1
Reference: Book/Page # KR1540/141																						

* Mean (Day 2- day 21)

Ethinyl Estradiol
RLD Batch M036725

Table 2. Summary of In-Vitro Dissolution – NuvaRing® (Ethinyl Estradiol)																						
Product Name: Nuvaring **Lot #** M036725					**Expiry Date:** 08/2019 **Analysis Date:** 9/27/2016						**Method #** 469-DS **Apparatus:** Innova® Incubator Shaker **Medium:** 50 mM Acetate buffer, pH 4.2						**Volume:** 250 mL **Speed:** 50 rpm, **Temperature:** 37°C ± 0.5°C						
Unit #	**µg Dissolved (EE)**																					
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**Mean***
1	(b) (4)																					
2																						
3																						
4																						
5																						
6																						
7																						
8																						
9																						
10																						
11																						
12																						
Mean	26	20	19	19	18	18	18	17	15	17	16	17	16	16	16	16	15	15	15	15	14	17
Min	(b) (4)																					
Max																						
%RSD	1.9	2.3	3.0	3.5	0.0	2.5	2.9	0.0	2.6	2.3	3.1	3.1	2.7	3.1	1.8	3.3	1.9	2.6	3.4	0.0	3.2	1.0
Reference: Book/Page # KR1540/93																						

*Mean (Day 2- day 21)

Test Product PW-ST-16056A

Table 4. Summary of In-Vitro Dissolution – Amneal's Etonogestrel/Ethinyl Estradiol Vaginal Ring (Ethinyl Estradiol)			
Product Name: Amneal's Etonogestrel/ Ethinyl Estradiol Vaginal Ring **Lot #** PW-ST-16056A	**Mfg. Date:** 07/27/2016 **Analysis Date** :9/27/2016	**Method #** 469-DS **Apparatus:** Innova® Incubator Shaker **Medium:** 50 mM Acetate buffer, pH 4.2	**Volume:** 250 mL **Speed:** 50 rpm, **Temperature:** 37°C ± 0.5°C

Unit #	µg Dissolved (EE)																					
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**Mean***
1	(b) (4)																					
2																						
3																						
4																						
5																						
6																						
7																						
8																						
9																						
10																						
11																						
12																						
Mean	25	19	18	18	17	17	17	16	16	16	16	16	15	15	15	15	15	15	14	14	14	16
Min	(b) (4)																					
Max																						
%RSD	2.1	4.2	3.5	2.9	3.4	2.9	3.9	3.2	2.8	3.1	3.2	2.8	3.8	2.8	1.9	2.6	3.5	3.5	4.7	2.1	3.5	2.2
Reference: Book/Page # KR1540/87																						

*Mean (Day 2- day 21)

Test Product PW-ST-16052A

Table 2. Summary of In-Vitro Dissolution – Amneal's Etonogestrel/Ethinyl Estradiol Vaginal Ring (Ethinyl Estradiol)			
Product Name: Amneal's Etonogestrel/ Ethinyl Estradiol Vaginal Ring **Lot #** PW-ST-16052A	**Mfg Date:** 07/14/2016 **Analysis Date** :9/27/2016	**Method** # 469-DS **Apparatus:** Innova® Incubator Shaker **Medium:** 50 mM Acetate buffer, pH 4.2	**Volume:** 250 mL **Speed:** 50 rpm **Temperature:** 37°C ± 0.5°C

Unit #	µg Dissolved (EE)																					
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	***Mean**
1	(b) (4)																					
2																						
3																						
4																						
5																						
6																						
7																						
8																						
9																						
10																						
11																						
12																						
Mean	22	17	17	16	16	16	16	15	17	15	15	15	14	14	14	14	14	14	14	14	13	15
Min	(b) (4)																					
Max																						
%RSD	2.3	5.2	4.8	3.2	1.8	2.9	3.9	1.9	3.0	2.6	3.5	3.4	3.2	4.1	2.1	2.8	2.8	3.3	3.3	3.9	3.0	2.3
Reference: Book/Page # KR1540/140																						

* Mean (Day 2- day 21)

Test Product PW-ST-16055A

Table 4. Summary of In-Vitro Dissolution – Amneal's Etonogestrel/Ethinyl Estradiol Vaginal Ring (Ethinyl Estradiol)																					
Product Name: Amneal's Etonogestrel/ Ethinyl Estradiol Vaginal Ring **Lot** # PW-ST-16055A					**Mfg Date:** 07/21/2016 **Analysis Date** :9/27/2016						**Method** # 469-DS **Apparatus:** Innova® Incubator Shaker **Medium:** 50 mM Acetate buffer, pH 4.2						**Volume:** 250 mL **Speed:** 50 rpm **Temperature:** 37°C ± 0.5°C					
Unit #	**µg Dissolved (EE)**																				
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	***Mean**
1	(b) (4)																				
2																					
3																					
4																					
5																					
6																					
7																					
8																					
9																					
10																					
11																					
12																					
Mean	24	18	17	17	17	16	16	16	16	15	15	15	15	15	15	14	14	14	14	14	13	15
Min	(b) (4)																				
Max																					
%RSD	1.2	2.5	2.6	1.7	2.3	2.4	1.8	2.5	3.4	3.3	1.9	2.6	1.9	3.4	2.6	2.0	3.2	2.0	2.0	2.1	3.7	1.2
Reference: Book/Page # KR1540/142																					

* Mean (Day 2- day 21)

Dissolution Result of Scale-Up R&D Batch #B17K058076A

Daily Release (Etonogestrel), µg/day																									
Days	Int 1	Int 2	Int 3	Int 4	Int 5	Int 6	Int 7	Int 8	Int 9	Int 10	Int 11	Int 12	Int 13	Int 14	Int 15	Int 16	Int 17	Int 18	Int 19	Int 20	Mean	%RSD	SD	Criteria
1	(b) (4)																				202	2.7	5.4	187-221
2																					158	2.8	4.4	
6																					144	2.4	3.4	
7																					134	3.0	4.0	
8																					132	3.0	3.9	112-144
9																					133	2.4	3.2	
10*																					132	1.9	2.5	
11*																					131	1.6	2.1	
12*																					130	1.8	2.3	
13																					129	2.3	3.0	
14																					120	1.9	2.3	
15																					117	2.6	3.0	
16																					116	2.0	2.3	
20																					113	1.6	1.8	
21																					109	1.9	2.0	NLT 100

Daily Release (Ethinyl Estradiol), µg/day																								
Days	Int 1	Int 2	Int 3	Int 4	Int 5	Int 6	Int 7	Int 8	Int 9	Int 10	Int 11	Int 12	Int 13	Int 14	Int 15	Int 16	Int 17	Int 18	Int 19	Int 20	Mean	%RSD	SD	Criteria
1	(b) (4)																				24	3.4	0.8	21-26
2																					17	3.5	0.6	
6																					17	3.4	0.6	
7																					16	4.2	0.7	
8																					16	3.8	0.6	13-19
9																					16	4.0	0.6	
10*																					16	2.8	0.4	
11*																					16	2.5	0.4	
12*																					16	2.5	0.4	
13																					16	3.2	0.5	
14																					15	1.5	0.2	
15																					15	3.0	0.4	
16																					14	6.3	0.9	
20																					14	3.6	0.5	
21																					13	3.8	0.5	NLT 13

*Extrapolated data

Dissolution Result of Scale-Up R&D Batch #B17K058076A [Approx. 12-months (349 days) Stability Samples, stored at 2°C - 8°C]

Daily Release (Etonogestrel), µg/day																		
Day	Ring 1	Ring 2	Ring 3	Ring 4	Ring 5	Ring 6	Ring 7	Ring 8	Ring 9	Ring 10	Ring 11	Ring 12	Min	Max	Mean (µg)	SD	%RSD	Criteria (µg)
1														(b) (4)	214	3.7	1.7	187-221
8															137	3.0	2.2	
9															136	2.5	1.9	
10															131	2.8	2.2	
11															129	2.9	2.2	112-144
12															125	3.8	3.0	
13															125	3.0	2.4	
14															122	3.3	2.7	
21															114	2.4	2.1	NLT 100
Daily Release (Ethinyl Estradiol), µg/day																		
Day	Ring 1	Ring 2	Ring 3	Ring 4	Ring 5	Ring 6	Ring 7	Ring 8	Ring 9	Ring 10	Ring 11	Ring 12	Min	Max	Mean (µg)	SD	%RSD	Criteria (µg)
1														(b) (4)	25	0.5	2.1	21-26
8															16	0.5	3.1	
9															17	0.5	3.0	
10															16	0.5	3.2	
11															16	0.4	2.5	13-19
12															16	0.5	3.4	
13															16	0.5	3.3	
14															15	0.5	3.3	
21															15	0.4	2.8	NLT 13

APPENDIX 2

Biopharmaceutics Information Requests and Applicant Responses

Information Request (IR) 1

After the OPQ kickoff meeting, a two-item Biopharmaceutics IR was sent to the Applicant on 10/30/2017. On 11/29/2017, the Applicant responded to the IR. The following are the Biopharmaceutics IR, the Applicant's response, and this Reviewer's assessment of the Applicant's response.

IR 1 Item 1

1) You need to submit a full in vitro release method development report to the Agency for review. The report should include the following:
   - Detailed description of the in vitro release test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed in vitro release method as the optimal test for your product.
   - Sufficient data to support the discriminating ability of the selected method, including the complete in vitro release data (individual, mean, SD, RSD, and profile). In general, the testing conducted to demonstrate the discriminating ability of the selected method should compare the in vitro release profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected in vitro release method is able to reject batches that are not bioequivalent. Please be advised that you need to use the cumulative release profiles instead of daily release to evaluate the discriminating ability.

The Applicant's response to IR 1 Item 1

The Applicant stated that they submitted the full dissolution method report in Module 5.3.1.3. This Reviewer summarized the Applicant's response as follows:

1. Dissolution method development

The Applicant developed the following dissolution method for their proposed product:

Apparatus	Innova Shaker with ring holder, Ring Holder: Diameter 2"

Dissolution Medium	Acetate buffer, 50 mM, pH 4.2
Volume	250 mL
Rotation Speed	50 rpm
Temperature	37 ± 0.5 °C
Sampling time points	daily for 21 days

a. Selection of dissolution medium volume

250 mL was selected as the volume of the dissolution medium. The solubilities of Etonogestrel and Ethinyl Estradiol in pH (b) (4) respectively. The maximum drug release for Etonogestrel/Ethinyl Estradiol Vaginal Ring is (b) (4) for Etonogestrel and Ethinyl Estradiol, respectively. 250 mL is sufficient to provide the sink condition for both Etonogestrel and Ethinyl Estradiol at the maximum drug release.

In addition, the selected volume can ensure HPLC has sufficient sensitivity to detect the Etonogestrel and Ethinyl Estradiol dissolved in dissolution medium.

b. Selection of apparatus

The Innova (orbital) shaker combined with the dissolution jar was selected because it can provide an enclosed system that can maintain a small quantity of the dissolution medium (250 mL) over a long period of time. The ring holder can prevent the vaginal rings from floating on the surface of the dissolution medium.

c. Selection of dissolution medium

The Applicant compared the dissolution profiles of Etonogestrel and Ethinyl Estradiol (b) (4), 50 mM Acetate Buffer (pH 4.2), (b) (4) and the dissolution results are demonstrated in the following figures:

Figure 1. Release of Etonogestrel in different pH Media

Figure 2. Release of Ethinyl Estradiol in different pH Media

(b) (4)

. pH 4.2 was selected because it is closer to the vaginal fluid pH (b) (4) In addition, pH 4.2 buffer has higher buffer capacity (b) (4)

d. Selection of medium concentration (b) (4)

(b) (4)

Figure 3. Release of Etonogestrel in Different Buffer Concentrations

Figure 4. Release of Ethinyl Estradiol in Different Buffer Concentrations

(b) (4)

. Therefore, 50 mM was selected as the target buffer concentration of the dissolution method.

e. Selection of rotation speed

The Applicant compared the release profiles of Etonogestrel and Ethinyl Estradiol at (b) (4) 50 rpm, (b) (4)

Figure 5. Release of Etonogestrel at Different rotation speeds

Figure 6. Release of Ethinyl Estradiol at different rotation speeds

Figures 5 and 6 show that the rotation speed has minimal effect on the drug release of Etonogestrel and Ethinyl Estradiol. 50 rpm was selected as the rotation speed of the dissolution method.

2. Discriminatory power of the proposed dissolution method

The Applicant intentionally manufactured five batches of vaginal rings with different thickness of the ring membrane: 80 µm, 90 µm, 100 µm (target), 110 µm, and 120 µm. Etonogestrel and Ethinyl Estradiol dissolution profiles were compared using the above dissolution method.

Table 3. Cumulative Etonogestrel Release of the batches with different thickness

Batch/Time points (Day)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Batch G16K058057P (80 µm)	(b) (4)																				
Batch G16K058057T (90 µm)																					
G16K058057J (100 µm)-Target																					
Batch G16K058057U (110 µm)																					
Batch G16K058057Q (120 µm)																					

Table 4. Cumulative Ethinyl Estradiol Release of the batches with different thickness

Batch/Time points (Day)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Batch G16K058057P (80 µm)	(b) (4)																				
Batch G16K058057T (90 µm)																					
G16K058057J (100 µm)-Target																					
Batch G16K058057U (110 µm)																					
Batch G16K058057Q (120 µm)																					

Figure 7. Cumulative Etonogestrel Release of the batches with different thickness of the ring membrane

(b) (4)

Figure 8. Cumulative Ethinyl Estradiol Release of the batches with different thickness of the ring membrane

(b) (4)

Reviewer's comment

The Applicant's response is adequate.

The data in Table 6 show that all five trial batches have similar (b) (4) *for both Etonogestrel and Ethinyl Estradiol. In order to simplify the calculation, the cumulative Etonogestrel and Ethinyl Estradiol releases of the Target formulation at Day 21 was taken as reference (100%), the cumulative release percentage of Etonogestrel and Ethinyl Estradiol release at each time point for all five trial batches is calculated in Tables 8 and 9.*

Table 8. Cumulative Etonogestrel release percentage of the batches with different thickness

Batch/Time points (Day)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Batch G16K058057P (80 µm)																					(b) (4)
Batch G16K058057T (90 µm)																					
G16K058057J (100 µm)-Target																					
Batch G16K058057U (110 µm)																					
Batch G16K058057Q (120 µm)																					

Table 9. Cumulative Ethinyl Estradiol release percentage of the batches with different thickness

Batch/Time points (Day)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Batch G16K058057P (80 µm)																					(b) (4)
Batch G16K058057T (90 µm)																					
G16K058057J (100 µm)-Target																					
Batch G16K058057U (110 µm)																					
Batch G16K058057Q (120 µm)																					

Figure 12. Cumulative Etonogestrel Release Percentage of the batches with different thickness of the ring membrane

Figure 13. Cumulative Ethinyl Estradiol Release Percentage of the batches with different thickness of the ring membrane

The similarity factors between the target formulation and other varied formulations were calculated and listed in Tables 10 and 11.

Table 10. Similarity factor between the target formulation and other varied formulations for Etonogestrel

Comparison	*F2*
G16K058057J (100 µm)-Target vs. Batch G16K058057P (80 µm)	*47.60*
G16K058057J (100 µm)-Target vs. Batch G16K058057T (90 µm)	*62.60*
G16K058057J (100 µm)-Target vs. Batch G16K058057U (110 µm)	*60.61*
G16K058057J (100 µm)-Target vs. Batch G16K058057Q (120 µm)	*44.93*

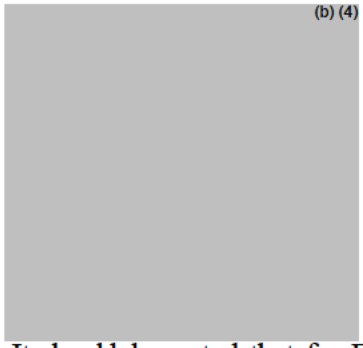
Table 11. Similar factor between the target formulation and other varied formulations for Ethinyl Estradiol

Comparison	*F2*
G16K058057J (100 µm)-Target vs. Batch G16K058057P (80 µm)	*45.06*
G16K058057J (100 µm)-Target vs. Batch G16K058057T (90 µm)	*60.69*
G16K058057J (100 µm)-Target vs. Batch G16K058057U (110 µm)	*59.72*
G16K058057J (100 µm)-Target vs. Batch G16K058057Q (120 µm)	*44.31*

The data in Tables 10 and 11 show that the proposed dissolution method is able to discriminate the changes in the ring membrane thickness when ± 20% change is made.

IR 2 Item 2

2. Based on the data provided, your proposed specifications are not appropriate. We request that you acknowledge your acceptance of the following specifications for your proposed products:



It should be noted that for Days 8-14, daily release rate should be used to determine if it meets the above the specifications. Acceptance Table 1 of USP <724> should be used to determine whether the acceptance criteria are met at different stages.

Acknowledge your acceptance of the above dissolution specifications and update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If

dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

The Applicant's response to IR 2 Item 2

The Applicant stated that they accept FDA recommended specifications for Day 1 and Day 21 for both Etonogestrel and Ethinyl Estradiol. However, based on the Long-Term Stability Study data throughout 18 months, they proposed to slightly move up the upper limit of the recommended specification for Day 8-14 while keeping the lower limit unchanged for both Etonogestrel and Ethinyl Estradiol (Table 13).

Table 13. Amneal's Proposed Specification for Dissolution

		FDA's Recommendation	Amneal' s Proposed Specification
Etonogestrel	Day 1:	(b) (4)	
	Days 8-14:*		
	Day 21:		
Ethinyl Estradiol	Day 1:		
	Days 8-14:*		
	Day 21:		

The applicant provided the following justification to support this acceptance criteria:
As the stability data indicates, the drug release increases slightly from the initial to 9-month and 12-month and plateaus at 18-month. The pattern of the drug release shows the rapid drop from day 1 to around Day 8 and Day 9, which means that Day 8 and Day 9 are still on the relatively faster slope of the release. The upper limit of (b) (4) for Etonogestrel and (b) (4) for Ethinyl Estradiol maintains an appropriate gap from the lower limit of day 1, i.e. (b) (4) for Etonogestrel and (b) (4) for Ethinyl Estradiol. RLD also demonstrates same in-vitro drug release behavior.

In addition, the Applicant has further tightened the following specifications for their proposed product:

- Average skin thickness [from (0.090mm- 0.110 mm) to (0.090mm- 0.105mm)]
- Ovality of ring [from (0-0.200) to (0- 0.180)]

Reviewer's comment

Acceptance criteria are typically based on fresh batch data.
Additional data are needed to better understand variability in in vitro release data before finalizing acceptance criteria.

IR 2 Item 3

3. Clarify if you have manufactured any commercial (scale-up) batches. If yes, submit the complete dissolution data (individual, mean, SD, RSD, profiles) to the Agency for review.

The Applicant's response to IR 2 Item 3

The Applicant stated that they have manufactured one scale-up R&D Batch # B17K058076A as a part of product development. The complete dissolution data were provided in this IR response, which are listed in Appendix I for details. The data of Days 10, 11 and 12 are extrapolated data using the linear equation established between Day 9 and Day 13 (Figure 14).

Figure 14 Dissolution Graph of Scale-Up R&D Batch #B17K058076A

Additionally, twelve (12) rings from composite sample of the same scale-up R&D batch (# B17K058076A, Approx. 12-months (349 days) samples stored at 2°C - 8°C) were tested as per the revised dissolution specification, recommend by the Agency. The data of day 8, 9, 10, 11, 12, 13 and 14 are available as a reference to supplement the extrapolated data in the initial

testing. The data of Days 8, 9, 10, 11, 12, 13, and 14 are consistent with the extrapolated data in the initial testing.

Reviewer's comment

The response is adequate. This Reviewer confirmed that R&D Batch # B17K058076A meets the newly proposed specifications.

IR #3

The following deficiency should be included in the Action Letter:

(b) (4)

Hansong Chen

Digitally signed by Hansong Chen
Date: 5/29/2018 04:41:49PM
GUID: 525d7d660003845a197a2e1682433d0d

Vidula Kolhatkar

Digitally signed by Vidula Kolhatkar
Date: 5/30/2018 07:37:05AM
GUID: 5424aeae00c3274f93e50573f7ca407e

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210830

OTHER REVIEWS

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation

ANDA210830: Amneal Pharmaceuticals Etonogestrel/Ethinyl Estradiol Ring– Device Consult

DATE: July 2, 2019

FROM: Jason Roberts, Ph.D., Biomedical Engineer
CDRH/ODE/DRGUD/OGDB

TO: Steven Yang
CDER/OPQ/OPRO/DRBPMI/RBPMBII

CC: Sharon Andrews, Branch Chief
CDRH/ODE/DRGUD/OGDB

Joyce Whang, Ph.D., Deputy Director, Science
CDRH/ODE/DRGUD

Lead Consulting Reviewer: Jason Roberts, Ph.D. Biomedical Engineer CDRH/ODE/DRGUD/OGDB
Biocompatibility Reviewer: Pushya Potnis, Ph.D. Toxicologist CDRH/ODE/DRGUD/ULDB

I. Purpose of Submission and Scope:

The submission is a new drug application for the Amneal Pharmaceuticals Etonogestrel/Ethinyl Estradiol Ring. In the original consult, the initiating division asked that CDRH to identify any general concerns with a vaginal ring type product from a device perspective. CDRH provided several comments, which were communicated to the applicant in a Complete Response Letter on June 22, 2018.

The applicant then requested a meeting to discuss their responses to the Complete Response Letter, issued June 22, 2018. The initiating division asked that CDRH provide written feedback for the applicant addressing their questions. CDRH provided the initiating division with additional comments, which were discussed in a teleconference with the applicant on August 7, 2018.

The applicant then submitted a response to the Complete Response letter, which took into consideration FDA feedback provided in the August 7, 2018 teleconference. After review of the applicant's response, CDRH identified two additional deficiencies, one with respect to the biocompatibility data in the submission, and the other with respect to the labeling of the product. CDER elected to communicate the biocompatibility deficiency, but did not communicate the deficiency regarding labeling.

The current submission includes the applicant's response to CDRH's deficiency.

In this review memo, I will provide an overview of the information provided along with my comments. Review issues will be identified and appear **in bold** in the review below.

II. Device Description:

Intended use

The Amneal Pharmaceuticals Etonogestrel/Ethinyl Estradiol Ring is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.

Product description

The device is a clear, flexible ethylene vinylacetate ring intended to be placed in the vagina (figure below).

The device has the following dimensional specifications:

Specification	Value
Weight	(b) (4)
Color	Colorless to nearly colorless (cloudy white)
Outer diameter	(b) (4)
Cross sectional diameter	

Surface area	(b) (4)
Volume	

The submission includes a single dose ring intended to delivery 0.120/0.015 mg/day Etonogestrel/Ethinyl estradiol. The ring is primarily ethylene vinylacetate, but contains the two drug products etonorgestrel and ethinyl estradiol and excipient magnesium stearate. The exact formulation is the following:

Ingredient	Quantity per ring (mg)	%w/w of total ring weight
Ethinyl estradiol	2.700	(b) (4)
Etonorgestrel	11.700	
Ethylene vinylacetate copolymer, 28% vinylacetate (b) (4) (b) (4)	(b) (4)	
Ethylene vinylacetate copolymer, 9% vinylacetate (b) (4) (b) (4)		
Magnesium stearate		
		(b) (4)

(b) (4) and are individually packaged into re-closable aluminum laminate sachets. Three sachets will be packaged per carton of product.

III. Applicant responses to FDA deficiencies from Complete Response Letter dated April 12, 2019

The applicant has provided responses to FDA's deficiencies in the CRL letter. Deficiency 2 originated from CDRH and is within the scope of this review.

Deficiency #2

You have provided the 90-days study test reports (# 17-00131-G12 and 17-00891-G1) in your amendment received on October 19, 2018. Per the test reports, the test ring (Amneal) and Amneal's placebo ring (Sponsor Control) were dipped (b) (4) *prior to being implanted in the animals. We are concerned that this process might remove potentially harmful extractive leachable substances and affect the overall leachable profile of the test article extract, which could result in false negative results. Since your subject device [test ring (Amneal)] is provided as non-sterile, finished product, biocompatibility testing should be done on the representative test article without* (b) (4) *Please provide justification as to how the test article dipped* (b) (4) *prior to testing, represents your final, device that is intended to be inserted vaginally without such*

treatment.

Applicant response:

The applicant notes that sample preparation was done per (b) (4) SOP, which states that "In order to make the test articles aseptic prior to implantation, each piece was then dipped (b) (4) for approximately 10 seconds (b) (4) The sponsor notes that to address FDA's concern, they conducted an extractable/leachables study on samples prepared in a similar fashion (30 seconds in (b) (4) (b) (4) for a worst-case scenario). Sample extracts were evaluated with HS/GC/MS, DI/GC/MS and HPLC/UV for volatile, semi-volatile and non-volatile compounds.

Reviewer comment:

Dr. Potnis reviewed the study, and noted that the study supported the treatment of samples did not remove extractive/leachable substances (see Appendix 1 below for additional detail from Dr. Potnis). Therefore, the biocompatibility testing is acceptable.

IV. Summary/Recommendations:

The applicant has adequately addressed the deficiency. There are no other outstanding deficiencies.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Jason Roberts -S 2019.07.03 07:58:06 -04'00'
Team Sign-Off	Sharon M. Andrews -S 2019.07.03 14:25:18 -04'00'

Consult Memo

Date: July 1st, 2019

To: Jason Roberts, DHT3/OHT3B/OPEQ

From: Pushya Potnis, DHT3/OHT3B/OPEQ

RE: Etonogestrel/Ethinyl Estradiol Vaginal Ring (ANDA 210830) (SEQUENCE # 0016)

This consult is provided to Dr. Roberts to review the Sponsor's response to the additional information requested for biocompatibility review of the subject device, Etonogestrel/Ethinyl estradiol vaginal ring that is indicated for the prevention of pregnancy while providing menstrual cycle control.

The combination product is manufactured by Amneal Pharmaceuticals.

The scope of this memorandum is limited to the biocompatibility testing provided by the Sponsor.

Recommendation:

The Sponsor has provided adequate information and chemical characterization data to demonstrate that dipping of the test articles in (b) (4) before implantation in Study No 17-00131-G12 and 17-00891-G1, conducted by (b) (4) did not remove any potential extractive leachable substances and affect the leachable profile.

From a biocompatibility perspective, there are no significant concerns associated with the use of the subject device.

Pushya Potnis, PhD

The Sponsor's response to the additional information requested via the Major Complete Response Amendment as per the deficiency letter dated 4/12/2019 is summarized below:

FDA Comment # 2:

You have provided the 90-days study test reports (# 17-00131-G12 and 17-00891-G1) in the current Amendment. Per the test reports, the test ring (Amneal) and Amneal's placebo ring (Sponsor Control) were dipped (b) (4) prior to being implanted in the animals. We are concerned that this process might remove potentially harmful extractive leachable substances and affect the overall leachable profile of the test article extract, which could result in false negative results. Since your subject device [test ring (Amneal)] is provided as non-sterile, finished product, biocompatibility testing should be done on the representative test article without (b) (4) Please provide justification as to how the test article dipped (b) (4) (b) (4) prior to testing, represents your final, device that is intended to be inserted vaginally without such treatment.

Comments to sponsor's Response:

- The sponsor indicates that the 90 Day Systemic Toxicity in Rats Studies (Test reports # 17-00131-G12 and 17-00891-G1) were conducted per the SOP guidelines of (b) (4)

- Accordingly, unless the test article is supplied sterile, the test and control specimens are required to be subjected to a minimum sanitized level or sterilization to prevent or minimize infection that would impact the sensitivity of the study.

- To address the concern raised by the FDA regarding misrepresentation of the subject device based on dipping of test specimen in (b) (4) the sponsor conducted and (b) (4) study.

- The report (test report # PWY-19MIS-018) for the study is provided as an attachment. See summary below:

    - The test article identified as 'Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg' was subjected to sample preparation steps (b) (4) that were used by (b) (4) for the 90 Day Systemic Toxicity in Rats Studies.

    - Test samples were dipped (b) (4) for 10 sec and 30 sec before extraction with (b) (4) (b) (4)

- The samples were carefully removed from the solvent and then tested for chemical analysis.
- The extracts were analyzed for Volatile, Semi-Volatile and Non-Volatile extractable compounds by HS/GC/MS, DI/GC/MS and HPLC/UV analytical techniques.

- For VOC analysis: the chromatographic profile of the Test DP was identical to the Extraction Blank, confirming that no VOCs were extracted from the test article dipped (b) (4) The representative chromatographs are provided in Annex 1-2.

- For SVOC analysis: the chromatographic profiles of the Placebo ring extract and Extraction Blank were found to be identical, confirming that no SVOC were extracted from the EVA material of the ring when dipped (b) (4) The representative chromatographs are provided in Annex 3-6.

- For NVOC analysis: the chromatographic profiles of the Placebo ring extract and Extraction Blank were found to be identical, confirming that no NVOC were observed from the EVA material of the ring when dipped (b) (4) The representative chromatographs are provided in Annex 7-9.

- The study concludes that no potential VOC, SVOC and NVOC migrants were extracted from Placebo EVA ring, Ink and Pouch material when dipped (b) (4) for 10 and 30 seconds.

- A more realistic approach would be to conduct a comparative chemical analysis to demonstrate equivalency between the (b) (4) dipped versus non-dipped test articles and their respective leachable profile. This would provide more meaningful qualitative and quantitative analytical information of the leachable profiles for comparison of the two-test specimen.

- However, based on the provided chemical characterization of the (b) (4) that was obtained after dipping the subject device for 10 and 30 seconds, the sponsor has demonstrated that no impurities are leached out by (b) (4) treatment based on the observation that no VOC, SVOC and NVOC migrants were extracted from the specimens.

- The results of the study indicate that dipping of the test articles (b) (4) before implantation in Study No 17-00131-G12 and 17-00891-G1, conducted by (b) (4) did not remove any potential extractive leachable substances and affect the leachable profile.

- The sponsor has addressed the concern raised in the previous deficiency regarding misrepresentation of the subject device based on dipping of test specimen (b) (4) (b) (4)

- The sponsor's response to FDA Comment # 2 is acceptable.

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation

ANDA210830: Amneal Pharmaceuticals Etonogestrel/Ethinyl Estradiol Ring– Device Consult

DATE: December 18, 2018

FROM: Jason Roberts, Ph.D., Biomedical Engineer
CDRH/ODE/DRGUD/OGDB

TO: Steven Yang
CDER/OPQ/OPRO/DRBPMI/RBPMBII

CC: Sharon Andrews, Branch Chief
CDRH/ODE/DRGUD/OGDB

Joyce Whang, Ph.D., Deputy Director, Science
CDRH/ODE/DRGUD

Lead Consulting Reviewer: Jason Roberts, Ph.D. Biomedical Engineer CDRH/ODE/DRGUD/OGDB
Biocompatibility Reviewer: Pushya Potnis, Ph.D. Toxicologist CDRH/ODE/DRGUD/ULDB

I. Purpose of Submission and Scope:

The submission is a new drug application for the Amneal Pharmaceuticals Etonogestrel/Ethinyl Estradiol Ring. In the original consult, the initiating division asked that CDRH to identify any general concerns with a vaginal ring type product from a device perspective. CDRH provided several comments, which were communicated to the applicant in a Complete Response Letter on June 22, 2018.

The applicant then requested a meeting to discuss their responses to the Complete Response Letter, issued June 22, 2018. The initiating division asked that CDRH provide written feedback for the applicant addressing their questions. CDRH provided the initiating division with additional comments, which were discussed in a teleconference with the applicant on August 7, 2018.

The current submission includes the applicant's response to the Complete Response Letter, issued June 22, 2018 which takes into consideration FDA feedback provided on August 7, 2018.

In this review memo, I will provide an overview of the information provided along with my comments. Review issues will be identified and appear **in bold** in the review below.

II. Device Description:

Intended use

The Amneal Pharmaceuticals Etonogestrel/Ethinyl Estradiol Ring is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.

Product description

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The device has the following dimensional specifications:

Specification	Value
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Outer diameter	(b) (4)
Cross sectional diameter	
Surface area	
Volume	

The submission includes a single dose ring intended to delivery 0.120/0.015 mg/day Etonogestrel/Ethinyl estradiol. The ring is primarily ethylene vinylacetate, but contains the two drug products etonorgestrel and ethinyl estradiol and excipient magnesium stearate. The exact formulation is the following:

Ingredient	Quantity per ring (mg)	%w/w of total ring weight
Ethinyl estradiol	2.700	(b) (4)
Etonorgestrel	11.700	
Ethylene vinylacetate copolymer, 28% vinylacetate (b) (4) (b) (4)	(b) (4)	
Ethylene vinylacetate copolymer, 9% vinylacetate (b) (4) (b) (4)		
Magnesium stearate (b) (4)		

(b) (4) and are individually packaged into re-closable aluminum laminate sachets. Three sachets will be packaged per carton of product.

III. Applicant responses to FDA deficiencies from CRL letter dated June 22, 2018

The applicant has provided responses to FDA's deficiencies in the CRL letter. Deficiencies 10-14 originated from CDRH and are within the scope of this review.

Deficiency #10

(b) (4)

Applicant response:

In response to the deficiency, the applicant noted that the original studies were designed as three arm with a placebo ring to control for the effects of the drug product. In addition, the applicant noted that they had conducted additional 90-day toxicity studies that were not provided in the original ANDA. These reports were provided in Module 4 of the current submission. Dr. Potnis, Toxicologist, reviewed the additional information (for additional information not provided in the following summary, please refer to appendix 1 for Dr. Potnis' complete memo).

Dr. Potnis noted that the applicant's 90 day study supported that the results of the previously-submitted 28 day studies was due to the drug component. However, Dr. Potnis noted that in sample preparation, the applicant dipped the rings (b) (4) Dr. Potnis noted that this step could remove potentially harmful extractive leachable substances and affect the overall profile of the device. Therefore, Dr. Potnis recommended the following deficiency be communicated to the applicant:

You have provided the 90-days study test reports (# 17-00131-G12 and 17-00891-G1) in the current Amendment. Per the test reports, the test ring (Amneal) and Amneal's placebo ring (Applicant Control) were dipped (b) (4) *prior to being implanted in the animals. We are concerned that this process might remove potentially harmful extractive leachable substances and affect the overall leachable profile of the test article extract, which could result in false negative results. Since your subject device [test ring (Amneal)] is provided as non-sterile, finished product, biocompatibility testing should be done on the representative test article without* (b) (4) *Please provide justification as to how the test article dipped* (b) (4) *prior to testing, represents your final, device that is intended to be inserted vaginally without such treatment.*

Reviewer comment:

I recommend Dr. Potnis' deficiency be communicated to the applicant.

Deficiency #11

(b) (4)

Applicant response:

The applicant notes that there are no other processing agents used during manufacture other that the drug product and the active and inactive ingredients as previously provided in Module 3.2.P.1. These are as follows:

Table 1. Composition of Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day			
Ingredients	mg/Unit	% w/w	Component Function
Ethinyl Estradiol, USP (b) (4)	2.700	(b) (4)	Active
Etonogestrel (b) (4)	11.700		Active
Ethylene Vinylacetate Copolymer, 28% Vinylacetate (b) (4)	(b) (4)		(b) (4)
Ethylene Vinylacetate Copolymer, 9% Vinylacetate (b) (4)			
Magnesium Stearate, NF			
(b) (4)	N/A*		
Total	(b) (4)	100.0	
Notes:			
(b) (4)			

Dr. Potnis reviewed the information, and had no further concerns. This deficiency is resolved.

Deficiency #12

(b) (4)

Applicant response:

(b) (4)

The applicant evaluated 12 samples from each of three batches stored for 24 months, one newly manufactured batch, and one reference sample of Nuvaring (the non-generic comparator product).

The results of the testing are summarized below:

(b) (4)

The results indicate the subject product has similar tensile properties to the reference product. There appears to be slightly more variability in tensile properties in the subject product as compared to the reference product, and the aged product appears to have a slight mean decrease in tensile properties. However, these differences do not appear significant. (b) (4) Therefore, the results support the tensile properties of the subject product are comparable to the reference product and are maintained throughout the shelf-life under expected storage conditions. This is acceptable.

Hardness (durometer):

Durometer testing was conducted by the third-party lab (b) (4) October 9, 2018). The applicant utilized ASTM-D2240 Standard Test Method for Rubber Property – Durometer Hardness. Although this standard is not recognized by CDRH, I reviewed the methods provided, and find them acceptable. Further, the applicant provides validation results for the methods, which indicate appropriate test precision.

The applicant evaluated 12 samples from each of three batches stored for 24 months, one newly manufactured batch, and one reference sample of Nuvaring (the non-generic comparator product).

The results of the testing are summarized below:

The durometer results indicate that the subject product has similar hardness to that of the reference product and that it maintains its hardness after aging for 24 months. This is acceptable.

(b) (4)

The applicant evaluated 12 samples from each of three batches stored for 24 months, one newly manufactured batch, and one reference sample of Nuvaring (the non-generic comparator product).

The results of the testing are summarized below:

Reviewer comment:

The results of mechanical testing demonstrate that the mechanical properties of the subject product are similar to the reference product (NuvaRing) and that the subject product maintains mechanical properties throughout the proposed shelf-life. This is acceptable; the deficiency has been adequately addressed.

Deficiency #13

In the intended use population, other intravaginal devices such as personal lubricants may come into contact with the subject device (to supplement lubrication during intercourse). Please provide a risk analysis that evaluates the risks associated with the use of your product with other intravaginal devices, and any proposed mitigations (e.g., labeling) to ensure that there is no negative impact/effect on the IVR or other intravaginal devices.

Applicant response:

In response to the deficiency, the applicant provides a risk analysis in module 5.2.5 concerning the use of the subject product with other intravaginal devices. Based upon the conducted risk analysis, the applicant concludes that there are no new risks associated with the subject product as compared to the NuvaRing that would necessitate changes to the prescribing information for the subject product.

With respect to personal lubricants, the applicant summarizes a small study, Haring & Mulders, 2003, conducted with the Nuvaring and nonoxyonol-9 containing spermicide gel. In that study of 12 women, there were no changes in serum concentrations of etonogestrel or ethinyl estradiol in any of the women using the gel. Although this is not a study of personal lubricants, spermicidal gels have similar properties to personal lubricants. In this case, the spermicide (Contraceptol), is a water/glycol based gel. Further, the applicant provides a discussion of a recently approved IVR – Annovera (NDA 209627) for which the prescribing information notes that the ring is compatible with vaginal lubricants that are water-based, but that oil and silicone-based lubricants will affect the release of ethinyl estradiol and segesterone acetate. Further, the applicant notes that a study of oil-based medications (antimycotic suppository) and NuvaRing, single doses of the anti-mycotic resulted in 17% increases in serum ethinyl estradiol and repeat doses resulted in serum concentration increases of 40%. These oil-based medication study results are currently in the NuvaRing prescribing information.

Reviewer comment:

Based upon the discussion of the available literature, (b) (4) **The available evidence suggests that the subject device may not be compatible due to its similarity to other studied products. Therefore, I recommend that the prescribing information reflect that of the recently-approved NDA 209627 and** (b) (4) **vaginal products may interfere with the release of ethinyl estradiol and etonogestrel. Alternatively, the applicant may provide evidence to support the compatibility of the subject produc** (b) (4) **with similar vaginal rings products. Therefore, I feel it is appropriate not to comment on the compatibility in the prescribing information.**

With respect to tampon use, the applicant notes that there are few published cases of TSS associate with the use of tampons with other intravaginal products such as diaphragms or contraceptive sponge. However, the applicant notes that a causal relationship between TSS and vaginal rings has not been established. The applicant notes that the Nuvaring and subsequently their product's prescribing information address TSS, so therefore, no modification is needed to their prescribing information.

Reviewer comment:
With respect to tampon use, I agree with the applicant that no further information regarding tampon use and TSs is necessary. However, the applicant did not discuss the use of tampons and their potential effect on hormone exposure. In NDA 209627, the following statement is provided in section 7.3 of the USPI: "The effect of tampon use on the systemic exposure of SA and EE from ANNOVERA™ has not been studied." (b) (4)

(b) (4)

Deficiency #14

(b) (4)

(b) (4)

Applicant response:

(b) (4)

of 3 brands of NRL, 1 brand of synthetic polyisoprene, and 1 brand of polyurethane condom. As discussed and agreed upon in the August 7, 2018 CRL teleconference, (b) (4)

Testing was conducted by the third-party lab (b) (4) Report 361802285). The subject product and reference product NuvaRing were evaluated. The following condoms were tested:

- Trojan Enz non-lubricated latex [lot TT8061UZ); 510(K) number K901191]
- Lifestyles non-lubricated latex [lot 1711972422); 510(K) number K120394]
- Atlas non-lubricated latex [lot 17X1602); 510(K) number K141059]
- Lifestyles Skyn lubricated polyisoprene [lot 1710971622) ;510(K) number K160399]
- Trojan Supra lubricated polyurethane [lot CZ7360M5); 510(K) number K100767]

The following table summarizes the results of testing:

Subject product:

Condom Type	Exposure	Tensile Break Force and SD (N)	SD	Tensile Elongation and SD (%)	SD
TrojanENZ latex (non-lubricated) Lot # TT8061UZ	Control	104.0	6.4	893	12
	Sample	105.0	8.5	898	18
Lifestyles latex (non-lubricated) Lot # 1711972422	Control	87.1	9.7	824	19
	Sample	86.2	7.1	829	14
Atlas latex (non-lubricated) Lot # 17X1602	Control	94.5	6.3	922	17
	Sample	93.7	6.0	926	18
LifestylesSkyn polyisoprene (lubricated) Lot # 1710971622	Control	92.8	10.0	1090	29
	Sample	92.9	9.2	1100	23
TrojanSupra polyurethane (lubricated) Lot # CZ7360M5	Control	53.3	7.9	595	17
	Sample	54.1	7.4	585	37
Condom Type	**Exposure**	**Burst Pressure and SD (kPa)**	**SD**	**Burst Volume and SD (L)**	**SD**
TrojanENZ latex (non-lubricated) Lot # TT8061UZ	Control	2.075	0.177	31.750	2.49
	Sample	2.033	0.233	33.830	3.24
Lifestyles latex (non-lubricated) Lot # 1711972422	Control	2.390	0.147	42.130	2.87
	Sample	2.365	0.143	43.350	3.33
Atlas latex (non-lubricated) Lot # 17X1602	Control	2.197	0.098	40.420	1.84
	Sample	2.163	0.105	41.050	2.85
LifestylesSkyn polyisoprene (lubricated) Lot # 1710971622	Control	1.962	0.118	49.950	4.82
	Sample	1.845	0.236	46.900	9.69
TrojanSupra polyurethane (lubricated) Lot # CZ7360M5	Control	10.285	0.510	5.150	0.76
	Sample	10.745	0.890	5.030	0.38

NuvaRing:

Condom Type	Exposure	Tensile Break Force and SD (N)	SD	Tensile Elongation and SD (%)	SD
TrojanENZ latex (non-lubricated) Lot # TT8061UZ	Control	104.0	6.4	893	12
	Sample	99.7	8.1	890	18
Lifestyles latex (non-lubricated) Lot # 1711972422	Control	87.1	9.7	824	19
	Sample	81.3	8.8	820	26
Atlas latex (non-lubricated) Lot # 17X1602	Control	94.5	6.3	922	17
	Sample	93.4	8.8	923	22
LifestylesSkyn polyisoprene (lubricated) Lot # 1710971622	Control	92.8	10.0	1090	29
	Sample	85.8	10.0	1080	24
TrojanSupra polyurethane (lubricated) Lot # CZ7360M5	Control	53.3	7.9	595	17
	Sample	51.9	8.6	590	15
Condom Type	**Exposure**	**Burst Pressure and SD (kPa)**	**SD**	**Burst Volume and SD (L)**	**SD**
TrojanENZ latex (non-lubricated) Lot # TT8061UZ	Control	2.075	0.177	31.750	2.49
	Sample	2.065	0.137	32.850	1.93
Lifestyles latex (non-lubricated) Lot # 1711972422	Control	2.390	0.147	42.130	2.87
	Sample	2.373	0.123	43.000	3.41
Atlas latex (non-lubricated) Lot # 17X1602	Control	2.197	0.098	40.420	1.84
	Sample	2.180	0.088	41.130	2.56
LifestylesSkyn polyisoprene (lubricated) Lot # 1710971622	Control	1.962	0.118	49.950	4.82
	Sample	1.825	0.146	52.400	6.54
TrojanSupra polyurethane (lubricated) Lot # CZ7360M5	Control	10.285	0.510	5.150	0.76
	Sample	10.298	0.684	5.050	0.43

In addition to the above, the applicant also provided the baseline and mineral oil values (not shown here). The baseline and positive controls behaved as expected. The observed changes are summarized below:

Subject product:

Condom Type		Break Force (%) Change	Elongation (%) Change	Burst Pressure (%) Change	Burst Volume (%) Change
TrojanENZ latex (non-lubricated) Lot # TT8061UZ	Sample 1 vs Control	1.0	0.6	-2.0	6.6
Lifestyles latex (non-lubricated) Lot # 1711972422	Sample 1 vs Control	-1.0	0.6	-1.0	2.9
Atlas latex (non-lubricated) Lot # 17X1602	Sample 1 vs Control	-0.8	0.4	-1.5	1.6
LifestylesSkyn polyisoprene (lubricated) Lot # 1710971622	Sample 1 vs Control	0.1	0.9	-6.0	-6.1
TrojanSupra polyurethane (lubricated) Lot # CZ7360M5	Sample 1 vs Control	1.5	-1.7	4.5	-2.3

NuvaRing:

Condom Type		Break Force (%) Change	Elongation (%) Change	Burst Pressure (%) Change	Burst Volume (%) Change
TrojanENZ latex (non-lubricated) Lot # TT8061UZ	Sample 2 vs Control	-4.1	-0.3	-0.5	3.5
Lifestyles latex (non-lubricated) Lot # 1711972422	Sample 2 vs Control	-6.7	-0.5	-0.7	2.1
Atlas latex (non-lubricated) Lot # 17X1602	Sample 2 vs Control	-1.2	0.1	-0.8	1.8
LifestylesSkyn polyisoprene (lubricated) Lot # 1710971622	Sample 2 vs Control	-7.5	-0.9	-7.0	4.9
TrojanSupra polyurethane (lubricated) Lot # CZ7360M5	Sample 2 vs Control	-2.6	-0.8	0.1	-1.9

Reviewer comment:

The testing was conducted appropriately and per FDA recommendations. The results support that the subject product is compatible with natural rubber latex, synthetic polyisoprene and polyurethane condoms. I have no concerns with the information provided. The deficiency is resolved. However, I recommend this compatibility information be communicated in the labeling (prescribing information).

IV. Summary/Recommendations:

The applicant has adequately addressed CDRH deficiencies 10, 12, and 14. For deficiency 11, the applicant should provide a rationale for why the preprocessing (b) (4) exposure in their 90 day implantation study did not impact the validity of the results. Specifically, I recommend the following deficiency be sent to the applicant:

1. You have provided the 90-days study test reports (# 17-00131-G12 and 17-00891-G1) in the current Amendment. Per the test reports, the test ring (Amneal) and Amneal's placebo ring

(Sponsor Control) were dipped [redacted] prior to being implanted in the animals. We are concerned that this process might remove potentially harmful extractive leachable substances and affect the overall leachable profile of the test article extract, which could result in false negative results. Since your subject device [test ring (Amneal)] is provided as non-sterile, finished product, biocompatibility testing should be done on the representative test article without [redacted] Please provide justification as to how the test article dipped [redacted] prior to testing, represents your final, device that is intended to be inserted vaginally without such treatment.

With respect to deficiency 13, the sponsor has provided the requested information. However, based upon the presentation of the available literature, I recommend that the labeling be updated to reflect the risks associated with the use of intravaginal products. Specifically, [redacted] tampons. [redacted] For the subject product, this should include the following:

[redacted]

Digital Signature Concurrence Table	
Reviewer Sign-Off	Jason Roberts -S 2018.12.19 07:47:11 -05'00'
Branch Sign-Off	Sharon M. Andrews -S 2018.12.19 09:23:34 -05'00'
Division Sign-Off	Joyce M. Whang -S 2018.12.19 18:18:42 -05'00'

Consult Memo

Date: December 18th, 2018

To: Jason Roberts, DRGUD/OGDB/ODE

From: Pushya Potnis, DRGUD/ULDB/ODE

RE: Etonogestrel/Ethinyl Estradiol Vaginal Ring (ANDA210830)

This consult is provided to Dr. Roberts to review the Sponsor's response to the additional information requested for biocompatibility review of the subject device, Etonogestrel/Ethinyl estradiol vaginal ring that is indicated for the prevention of pregnancy while providing menstrual cycle control.

The combination product is manufactured by Amneal Pharmaceuticals.

The scope of this memorandum is limited to the biocompatibility testing provided by the Sponsor.

Recommendation:

The Sponsor has provided adequate responses to the previously requested deficiencies. The new 90-day exposure test data demonstrate that systemic toxicity effects observed in the previously submitted 28-day studies are attributed to the drug component of the IVR product and that the ring-component, itself, is not inherently toxic to systemic organs.

To fully evaluate the biocompatibility of the subject device, additional information/clarification is needed to address a minor concern in the deficiencies listed below (Page 6 of this memorandum).

_____

Pushya Potnis, PhD

The Sponsor's response to the additional information requested via the Major Complete Response Amendment (biocompatibility-deficiencies # 10 and 11), is summarized below:

Deficiency # 10:

(b) (4)

Comments based on Sponsor's response:

- The Sponsor states that they have provided a set of two 90-day systemic toxicity studies in this Amendment that were not submitted in the original ANDA.

- Table below lists all four toxicity studies that have been carried out as part of the systemic biocompatibility assessment:

Acute and Chronic Systemic Toxicity Studies Conducted by Amneal

Study	(b) (4) Study #	Dates of Initiation and Completion	Title	Study articles
1	17-00131-G1	2/23/2017 to 5/22/2017	28-Day systemic toxicity in rats via intramuscular implantation	Test ring (Amneal) versus Negative Control (b) (4)
2	17-00131-G12	2/21/2017 to 8/4/2017	90-day systemic toxicity in rats via intramuscular implantation	

3	17-01333-G1	5/2/2017 to 6/27/2017	28-Day systemic toxicity in female rats via intramuscular implantation	RLD ring (Nuvaring) versus Negative Control (b) (4) versus Amneal's Placebo ring (Sponsor Control)
4	17-00891-G1	3/22/2017 to 9/26/2017	90-day systemic toxicity in female rats via intramuscular implantation	

- Accordingly, the Sponsor has provided the 90-days studies (# 17-00131-G12 and 17-00891-G1) in the current Amendment.

- The studies were conducted in (b) (4) lab facility on the Test ring (final, finished device with drug), currently marketed product as a comparator (Nuvaring), Amneal's placebo (final, finished device with no drug) and a negative control (plastic material).

- In both studies conducted, the dose extrapolation from animals to human clinical dose is acceptable based on an exaggerated safety factor of 10x, calculated on the basis of test article surface-area-to-body mass ratio (exposure in rats : human clinical dose).

- The studies evaluated tissue response to the implanted test specimen for local and systemic toxicity effects. Per the test reports (# 17-00131-G12 and 17-00891-G1), the Sponsor Control and Amneal's Etonogestrel/Ethinyl Estradiol Vaginal Ring in both the 90-day studies were dipped (b) (4) prior to surgical implantation in the animal. Additional clarification is required from the Sponsor. A summary of the study design, results and conclusions is provided at the end of this memorandum.

- On the basis of these studies, an overall toxicological assessment of Amneal's intravaginal ring delivery device and Nuvaring has been carried out. The results indicate that both products display similar systemic effects characteristic of the two hormones as compared to the negative controls and placebo rings. The studies also revealed that (b) (4) negative controls and Amneal's placebo ring performed comparably and no significant toxicities attributable to Amneal's placebo ring were noted. These observations indicate that the concerns raised in the previous review of the 28-day systemic toxicity studies in rats via intramuscular implantation ((b) (4) Test Reports # 17-00131-G1 and 17-00133-G1) are mitigated based on the understanding that certain positive findings, necropsy data and reproductive organ histopathology effects are attribute to the drug contained in the IVR and are NOT secondary to exposure to the IVR material itself.

- The Sponsor has also provided a comparison table of hormone-mediated effects from 28-day and 90-day studies as a snapshot. See the attached Table below:

Parameter	28-Day Study		90-Day Study	
	Amneal	**RLD**	**Amneal**	**RLD**
Body Wt./Body Wt. Gains	Decrease	Decrease	Decrease	Decrease
Hematology	Decrease RBC, HGB, HCT	Decrease RBC, HGB, HCT	No effect	No effect
Clinical Chemistry	No effect	No effect	No effect	No effect
Coagulation	No effect	No effect	No effect	No effect
Implantation Sites (Macroscopic)	No effect	No effect	No effect	No effect
Organs (Macroscopic) and Organ weights	Hormone: Small thymus, decrease in weight for thymus	Hormone: Small thymus), decrease in weight for thymus & ovary (abs. & rel.) and incr.* for spleen (rel.) but decr* (abs.)	Hormone decrease for thymus & ovary	Hormone decrease for thymus & ovary
Implantation Sites (Microscopic)	No effect (Bioreactivity 0.0)	No effect (Bioreactivity 0.0)	No effect (Bioreactivity 0.0)	No effect (Bioreactivity 0.2 vs. NC and 0.3 vs. SC)
Organs (Microscopic)	Effects on thymus, ovary, ovary duct, uteri, cervix and spleen (EMH). Hormone & NC incr. EMH	Effects on, thymus, ovary, ovary duct, uteri, cervix, and spleen (EMH). Hormone, NC & SC incr. EMH	Hormone -related findings for thymus, ovary, ovary duct, uteri, cervix and spleen (EMH & pigmentation)	Hormone- related findings for thymus, ovary, ovary ducts, uteri, cervix, and spleen (Pigmentation)

- From the Table, it indicates that the decreasing trends in body weights and hematological parameters in response to Amneal's product and Nuvaring are not observed following exposure to Amneals' placebo ring (Sponsor's control) and the negative control (plastic) used in the studies.

- Additionally, there were no effects of Amneal's product and Nuvaring on the clinical chemistry, coagulation parameters, and macroscopic as well as microscopic assessments of implantation sites. These observations correlate with those secondary to exposure to Amneals' placebo ring (Sponsor's control) and the negative control (plastic) used in the studies.

- The expected systemic effects of hormones were seen comparably in both 28-day study and 90-day study for Amneal's product and Nuvaring in thymus, ovary, ovary duct, uteri, cervix, and spleen by microscopic and histopathologic assessments.

- Tables 3 and 4 in the Sponsor's response show summary of effects of 28-day and 90-day toxicity studies.

- Overall, similar hormone effects were seen for Nuvaring and Amneal's device which were not seen in either negative controls or Amneal's placebo device. Findings from the four studies clearly demonstrated that the observed tissue responses seen in Amneal's generic and Nuvaring resulted from drug interference with systemic organs and ruled out the possibility that the observed systemic effects are secondary to exposure to the vaginal ring component.

- The Sponsor's response to Deficiency # 10 is acceptable. However, further clarification will be required to document why test article was dipped in (b) (4) prior to implanting in animals. [**See New Deficiency # 1 on Page 6 of this memorandum**].

Deficiency # 11:

(b) (4)

Comments based on Sponsor's response:

- (b) (4) Active and Inactive Ingredients.
- The Sponsor has referred to the respective Modules of the Original ANDA submission to locate information on the following:

- Supplier information of Active Ingredients: Module 3.2.S.2.1
- Specification of Active Ingredients: 3.2.S.4.1
- Supplier information, material-grade, specification of Inactive Ingredients: Modules 3.2.P.4.1 and 3.2.P.4.4.

- The Sponsor has clarified that no other processing agents are used in the manufacturing of the subject device.

- The Sponsor's response to Deficiency # 11 is acceptable.

New Deficiency:

2. You have provided the 90-days study test reports (# 17-00131-G12 and 17-00891-G1) in the current Amendment. Per the test reports, the test ring (Amneal) and Amneal's placebo ring (Sponsor Control) were dipped (b) (4) prior to being implanted in the animals. We are concerned that this process might remove potentially harmful extractive leachable substances and affect the overall leachable profile of the test article extract, which could result in false negative results. Since your subject device [test ring (Amneal)] is provided as non-sterile, finished product, biocompatibility testing should be done on the representative test article without (b) (4) Please provide justification as to how the test article dipped (b) (4) prior to testing, represents your final, device that is intended to be inserted vaginally without such treatment.

Biocompatibility Review – Review of muscle implantation in rats (90-day)

Test Facility: (b) (4)

GLP Study Number: 17-00891-G1.

Method: The test article, identified as "Nuvaring Ethinyl Estradiol Vaginal Ring, delivers 0.120mg/0.015 mg per day" was surgically implanted intramuscularly in female rats to evaluate potential local tissue response at the implantation site as well as systemic responses, per ISO 10993-6 and ISO 10993-11, respectively. The Amneal placebo ring (subject ring with no drug) identified as "Sponsor Control" was also implanted in separate animals to evaluate tissue response to the subject ring with no drug. A total of 10 rats were assigned to two each group (treatment, Sponsor control and negative control (plastic) – 3 groups total).

The test article was aseptically cut to 1 cm in length piece and 3 mm in diameter. The vaginal ring used clinically in humans has a length of approximately 16 cm. As a result, 16 cm per adult female (60 kg) corresponds to ~ 0.26 cm/kg of ring surface area to body mass ratio under clinical use in humans. Based

on this clinical ratio, approximately one specimen of 1 cm in length and 3 mm in diameter was placed on either side of the spine intramuscularly in rats (with body mass of 0.35 kg). This represents an exaggerated factor of 10 x given that the calculated surface of test specimen was 0.9 cm (0.9/0.35 = 2.6 ring surface area to body mass ratio).

The steam sterilized control article was also cut to measure approximately 1 cm in length and intramuscularly implanted in the same way. The Sponsor control was dipped (b) (4) prior to being prepared for implantation at dimensions of 1 cm (length) x 3 mm (width). It is unclear why the Sponsor control was dipped (b) (4) to surgical implantation in the animal.

Each animal was weighed prior to implantation. The animals were maintained for a period of 90 days. During the study, all test animals were monitored for general health condition, body weight changes and food consumption. 90-days following implantation, blood samples were collected for clinical pathology parameters evaluation prior to humane euthanasia and gross necropsy. Tissues were collected and select organ weights were measured. All collected tissues were prepared for microscopic examination and evaluated. Implant sites were evaluated microscopically as well as macroscopically.

Evaluation and Statistical Analysis: Quantitative data from this study, e.g. body weights, were analyzed by appropriate statistical procedures. Any significant differences are further assessed for biological relevance by comparison to the literature and historical data. Any differences between control and treated animals are considered statistically significant only if the probability of the differences being due to chance is equal to or less than 5% ($p \sim 0.05$).

Results:

- At tissue trimming, it was observed that Animal #18, intended as a test animal, was implanted with the plastic control and Animal #29, intended as a plastic control animal was found implanted with test material. These animals were removed from the assigned groups and reassigned and evaluated in the appropriate groups.

- None of the test or control animals exhibited any abnormal clinical observations and none of the animals exhibited signs of toxicity over the course of the study. All animals survived the duration of the study.

- All animals gained weight over the course of the study. The test and Sponsor control animals both gained weight, however, weight gains in the Sponsor control and negative control animals at each time period were greater than that in the test group of animals. Weight gains over the course of the study between Sponsor control and plastic control groups were not statistically different.

- The Sponsor control and negative control animals were observed with statistically significant greater hematocrit parameters and statistically significant lower platelet concentration (in the Sponsor control) as compared to the test animals. There were no significant differences between the test group and the plastic control group for any of the hematology parameters.

- Clinical Chemistry: The differences between Sponsor control and plastic control groups were not considered biologically significant or test article related based on the (b) (4) historical ranges. The results observed indicate there were no Sponsor control article related effects on clinical chemistry parameters.

- There were no statistically significant differences between the test article, Sponsor control and negative control groups for coagulation parameters.

- Organ Weights: The Sponsor control and negative control groups were observed with statistically significant lower relative (organ weight to body weight) brain weights, absolute and relative liver weights, absolute and relative kidney weights, and relative spleen weights as compared to the test group. There were no abnormal microscopic findings in the brains of test or Sponsor control animals. There were no statistically significant differences between the Sponsor control group and the plastic control group for organ weights or relative organ weights.

- Microscopic assessment of the implant sites demonstrated no significant difference between the test and control implantation sites. The responses to the test or either of the control articles were minimal. The Bioreactivity Ratings for the 90-day time period was 0.3 as compared to the Sponsor control (score of 0) and 0.2 as compared to the plastic control (score of 0), each indicating no reaction as to the Sponsor or plastic control sites.

- The main microscopic findings were in the reproductive organs (ovaries, uteri and cervixes), such as hypoplasia (decreased numbers or absent corpora luteum) in the ovaries (average score: 0.4 in the Sponsor control group, 3.8 in the test group, and 0 in the plastic control group), squamous metaplasia (0 of 10 in the Sponsor control group, 8 of 10 in the test group, and 0 of 10 in the plastic control group) and cytoplasmic vacuoles (0 of 10 in the Sponsor control group, 2 of 10 in the test group, and 0 of 10 in the plastic control group) in the uteri, and hypertrophic epithelium (1 of 10 in the Sponsor control group, 4 of 10 in the test group, and 0 of 9 in the plastic control group) and inflammatory cells (1 of 10 the Sponsor control group, 3 of 10 in the test group, and 0 of 9 in the plastic control group) in the cervixes. The numbers of follicles in the ovaries were close with no significant differences between the three groups.

Conclusion:

- The focus of all findings was on the Sponsor control (which is the subject device for ANDA210830 but with no drug). Accordingly, tissue response (systemic and local) to the Sponsor control is considered to be not statistically significant than that in response to the negative plastic control. Therefore, the concerns observed in the previous study on the subject IVR with drug are mitigated.

- There was no evidence of systemic toxicity from the test article following intramuscular implantation in rats with Amneal ring (with no drug) for 90 weeks. This indicates that the Amneal ring itself is no inherently toxic and is systemically and locally tolerable.

Comments:

- The animals were evaluated for local and systemic indications of toxicity related to the test article. There was no evidence of local irritation and tissue response to the test specimen.

- Dosing exaggeration of 10 x in rats is acceptable.

- Intramuscular implantation as a substitute for chronic systemic toxicity testing is acceptable because of the following considerations done in the study:

    - Number of animals used for the study – 10 per group
    - Test and control specimens implanted in separate animals.
    - Dosing done represents exaggerated exposure-dose compared to that in humans during clinical use.
    - Duration of exposure is clinically relevant to subacute/subchronic exposure-duration, although clinically humans are exposed to new device after 90 days and this represents repeat dose exposure.
    - Exposure to test specimen represents a continuous, cumulative exposure for 90-days
    - Statistical analysis done appropriately taking into consideration separate analysis of treatment and control groups.
    - Route of exposure may not be directly relevant to the clinical route of IVR exposure via vaginal cavity, but it is not completely irrelevant considering possible exaggerated response due to increased vascularity in muscle tissue.
    - All parameters including local irritation response, hematology, clinical chemistry, organ weight, body weight, histology, and necropsy of tissues done as recommended in ISO 10993-11 for assessing systemic toxicity in animals.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)
Division of Manufacturing and Quality (DMQ)

ICCR QUALITY SYSTEM REVIEW MEMO

Date:	June 15, 2018
To:	Laurie Nelson, Consumer Safety Officer OMPT/CDER/OPQ/OPF/DIA/IABIII Laurie.Nelson@fda.hhs.gov
CC:	Office of Combination Product, Combination@fda.hhs.gov Steven Yang, Regulatory Business Project Manager OPRO/DRPMI/RBPMBII, Office of Pharmaceutical/CDER Steven.Yang@fda.hhs.gov CDER/OPQ/OPF, Juandria.Williams@fda.hhs.gov
Through:	Nazia Rahman, Lead Consumer Safety Officer, Office of Compliance, CDRH, WO 66, Rm 3458, Nazia.Rahman@fda.hhs.gov
From:	Therese Barber, Consumer Safety Officer, Office of Compliance, CDRH, WO 66, Rm 3430, Therese.Barber@fda.hhs.gov
Applicant/Licensure:	Amneal Pharmaceuticals FEI# 3008861605
Submission (Type & Number):	ANDA 210830
Combination Product Name:	Etonogestrel/Ethinyl Estradiol Ring
Combination Product Indications for Use:	This combination product is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.
Device Constituent (Type):	Vaginal Ring

ICCR Sharepoint Tracking Number:	ICCR2018-02958
ICCR CTS Tracking Number:	ICC1800432
Pre-Approval Facility Inspection:	Yes, Post-Approval Inspections Also Requested
Documentation Review (Status):	**Response Adequate**
CDRH/OC Recommendation:	**Approvable**

CDRH received consults from CDER requesting the identification of the device manufacturing sites for ANDA 210830 which will require a device inspection. The initial consult (ICC1700845/ICCR2017-01796) was completed on April 23, 2018. Specifically, for this consult, CDER requested review of the FDA-483, EIR and the firm's response to the FDA-483 (see ICC1800432_ICCR2018_02958 NAI/VAI EIR Review Checklist 15 June 2018).

PRODUCT DESCRIPTION

The firm's Etonogestrel/Ethinyl estradiol vaginal ring is a non-biodegradable, flexible, transparent, combination contraceptive vaginal ring containing two active components, a progestin, Etonogestrel (13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one) and an estrogen, Ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol). Etonogestrel/Ethinyl estradiol vaginal ring is indicated for the prevention of pregnancy while providing menstrual cycle control. The route of administration is vaginal. Each ring is to be used for one cycle; a cycle consists of 3 weeks of ring use followed by a one-week ring-free interval. When placed in the vagina, each ring releases on average 0.120 mg/day of Etonogestrel and 0.015 mg/day of Ethynyl estradiol over a three-week period of use. The (b) (4) is made of Ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate and contains 11.7 mg Etonogestrel and 2.7 mg Ethynyl estradiol. It has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.

REGULATORY HISTORY

The following facility was identified as being involved in the manufacturing and/or development of the combination product, Etonogestrel/Ethinyl Estradiol Ring, in ANDA 210830.

Combination Product Applicant

Firm Name: Amneal Pharmaceuticals
Address: 1 New England Avenue, Piscataway, NJ 08854
FEI: 308861605

Responsibility – This is the applicant and manufacturer of container/closure system for this combination product. Therefore, this facility is responsible for addressing the 21 CFR 820 Quality System (QS) requirements.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted 3/6/2017 to 3/20/2017. The inspection covered drug CGMP and was classified NAI.

Inspection Recommendation:

An inspection is not required because a recent medical device inspection of the firm was acceptable.

DOCUMENTATION REVIEW

Combination Product ANDA 210830 Proposed Indication for Use: This combination product is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.

1.	Was the last inspection of the finished combination product manufacturing site, OAI for drug or device observations?	YES ☐	NO ☒	NA ☐
2.	Is the device constituent a PMA or class III device?	YES ☐	NO ☒	UNK ☐
3.	Is the final combination product meant for emergency use?	YES ☐	NO ☒	UNK ☐
4.	Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	YES ☐	NO ☒	UNK ☐
5.	Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	YES ☐	NO ☒	UNK ☐

6. Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	YES ☐	NO ☒	UNK ☐
7. Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	YES ☐	NO ☒	UNK ☐

cGMP Risk: ☒ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.

☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.

The Quality System requirements applicable to a particular manufacturer may vary based upon the type of constituent parts being manufactured and the aspects of their manufacture that are being performed at that site. All manufacturers are responsible for ensuring compliance with all requirements applicable to the manufacturing activities at their facilities. Where multiple facilities bear responsibility for various aspects of the manufacturing process, only the holder of the application or clearance for the product is responsible for compliance with all aspects of the Quality System requirements applicable to the entire manufacturing process and across all facilities.

Applicant: Amneal Pharmaceuticals
1 New England Avenue, Piscataway, NJ 08854
FEI: 308861605

Applicable Site	**Management Responsibility, 21 CFR 820.20**		
Amneal Pharmaceuticals ☐	The firm provided a summary of how the firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4).	YES ☒	NO ☐
	The firm provided a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.	YES ☒	NO ☐

	21 CFR 820.20 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product) See the ICCR review memo dated April 23, 2018 (page 4).		
Applicable Site Amneal Pharmaceuticals ☒	**Design Controls, General, 21 CFR 820.30** The firm explained how it utilized the design control process to develop the combination product under review and provided a description of its design control procedures.	YES ☒	NO ☐
	The firm provided a copy or a summary of the plan used to design the combination product.	YES ☒	NO ☐
	21 CFR 820.30 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product) See the ICCR review memo dated April 23, 2018 (pages 4-5).		
Applicable Site Amneal Pharmaceuticals ☒	**Purchasing Controls, 21 CFR 820.50** The sponsor firm should summarize its procedure(s) for purchasing controls.	YES ☒	NO ☐
	The summary should describe the firm's supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers.	YES ☒	NO ☐
	The summary should define how the firm maintains records of acceptable suppliers and how it addresses the purchasing data approval process.	YES ☒	NO ☐
	The summary should explain how the firm will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.	YES ☒	NO ☐
	The firm should explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product.	YES ☒	NO ☐
	The firm should provide a description of how it applied the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).	YES ☒	NO ☐
	21 CFR 820.50 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product) See the ICCR review memo dated April 23, 2018 (pages 5-6).		
Applicable Site	**Corrective and Preventive Action (CAPA), 21 CFR 820.100** The sponsor firm should provide a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System.	YES ☒	NO ☐

Amneal Pharmaceuticals ☒	The CAPA system should require: a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;	YES ☒	NO ☐
	b. Investigation of nonconformities and their causes;	YES ☒	NO ☐
	c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and	YES ☒	NO ☐
	d. Verification or validation of the actions taken.	YES ☒	NO ☐
	21 CFR 820.100 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product) See the ICCR review memo dated April 23, 2018 (page 6).		
Applicable Site Amneal Pharmaceuticals ☒ None: ☒	**Installation, 21 CFR 820.170 (check none if Installation is not required for the combination product)** Installation is not required for this combination product.	YES ☐	NO ☐
	21 CFR 820.170 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)		

Applicable Site Amneal Pharmaceuticals ☒ None: ☒	**Servicing, 21 CFR 820.200 (check none if Servicing is not required for the combination product)** Servicing is not required for this combination product.	YES ☐	NO ☐
	21 CFR 820.200 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)		
Applicable Site Amneal Pharmaceuticals ☒	**Production and Process Controls**	YES ☒	NO ☐
	Production and Process Control In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product) See the ICCR review memo dated April 23, 2018 (pages 5-6).		
Applicable Site Amneal Pharmaceuticals ☒	The sponsor should provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process. If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).	YES ☒	NO ☐
	Production and Process Control In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product) See the ICCR review memo dated April 23, 2018 (page 7-8).		
Applicable Site Amneal Pharmaceuticals ☒	The sponsor should explain how it will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. The firm should specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. The firm should also provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product. If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).	YES ☒	NO ☐
	Production and Process Control In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product) See the ICCR review memo dated April 23, 2018 (page 8).		

Documentation Review Recommendation:

No Deficiencies Identified. The application and the firm's response were searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application and response for compliance with the applicable quality system requirements showed no deficiencies. No additional information is required for the documentation review. Also, the review of the FDA-483, EIR, and the firm's response to the FDA-483 did not showed any deficiencies. The response dated 4/26/2018 appears to be adequate.

RECOMMENDATION

The application for ANDA 210830 Etonogestrel/Ethinyl Estradiol Ringis approvable from the perspective of the applicable Quality System Requirements.

OC Decision: Approvable (Recommend approval to CDER)

Reviewer: Digitally signed by Therese Barber -S
Date: 2018.06.18 18:11:21 -04'00'

Branch Chief or Lead CSO: Nazia Rahman -S
2018.06.18 14:25:40 -04'00'

(b) (4)

3. (b) (4)

4. (b) (4)

5.

6.

7.

Biopharmaceutics

1. You manufactured five batches with different thickness of ring membrane to conduct discriminatory power study of the proposed dissolution method. However, you did not report if these five batches (b) (4) Submit the (b) (4) information of the following five batches to the Agency for review:
   Batch G16K058057P (80 µm)
   Batch G16K058057T (90 µm)
   G16K058057J (100 µm)-Target
   Batch G16K058057U (110 µm)
   Batch G16K058057Q (120 µm)
   Also, provide the (b) (4) in each formulation of the above five batches.

2. Based on the data provided, your proposed specifications are not appropriate. We request that you acknowledge your acceptance of the following specifications for your proposed products:

   Etonogestrel

   (b) (4)

   Ethinyl Estradiol

   (b) (4)

   It should be noted that for Days 8-14, daily release rate should be used to determine if it meets the above the specifications. Acceptance Table 1 of USP <724> should be used to determine whether the acceptance criteria are met at different stages.

   Acknowledge your acceptance of the above dissolution specifications and update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

3. Clarify if you have manufactured any commercial (scale-up) batches. If yes, submit the complete dissolution data (individual, mean, SD, RSD, profiles) to the Agency for review.

CDRH-Device

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation

ANDA210830: Amneal Pharmaceuticals Etonogestrel/Ethinyl Estradiol Ring– Device Consult

DATE: December 20, 2017

FROM: Jason Roberts, Ph.D., Biomedical Engineer
CDRH/ODE/DRGUD/OGDB

TO: Steven Yang
CDER/OPQ/OPRO/DRBPMI/RBPMBII

CC: Sharon Andrews, Branch Chief
CDRH/ODE/DRGUD/OGDB

Joyce Whang, Ph.D., Deputy Director, Science
CDRH/ODE/DRGUD

Lead Consulting Reviewer: Jason Roberts, Ph.D. Biomedical Engineer CDRH/ODE/DRGUD/OGDB
Device Biocompatibility: Pushya Potnis, Ph.D. Toxicologist CDRH/ODE/DRGUD/ULDB

I. Purpose of Submission and Scope:

This submission is a new drug application for the Amneal Pharmaceuticals Etonogestrel/Ethinyl Estradiol Ring. The initiating division has asked that CDRH to identify any general concerns with a vaginal ring type product from a device perspective.

The initiating division specified that module 3 of the submission includes quality control tests, manufacturing process descriptions, and specifications. The initiating division also noted the sponsor references (b) (4) for the polymers utilized in the rings.

The following information was reviewed as part of this consult:

- Module 3.2.P, product description, specifications, manufacturing process, stability
- Module 4.2.3.7, biocompatibility

In this review memo, I will provide an overview of the information provide along with my comments. Review issues will be identified and appear **in bold** in the review below.

In review of intravaginal ring products, CDRH will review the product specifications as they relate to the physical properties of the ring, the biocompatibility of the product, mechanical performance, and compatibility with other intravaginal products and devices (such as male condoms). I will defer to the initiating division on review of the stability of the drug product and evaluation of the product labeling and clinical use.

II. Device Description:

Intended use

The Amneal Pharmaceuticals Etonogestrel/Ethinyl Estradiol Ring is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.

Product description

The device is a clear, flexible ethylene vinylacetate ring intended to be placed in the vagina (figure below).

The device has the following dimensional specifications:

Specification	Value
Weight	(b) (4)
Color	Colorless to nearly colorless (cloudy white)
Outer diameter	(b) (4)

Cross sectional diameter	(b) (4)
Surface area	
Volume	

The submission includes a single dose ring intended to delivery 0.120/0.015 mg/day Etonogestrel/Ethinyl estradiol. The ring is primarily ethylene vinylacetate, but contains the two drug products etonorgestrel and ethinyl estradiol and excipient magnesium stearate. The exact formulation is the following:

Ingredient	Quantity per ring (mg)	%w/w of total ring weight
Ethinyl estradiol	2.700	(b) (4)
Etonorgestrel	11.700	
Ethylene vinylacetate copolymer, 28% vinylacetate (b) (4) (b) (4)	(b) (4)	
Ethylene vinylacetate copolymer, 9% vinylacetate (b) (4) (b) (4)		
Magnesium stearate		
(b) (4)		

(b) (4) and are individually packaged into re-closable aluminum laminate sachets. Three sachets will be packaged per carton of product.

The device description information is complete. I have no concerns with the design of the ring.

III. Biocompatibility

CDRH recommends that biocompatibility of device be evaluated per the CDRH guidance "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process," issued June 16, 2016. Biocompatibility testing of devices is typically conducted on finished and final devices (i.e., after all processing, packaging, sterilization, etc.), so that any biocompatibility issues resulting from device or packaging materials, manufacturing processes and/or the packaging and handling processes can be elucidated. Biocompatibility evaluation of devices is risk based, depending on type and duration of contact. The subject product is intended to be in place for three weeks (21 days). However, due to its expected repeat use, it may be considered in contact with the patient for much longer than 21 days (as the patient will use a new ring to continue contraception). Therefore, it is considered a permanent (>30 day) mucosal contact device, and the CDRH guidance recommends the risks associated with cytotoxicity, sensitization, irritation, acute systemic

toxicity, material-mediated pyrogenicity, subchronic toxicity, chronic toxicity, genotoxicity and implantation be evaluated.

Dr. Pushya Potnis provided a consulting review of the biocompatibility testing conducted (see appendix 1 of this memo). His comments are summarized below:

Dr. Potnis reviewed reports for cytotoxicity, acute systemic toxicity, intracutaneous reactivity, material mediated pyrogenicity, vaginal irritation, sensitization, implantation/systemic toxicity (28d), and genotoxicity. These tests are those recommended in the CDRH guidance for devices of the >30 day mucosal contact.

Upon review of the information, Dr. Potnis had concerns with observations made in the 28-day systemic toxicity analysis in rats. The test data indicated extramedullary hematopoiesis, lower hematological and clinical chemistry parameters, and significant reduction in coagulation time in test animals as compared to the controls. There were also abnormal findings in the necropsy data. While Dr. Potnis noted this could be caused by the exposure to the drug, there are no data to rule out the possibility of systemic effects secondary to exposure to the vaginal ring component. Therefore, Dr. Potnis felt that additional information is necessary to demonstrate biocompatibility of the ring. Specifically, Dr. Potnis recommended the following deficiencies:

1. You provided test results of the 28-day systemic toxicity studies in rats via intramuscular implantation (b) (4) Test Reports # 17-00131-G1 and 17-00133-G1). The test data revealed greater extramedullary hematopoiesis observed in the spleens of the test animals, lower hematological and clinical chemistry parameters, and significant reduction in coagulation time as compared to those in the control animals. There is indication of test article related effects on the systemic organ weights, including heart, thymus and ovaries. The necropsy data shows evidence of thymus atrophy, hypoplasia in the ovaries, hypertrophic mucosa/cytoplasmic vacuoles in the ovary ducts, hypertrophic endometrium, and hypertrophic epithelium/cytoplasmic vacuoles/inflammatory cell in the cervices in the test group compared to those in the control group. Based on the results of the two separate studies, the observed tissue responses likely resulted from drug interference with systemic organs. However, there are no data to rule out the possibility that the observed systemic effects are secondary to exposure to the vaginal ring component of your product. In light of these findings, it is recommended that you conduct a sub-acute/sub-chronic systemic toxicity test on the finished vaginal ring component of your product (with no drug) to demonstrate that the ring-component, itself, is not inherently toxic to systemic organs.
2. (b) (4)

Based upon Dr. Potnis' recommendations, these deficiencies should be forwarded to the sponsor.

IV. Mechanical Performance

Mechanical performance is important to the safe and effective use of intravaginal ring products. CDRH recommends that sponsors evaluate the following mechanical properties of IVRs:

(b) (4)

In addition to mechanical strength measurements, dimensional specifications should be sufficiently robust to ensure performance of the product. As noted in the device description section above, the sponsor has adequately characterized the dimensions of the device. In addition, the sponsor has provided dimensional analysis to support that product continues to meet specification.

The sponsor states in their specifications that the ring tensile strength shall be no less than (b) (4) and no one ring less than (b) (4) in an average of 6 rings. The method is adopted from ASTM D1414-15, which is a method standard for o-rings. Results from validation demonstrate the tensile strength of each of 6 samples was greater than (b) (4). **This is acceptable.**

(b) (4)

V. Shelf-life

The determination of shelf-life for the vaginal ring should include an evaluation of the mechanical properties of the ring described in Section IV following storage to assess signs of degradation. In the submission, the sponsor has performed stability evaluation including tensile strength to the same methods as described in section IV above. **However, the sponsor should evaluate the additional recommended mechanical design/performance parameters over the course of the proposed shelf-life.**

VI. Condom and other Intravaginal Device Compatibility

Because of the extended time in which an IVR is in use, CDRH recommends that sponsors evaluate the risk associated with the use of other intravaginal products and devices during use. Of particular concern are male condoms, which, if incompatible with the IVR, pose an infection risk. Therefore, CDRH typically recommends that sponsors provide a risk analysis for the use of intravaginal products such as lubricants, and for sponsors to provide data demonstrating the ring is compatible with condoms. T**he sponsor did not provide a risk analysis of the use of other intravaginal products with the use of the IVR, and should provide this information. In addition, the sponsor did not provide evidence to demonstrate the ring is compatible with condoms. Therefore, the sponsor should provide additional supporting information demonstrating the ring's compatibility with condoms. Specifically, we recommend testing per (b) (4) properties upon exposure to the intravaginal ring.**

VII. Summary/Recommendations:

The sponsor has not provided sufficient information on the IVR product. In order to demonstrate the safety and effectiveness of the product, the sponsor will need to provide additional information regarding biocompatibility, mechanical properties, shelf-life, and compatibility with other intravaginal products. I recommend the initiating division communicate the following deficiencies to the sponsor:

Biocompatibility

1. You provided test results of the 28-day systemic toxicity studies in rats via intramuscular implantation ((b) (4) Test Reports # 17-00131-G1 and 17-00133-G1). The test data revealed greater extramedullary hematopoiesis observed in the spleens of the test animals, lower hematological and clinical chemistry parameters, and significant reduction in coagulation time as compared to those in the control animals. There is indication of test article related effects on the systemic organ weights, including heart, thymus and ovaries. The necropsy data shows evidence of thymus atrophy, hypoplasia in the ovaries, hypertrophic mucosa/cytoplasmic vacuoles in the ovary ducts, hypertrophic endometrium, and hypertrophic epithelium/cytoplasmic vacuoles/inflammatory cell in the cervices in the test group compared to those in the control group. Based on the results of the two separate studies, the observed tissue responses likely resulted from drug interference with systemic organs. However, there are no data to rule out the possibility that the observed systemic effects are secondary to exposure to the vaginal ring component of your product. In light of these findings, it is recommended that you conduct a sub-acute/sub-chronic systemic toxicity test on the finished vaginal ring component of your product (with no drug) to demonstrate that the ring-component, itself, is not inherently toxic to systemic organs.

2. (b) (4)

Non-clinical performance testing

3. (b) (4)

(b) (4)

Intravaginal Device Compatibility

4. (b) (4)

5.

(b) (4)

Digital Signature Concurrence Table	
Reviewer Sign-Off	Jason Roberts -S 2017.12.20 15:13:05 -05'00'
Branch Chief Sign-Off	Sharon M. Andrews -S 2017.12.20 15:25:49 -05'00'
Division Director Sign-Off	Charles Viviano -S 2017.12.20 16:42:00 -05'00'

Appendix 1: Biocompatibility memo; Pushya Potnis, Ph.D., CDRH/ODE/DRGUD/ULDB

Consult Memo

Date: December 20th, 2017

To: Jason Roberts, DRGUD/OGDB/ODE

From: Pushya Potnis, DRGUD/ULDB/ODE

RE: Nuvaring Ethinyl Estradiol Vaginal Ring (ANDA210830)

This consult is provided to Dr. Roberts in response to his request for the biocompatibility review of the subject device, Etonogestrel/Ethinyl estradiol vaginal ring that is indicated for the prevention of pregnancy while providing menstrual cycle control.

The combination product is manufactured by Amneal Pharmaceuticals.

The scope of this memorandum is limited to the biocompatibility testing provided by the Sponsor.

Recommendation:

To fully evaluate the biocompatibility of the subject device, additional information is needed to address the concerns in the deficiencies listed below (Page 4 of this memorandum).

_____

Pushya Potnis, PhD

Biocompatibility Review:

1. The subject device is a Etonogestrel/Ethinyl estradiol vaginal ring is a non-biodegradable, flexible, transparent to translucent ring (reported as colorless to almost colorless ring), that is circular in shape, and a combination contraceptive vaginal ring containing two active components, a progestin, Etonogestrel, and an estrogen, Ethinyl estradiol, estradiol vaginal ring.

2. The intravaginal ring (IVR) is manufactured by Amneal Pharmaceuticals.

3. The IVR is indicated for the prevention of pregnancy while providing menstrual cycle control

4. The route of administration is vaginal.

5. Each ring is to be used for one cycle; a cycle consists of 3 weeks of ring use followed by a one-week ring-free interval.

6. When placed in the vagina, each ring releases on average 0.120 mg/day of Etonogestrel and 0.015 mg/day of Ethynyl estradiol over a three-week period of use.

7. The (b) (4) is made of Ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate and contains 11.7 mg Etonogestrel and 2.7 mg Ethynyl estradiol.

8. The IVR has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.

9. The strength and formulation of the final, finished product are listed in the Table below:

Ingredients	**Finished Product Strength: 11.7 mg/2.7 mg**		**Component function**	**Quality Standard**
	mg/Unit	**%w/w**		
Ethinyl Estradiol, USP (b) (4)	2.700	(b) (4)	Active	USP
Etonogestrel (b) (4)	11.700		Active	USP
Ethylene Vinylacetate Copolymer, 28% Vinylacetate (b) (4)	(b) (4)		(b) (4)	Non-compendial*
Ethylene Vinylacetate Copolymer, 9% Vinylacetate (b) (4)				Non-compendial*
Magnesium Stearate, NF				USP/NF
(b) (4)				USP/NF
Total Tablet Weight		**100.0**		

10. Table below shows physical description of the Amneal's generic product:

Physical Description of Amneal's Generic Product		
Product		**Amneal's Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day**
Dimensions N = 10	Average Weight (mg)	(b) (4)
	Average Ring Outer Diameter (mm)	
	Average Cross Sectional Diameter (mm)	
	Surface Area (mm^2)	
	Volume (mm^3)	

11. No material-specific information on the ring material of the IVR is provided in the submission.

12. Given the intended use of the subject device, the IVR is considered to be a surface device, contacting mucosal membranes for prolonged duration of contact (> 30 days).

13. The following endpoints are recommended for assessment of biocompatibility of the IVR device: cytotoxicity, vaginal irritation, sensitization, acute systemic toxicity, sub-acute/sub-chronic systemic toxicity, material-mediated pyrogenicity, genotoxicity and implantation.

14. Biocompatibility testing was conducted on the test article identified as "Etonogestrel/ Ethinyl Estradiol Vaginal Rings, delivers 0.120mg/0.015 mg per day" and tested at (b) (4)

15. The Sponsor has provided the following test reports in for evaluating the biocompatibility of the subject device:

Test	Test Report	Location
Cytotoxicity (4 separate studies)	17-00131-G2	L-Drive
Acute systemic toxicity study	17-00131-G10	L-Drive
Intracutaenous Irritation testing	17-00131-G3	L-Drive
Material mediated pyrogenicity	17-00131-G9	L-Drive
Vaginal irritation test	17-00131-G8	L-Drive

Sensitization testing	17-00131-G4	L-Drive
Implantation/systemic toxicity 28-d	17-00131-G1	L-Drive
Implantation/systemic toxicity 28-d	17-00133-G1	L-Drive
Genotoxicity - Ames	17-00131-G11	L-Drive
Genotoxicity – Mouse lymphoma	17-00131-G6	L-Drive

[Detailed review of each test is provided as a separate attachment to this memorandum].

Deficiency:

1. You provided test results of the 28-day systemic toxicity studies in rats via intramuscular implantation (b) (4) Test Reports # 17-00131-G1 and 17-00133-G1). The test data revealed greater extramedullary hematopoiesis observed in the spleens of the test animals, lower hematological and clinical chemistry parameters, and significant reduction in coagulation time as compared to those in the control animals. There is indication of test article related effects on the systemic organ weights, including heart, thymus and ovaries. The necropsy data shows evidence of thymus atrophy, hypoplasia in the ovaries, hypertrophic mucosa/cytoplasmic vacuoles in the ovary ducts, hypertrophic endometrium, and hypertrophic epithelium/cytoplasmic vacuoles/inflammatory cell in the cervices in the test group compared to those in the control group. Based on the results of the two separate studies, the observed tissue responses likely resulted from drug interference with systemic organs. However, there are no data to rule out the possibility that the observed systemic effects are secondary to exposure to the vaginal ring component of your product. In light of these findings, it is recommended that you conduct a sub-acute/sub-chronic systemic toxicity test on the finished vaginal ring component of your product (with no drug) to demonstrate that the ring-component, itself, is not inherently toxic to systemic organs.

2. (b) (4)

Attachment – Review checklist for biocompatibility testing:

Includes biocompatibility testing done on the following:

Test	Test Report	Location
Cytotoxicity (4 separate studies)	17-00131-G2	L-Drive
Acute systemic toxicity study	17-00131-G10	L-Drive
Intracutaenous Irritation testing	17-00131-G3	L-Drive
Material mediated pyrogenicity	17-00131-G9	L-Drive
Vaginal irritation test	17-00131-G8	L-Drive
Sensitization testing	17-00131-G4	L-Drive
Implantation/systemic toxicity 28-d	17-00131-G1	L-Drive
Implantation/systemic toxicity 28-d	17-00133-G1	L-Drive
Genotoxicity - Ames	17-00131-G11	L-Drive
Genotoxicity – Mouse lymphoma	17-00131-G6	L-Drive

ISO In Vitro Cytotoxicity Study (ISO 10993-5:2009) – L929	
Test Report Documentation	
Report #: 17-00131-G13	FDA Submission Number: ANDA210830
Report Date: 02/14/17	Submission page/Att: Provided as separate attachments (available on L-drive)
Test Facility Name: (b) (4)	
Facility City: (b) (4)	

ISO In Vitro Cytotoxicity Study (ISO 10993-5:2009) –(Qualitative and Quantitative Test)		
Device Tested		
Test Article	☐✓ Finished sterilized device ☐ Other* Etonogestrel/ Ethinyl Estradiol Vaginal Rings, delivers	*Describe test article and check with focal point on acceptability of the justification for not testing the finished sterilized device.

ISO In Vitro Cytotoxicity Study (ISO 10993-5:2009) –(Qualitative and Quantitative Test)			
	0.120mg/0.015 mg per day		
Were only the direct and indirect patient contacting portions of the device tested?	☐✓ Yes	☐ No*	*If No, describe what has been tested and check with focal point on acceptability of the justification for not testing only the direct and indirect patient contacting portions of the device.
Was the study done under GLP conditions?	☐✓ Yes	☐ No*	*If No, ask sponsor to justify why not done under GLP requirements (for IDE and PMA submissions).
Extraction Conditions			
Test Article Extraction Ratio	☐ 6 cm^2: ml (<0.5mm thick) ☐✓ 3 cm^2: ml (>0.5mm thick) ☐ 1.25 cm^2: ml (elastomer >1mm thick) ☐ 0.2 g: ml (elastomers)* ☐ 0.1 g: ml (non-elastomers)* ☐ Other*: _____		*Check with focal point if weight based extraction conditions or non-traditional extraction conditions are used.
Extraction Vehicle(s)	☐✓ Culture medium with serum ☐ Culture medium without serum* ☐ Physiological saline solution* ☐ Other suitable solvent*_____		* Check with focal point if non-traditional extraction vehicles are used.
Time/ Temperature	☐✓ 24 h at 37°C (required for Culture medium with serum) ☐ 50°C for 72h* ☐ 70°C for 24h* ☐ 120°C for 1h*		* Check with focal point on acceptability of time/temperature conditions.

ISO In Vitro Cytotoxicity Study (ISO 10993-5:2009) –(Qualitative and Quantitative Test)			
	☐ Other*: _____		
pH Adjustment made to the sample extract	☐ Yes*	☐✓ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for adjusting the pH.
The Sample extract is filtered, centrifuged, diluted or processed in any other way	☐ Yes*	☐✓ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for the dilution.
Study Controls	☐✓ Extraction vehicles without test material ☐ Extract of material with no cytotoxic response* ☐ Extract of material with cytotoxic response* ☐ Other*: positive controls were SRM-A SRM-B and ZDBC; negative control was SRM-C as per guidlines		* Check with focal point on acceptability of controls.
Appearance of Extract	☐✓ Clear ☐ Cloudy* ☐ Particulates present in solution* ☐ Color*: _____		* Ask sponsor to explain extract appearance and justify validity of test results.
Extract Storage Conditions	☐✓ Used immediately ☐ Not mentioned in report* ☐ Storage Time*: _____ ☐ Storage Temperature*: _____		* Ask for updated test report to include description of storage conditions, and/or ask sponsor to justify why storage will not affect results, and check with focal point on validity of justification.
Methods			
Test System	☐✓ L-929 Mouse fibroblasts ☐ Suspension		* Check with focal point on acceptability of test system.

ISO In Vitro Cytotoxicity Study (ISO 10993-5:2009) –(Qualitative and Quantitative Test)			
	☐ Monolayer ☐ Other*:		
Assessment Times after Treatment	☐✓ Required: 24h at 37ºC ☐ Other*: 48 and 72 h		* Check with focal point if assessments do not include 24h timepoint and/or if non-traditional assessment times are included.
Assessment Methods (Qualitative Score of 2 or less may be acceptable)	☐✓ Qualitative evaluation: Test and control cultures assessed microscopically for changes in general morphology, vacuolization, detachment, cell lysis, and membrane integrity. Graded according to the following scale: 0 = No cytotoxicity 1 = Slight cytotoxicity 2 = Mild cytotoxicity 3 = Moderate cytotoxicity 4 = Severe cytotoxicity ☐ Quantitative evaluation: Measure cell death, inhibition of cell growth, cell proliferation or colony formation. The number of cells, amount of protein, release of enzymes, release of vital dye, reduction of vital dye or any other measurable parameter may be quantified by objective means (e.g., >30% reduction of cell viability is considered cytotoxic). * ☐ Other*:		* Check with focal point if non-traditional methods were used or if any quantitative parameters are observed.
Deviations	☐ Yes*	☐✓ No	*If Yes, describe the deviation, and check with focal point on acceptability of the justification for how the deviation may impact the results of the study.

ISO In Vitro Cytotoxicity Study (ISO 10993-5:2009) –(Qualitative and Quantitative Test)			
Results			
Did Study Cells Appear Normal Throughout the Study?	☐ Yes	☐✓ No*	* Check with focal point on acceptability of results.
Cell abnormalities reported?	☐ Yes*	☐✓ No	*If Yes, check with focal point to assess whether deaths are related to the use of the treatment extract, or to procedural issues.
Cytotoxicity Scores in Controls and Treated Cells Different?	☐✓ Yes* 73% cytotoxicity to neat extract (G13) 45% cytotoxicity to neat extract (G2) 104% cytotoxicity to neat extract (412-G1) 70% cytotoxicity to neat extract (418-G1)	☐✓ No	*If Yes, check with focal point to assess the extract should be considered cytotoxic.
Conclusion			
Cytotoxic Potential	☐✓ Non-Cytotoxic ☐ Cytotoxic*		*If the extract has cytotoxic potential, check with focal point.
Other comments			
Recommendation			
☐✓ Acceptable ☐ Unacceptable If Unacceptable, please discuss what the company will need to provide to resolve this issue:			

ISO Systemic Toxicity Study (ISO 10993-11:2006)	
Test Report Documentation	
Report #: 17-00131-G10 Report Date: 02/23/17 Test Facility Name: (b) (4) Facility City: (b) (4)	FDA Submission Number: ANDA210830 Submission page/Att: Provided as separate attachments (available on L-drive)

ISO Systemic Toxicity Study (ISO 10993-11:2006)			
Device Tested			
Test Article	☐✓ Finished sterilized device ☐ Other* Etonogestrel/ Ethinyl Estradiol Vaginal Rings, delivers 0.120mg/0.015 mg per day		*Describe test article and check with focal point on acceptability of the justification for not testing the finished sterilized device.
Were only the direct and indirect patient contacting portions of the device tested?	☐✓ Yes	☐ No*	*If No, describe what has been tested and check with focal point on acceptability of the justification for not testing only the direct and indirect patient contacting portions of the device.
Was the study done under GLP conditions?	☐✓ Yes	☐ No*	*If No, ask sponsor to justify why not done under GLP requirements (for IDE and PMA submissions).
Extraction Conditions			
Test Article Extraction Ratio	☐ 6 cm^2: ml (<0.5mm thick) ☐✓ 3 cm^2: ml (>0.5mm thick) ☐ 1.25 cm^2: ml (elastomer >1mm thick) ☐ 0.2 g: ml (elastomers)* ☐ 0.1 g: ml (non-elastomers)*		*Check with focal point if weight based extraction conditions or non-traditional extraction conditions are used.

ISO Systemic Toxicity Study (ISO 10993-11:2006)			
	☐ Other*: _____		
Extraction Vehicle(s)	☐✓ Required: 0.9% Sodium chloride [P]* ☐✓ Required: Vegetable oil [NP]* ☐ Alcohol in saline (1:20) ☐ Polyethylene Glycol (PEG) ☐ Other*: _____		* Check with focal point if test does <u>not</u> include both polar [P] and non-polar [NP] extracts and/or if non-traditional extraction vehicles are used.
Time/Temperature	☐ 37°C for 120h ☐ 37°C for 72h* ☐✓ 50°C for 72h ☐ 70°C for 24h ☐ 121°C for 1h ☐ Other*: _____		* Check with focal point on acceptability of time/temperature conditions.
pH Adjustment	☐ Yes*	☐✓ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for adjusting the pH.
Dilution	☐ Yes*	☐✓ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for the dilution.
Study Controls	☐ Extraction vehicles without test material ☐ Other*: _____		* Check with focal point on acceptability of controls.
Appearance of Extract	☐✓ Clear ☐ Cloudy* ☐ Particulates present in solution* ☐ Color*: ____		* Ask sponsor to explain extract appearance and justify validity of test results.

ISO Systemic Toxicity Study (ISO 10993-11:2006)			
Extract Storage Conditions	☐✓ Used immediately ☐ Not mentioned in report* ☐ Storage Time*: _____ ☐ Storage Temperature*: _____		* Ask for updated test report to include description of storage conditions, and/or ask sponsor to justify why storage will not affect results, and check with focal point on validity of justification.
Methods			
Test System	☐✓ 5 test and control mice/extract ☐ Other*: _____		* Check with focal point on acceptability of test system.
Injection Dose	☐✓ 50 ml/kg (saline, oil, alcohol) ☐ 10 g/kg PEG ☐ Other*: _____		* Check with focal point on acceptability of injection dose.
Injection Route	☐✓ Intravenous route (saline or alcohol extracts) ☐✓ Intraperitoneal route (oil and PEG) ☐ Other*: _____		* Check with focal point on acceptability of injection route.
Assessment Times	☐✓ Required: 4h* ☐✓ Required: 24h* ☐✓ Required: 48h* ☐✓ Required: 72h* ☐ Other*: ____		* Check with focal point if assessments do not include 4h, 24h, 48h, and 72h timepoints and/or if non-traditional assessment times are included.
Deviations	☐ Yes*	☐✓ No	*If Yes, describe the deviation, and check with focal point on acceptability of the justification for how the deviation may impact the results of the study.
Results			
Weight gain during course	☐✓ Yes	☐ No*	* Check with focal point on acceptability

ISO Systemic Toxicity Study (ISO 10993-11:2006)			
of study?			of results.
Deaths reported?	☐ Yes*	☐✓ No	*If Yes, check with focal point to assess whether deaths are related to the use of the treatment extract, or to procedural issues.
General appearance of animals during course of study as compared with controls?	☐✓ Similar ☐ Different*		*If Different, describe differences and check with focal point to assess whether the differences suggest toxicity.
Conclusion			
Systemic toxicity potential	☐✓ Not systemically toxic ☐ Systemically toxic		
Other comments			
Recommendation			
☐✓ Acceptable ☐ Unacceptable If Unacceptable, please discuss what the company will need to provide to resolve this issue:			

Material Mediated Pyrogenicity (USP 32-NF27 <151> Pyrogen Test)	
Test Report Documentation	
Report #: 17-00131-G9 Report Date: 02/01/17 Test Facility Name: (b) (4) Facility City: (b) (4)	FDA Submission Number: ANDA210830 Submission page/Att: Provided as separate attachments (available on L-drive)

Material Mediated Pyrogenicity (USP32-NF27 <151> Pyrogen Test)			
Device Tested			
Test Article	☐✓ Finished sterilized device ☐ Other* Etonogestrel/ Ethinyl Estradiol Vaginal Rings, delivers 0.120mg/0.015 mg per day		*Describe test article and check with focal point on acceptability of the justification for not testing the finished sterilized device.
Were only the direct and indirect patient contacting portions of the device tested?	☐✓ Yes	☐ No*	*If No, describe what has been tested and check with focal point on acceptability of the justification for not testing only the direct and indirect patient contacting portions of the device.
Was the study done under GLP conditions?	☐✓ Yes	☐ No*	*If No, ask sponsor to justify why not done under GLP requirements (for IDE and PMA submissions).
Extraction Conditions			
Test Article Extraction Ratio	☐ 6 cm^2: ml (<0.5mm thick) ☐✓ 3 cm^2: ml (>0.5mm thick) ☐ 1.25 cm^2: ml (elastomer >1mm thick) ☐ 0.2 g: ml (elastomers)* ☐ 0.1 g: ml (non-elastomers)* ☐ Other*: _____		*Check with focal point if weight based extraction conditions or non-traditional extraction conditions are used.
Extraction Vehicle(s)	☐✓ Required: 0.9% Sodium chloride [P]* ☐ Other*: _____		* Check with focal point if non-traditional extraction vehicle is used.
Time/Temperature	☐ 37°C for 120h ☐ 37°C for 72h* ☐✓ 50°C for 72h		* Check with focal point on acceptability of time/temperature conditions.

Material Mediated Pyrogenicity (USP32-NF27 <151> Pyrogen Test)			
	☐ 70°C for 24h ☐ 121°C for 1h ☐ Other*: _____		
pH Adjustment	☐ Yes*	☐✓ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for adjusting the pH.
Dilution	☐ Yes*	☐✓ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for the dilution.
Study Controls	☐ Optional: Extraction vehicle without test material ☐ Other*: _____		* Check with focal point on acceptability of controls.
Appearance of Extract	☐✓ Clear ☐ Cloudy* ☐ Particulates present in solution* ☐ Color*: _____		* Ask sponsor to explain extract appearance and justify validity of test results.
Extract Storage Conditions	☐ Used immediately ☐✓ Not mentioned in report* ☐ Storage Time*: _____ ☐ Storage Temperature*: _____		* Ask for updated test report to include description of storage conditions, and/or ask sponsor to justify why storage will not affect results, and check with focal point on validity of justification.
Methods			
Test System	☐✓ 3 test and 1 optional control rabbit ☐ Other*: _____		* Check with focal point on acceptability of test system.
Injection Dose	☐✓ 10 ml/kg (IV: marginal ear vein) ☐ Other*: _____		* Check with focal point on acceptability of injection dose.
Injection Route	☐ Intravenous route		* Check with focal point on

Material Mediated Pyrogenicity (USP32-NF27 <151> Pyrogen Test)			
	☐ Other*: _____		acceptability of injection route.
Assessment Times	☐ Required: 30 minutes* ☐✓ Required: 60 minutes * ☐✓ Required: 90 minutes * ☐✓ Required: 120 minutes * ☐✓ Required: 150 minutes * ☐✓ Required: 180 minutes * ☐ Other*: _____		* Check with focal point if assessments do not include 30, 60, 90, 120, 150, and 180 minute timepoints and/or if non-traditional assessment times are included.
Deviations	☐ Yes*	☐✓ No	*If Yes, describe the deviation, and check with focal point on acceptability of the justification for how the deviation may impact the results of the study.
Results			
Temperature rise greater than 0.5°C in a single rabbit?	☐ Yes*	☐✓ No	* Continue test using an additional 5 rabbits, material extract may be pyrogenic.
*Continued study: 3/8 animals with individual temperature rises > 0.5°C; or sum of all 8 animal's temperature rises > 3.3°C	☐ Yes*	☐✓ No	*If Yes, material extract is considered pyrogenic.
Conclusion			
Pyrogenicity potential	☐✓ Not pyrogenic ☐ Pyrogenic		
Other comments			
Recommendation			
☐✓ Acceptable			

Material Mediated Pyrogenicity (USP32-NF27 <151> Pyrogen Test)
☐ Unacceptable If Unacceptable, please discuss what the company will need to provide to resolve this issue:

ISO Maximization Sensitization Study (ISO 10993-10:2002)	
Test Report Documentation	
Report #: 17-00131-G4 Report Date: 03/20/17 Test Facility Name: (b) (4) Facility City: (b) (4)	FDA Submission Number: ANDA210830 Submission page/Att: Provided as separate attachments (available on L-drive)

ISO Maximization Sensitization Study (ISO 10993-10:2002)			
Device Tested			
Test Article	☐✓ Finished sterilized device ☐ Other* Etonogestrel/ Ethinyl Estradiol Vaginal Rings, delivers 0.120mg/0.015 mg per day		*Describe test article and check with focal point on acceptability of the justification for not testing the finished sterilized device.
Were only the direct and indirect patient contacting portions of the device tested?	☐✓ Yes	☐ No*	*If No, describe what has been tested and check with focal point on acceptability of the justification for not testing only the direct and indirect patient contacting portions of the device.
Was the study done under GLP	☐ Yes	☐✓ No*	*If No, ask the sponsor to justify why not done

ISO Maximization Sensitization Study (ISO 10993-10:2002)			
conditions?			under GLP requirements (for IDE and PMA submissions).
Extraction Conditions			
Test Article Extraction Ratio	☐ 6 cm^2: ml (<0.5mm thick) ☐✓ 3 cm^2: ml (>0.5mm thick) ☐ 1.25 cm^2: ml (elastomer >1mm thick) ☐0.2 g: ml (elastomers)* ☐ 0.1 g: ml (non-elastomers)* ☐ Other*: _____		*Check with focal point if weight based extraction conditions or non-traditional extraction conditions are used.
Extraction Vehicle(s)	☐✓ Required: 0.9% Sodium chloride [P]* ☐✓ Required: Vegetable oil [NP]* ☐ Other*: _____		* Check with focal point if test does <u>not</u> include both polar [P] and non-polar [NP] extracts and/or if non-traditional extraction vehicles are used.
Time/Temperature	☐ 37°C for 120h ☐ 37°C for 72h* ☐✓50°C for 72h ☐ 70°C for 24h ☐ 121°C for 1h ☐ Other*: _____		* Check with focal point on acceptability of time/temperature conditions.
pH Adjustment	☐ Yes*	☐✓ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for adjusting the pH.
Dilution	☐ Yes*	☐✓ No	*If Yes, describe the adjustment and check with focal point on the

ISO Maximization Sensitization Study (ISO 10993-10:2002)			
			acceptability of the justification for the dilution.
Study Controls	☐✓ Extraction vehicles without test material ☐ Other*: _____		* Check with focal point on acceptability of controls.
Positive Controls	☐✓ Dinitrochlorobenzene (DNCB)* ☐ Same source, strain, and treatment methods used for positive control testing and done within 3 months of test article test date? Concurrent positive control data provided in the test report		* If not, then the company should be asked to justify why testing should be considered capable of detecting a positive sensitizing response.
Appearance of Extract	☐✓ Clear ☐ Cloudy* ☐ Particulates present in solution* ☐ Color*:		* Ask sponsor to explain extract appearance and justify validity of test results.
Extract Storage Conditions	☐✓ Used immediately ☐ Not mentioned in report* ☐ Storage Time*: _____ ☐ Storage Temperature*: _____		* Ask for updated test report to include description of storage conditions, and/or ask sponsor to justify why storage will not affect results, and check with focal point on validity of justification.
Methods			
Test System	☐✓ 10 test and 5 control guinea pigs /extract # Male animals: ✓_____ # Female animals: ✓ Source: _____		*Check with focal point on acceptability of test system. Note: Pregnant female

ISO Maximization Sensitization Study (ISO 10993-10:2002)		
	Strain: Hartley Guinea Pigs ☐✓ If female animals used, the report states that the animals are nulliparous and not pregnant* - Need Clarification ☐ Other*: _____	animals are less likely to demonstrate a positive sensitization reaction with known sensitizing agents.
Induction Phase I	☐✓ Three pair of intrademal injections given on the backs of test animals: Test animals 1. 0.1 ml of a 1:1 FCA†/vehicle mixture 2. 0.1 ml of test extract 3. 0.1 ml of a 1:1 mixture of the 1:1 FCA and test extract Control animals 1. 0.1 ml of a 1:1 FCA†/vehicle mixture 2. 0.1 ml of vehicle 3. 0.1 ml of a 1:1 mixture of the 1:1 FCA and test extract ☐ Other*: _____	* Check with focal point on acceptability of the alternate method used.
Preparation for Induction II	☐✓ Day 6 after injection (approximately 24h before Induction II), injection sites clipped and treated with a 10% sodium lauryl sulfate (SLS) in petroleum jelly. Any remaining SLS to be removed prior to Induction II treatment. ☐ Other*: _____	* Check with focal point on acceptability of the alternate method used
Induction Phase II	☐✓ Day 7 after injection, 2x4 cm filter paper patches saturated (~0.3 ml) with test extract or control vehicle applied to injection area for 48 hours. Patches removed after 48 hours. ☐ Other*: _____	* Check with focal point on acceptability of the alternate method used
Challenge Phase	☐✓ Fourteen days after removal of Induction patches, the right and left flank areas of each guinea pig is clipped and 2x2 cm patches saturated (~0.3 ml) with test extract or control vehicle are prepared. One flank is treated with patch containing the test extract, while the other flank is treated with the control vehicle. Patches are left in place for 24 hours before removal.	* Check with focal point on acceptability of the alternate method used

ISO Maximization Sensitization Study (ISO 10993-10:2002)			
	☐ Other*:		
Assessment Times after Challenge Patch removal	☐✓ Required: 24h* ☐✓ Required: 48h* ☐ 72h ☐ Other*: _____		* Check with focal point if assessments do not include 24h, and 48h time points and/or if non-traditional assessment times are included.
Scoring of Challenge Patch Treatment Sites	☐✓ Test and control challenge patch sites assessed according to the following scale: * 0 = no visible change 1 = Discrete erythema 2 = Moderate erythema 3 = Severe erythema and edema ☐ Other*: _____		* Check with focal point if non-traditional methods were used.
Deviations	☐ Yes*	☐✓ No	*If Yes, describe the deviation, and check with focal point on acceptability of the justification for how the deviation may impact the results of the study.
Results			
Did Study Animals Appear Normal Throughout the Study?	☐✓ Yes	☐ No*	* Check with focal point on acceptability of results.
Deaths reported?	☐ Yes*	☐✓ No	*If Yes, check with focal point to assess whether deaths are related to the use of the treatment extract, or to procedural

ISO Maximization Sensitization Study (ISO 10993-10:2002)			
			issues.
Erythema and Edema Scores in Extract Controls and Treated Animals Different?	☐ Yes*	☐✓ No	*If Yes, check with focal point to assess whether erythema and edema scores reported suggest the extract should be considered a potential sensitizer.
Erythema and Edema Scores in Positive Controls and Treated Animals Different?	☐ Yes	☐ No*	*If No, check with focal point to assess whether erythema and edema scores reported suggest the extract should be considered a potential sensitizer.
Conclusion			
Sensitizing Potential	☐✓ Non-Sensitizing ☐ Sensitization Potential*		*If the extract has sensitizing potential, check with focal point.
Other comments			
Recommendation			
☐✓ Acceptable ☐ Unacceptable If Unacceptable, please discuss what the company will need to provide to resolve this issue:			

[†]FCA – Freund's Complete Adjuvant

Comment:

- No historical positive control provided in submission. Because, concurrent positive control study is provided, per ISO 10993-1, to ensure reproducibility and sensitivity of the test procedure, assays with positive controls using the same source and strain of animals should performed regularly (at least six

months). The test is considered acceptable because concurrent positive control study was done using the same source and strain of animals.

• ISO Vaginal Irritation Report (ISO 10993-10:2002)	
Test Report Documentation	
Report #: 17-00131-G8 Report Date: 03/02/17 Test Facility Name: (b) (4) Facility City: (b) (4)	FDA Submission Number: ANDA210830 Submission page/Att: Provided as separate attachments (available on L-drive)

ISO Vaginal Irritation Report (ISO 10993-10:2002)			
Device Tested			
Test Article	☐✓ Finished sterilized device ☐ Other* Etonogestrel/ Ethinyl Estradiol Vaginal Rings, delivers 0.120mg/0.015 mg per day		*Describe test article and check with focal point on acceptability of the justification for not testing the finished sterilized device.
Were only the direct and indirect patient contacting portions of the device tested?	☐✓ Yes	☐ No*	*If No, describe what has been tested and check with focal point on acceptability of the justification for not testing only the direct and indirect patient contacting portions of the device.
Was the study done under GLP conditions?	☐✓ Yes	☐ No*	*If No, ask sponsor to justify why not done under GLP requirements (for IDE and PMA submissions).
Extraction Conditions			
Test Article Extraction Ratio	☐ 6 cm^2: ml (<0.5mm thick) ☐✓ 3 cm^2: ml (>0.5mm thick) ☐ 1.25 cm^2: ml (elastomer >1mm thick)		*Check with focal point if weight based extraction conditions or non-traditional extraction conditions are used.

ISO Vaginal Irritation Report (ISO 10993-10:2002)			
	☐ 0.2 g: ml (elastomers)* ☐ 0.1 g: ml (non-elastomers)* ☐ Other*: _____		
Extraction Vehicle(s)	☐✓ Required: 0.9% Sodium chloride [P]* ☐✓ Required: Vegetable oil [NP]* ☐ Other*: _____		* Check with focal point if test does <u>not</u> include both polar [P] and non-polar [NP] extracts and/or if non-traditional extraction vehicles are used.
Time/ Temperature	☐ 37°C for 120h ☐ 37°C for 72h* ☐✓ 50°C for 72h ☐ 70°C for 24h ☐ 121°C for 1h ☐ Other*: _____		* Check with focal point on acceptability of time/temperature conditions.
pH Adjustment	☐ Yes*	☐✓ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for adjusting the pH.
Dilution	☐ Yes*	☐✓ No	*If Yes, describe the adjustment and check with focal point on the acceptability of the justification for the dilution.
Study Controls	☐✓ Extraction vehicles without test material ☐ Other*: _____		* Check with focal point on acceptability of controls.
Appearance of Extract	☐✓ Clear ☐ Cloudy* ☐ Particulates present in solution*		* Ask sponsor to explain extract appearance and justify validity of test results.

ISO Vaginal Irritation Report (ISO 10993-10:2002)		
	☐ Color*: _____	
Extract Storage Conditions	☐✓ Used immediately – within 24 h ☐ Not mentioned in report* ☐ Storage Time*: _____ ☐ Storage Temperature*: _____	* Ask for updated test report to include description of storage conditions, and/or ask sponsor to justify why storage will not affect results, and check with focal point on validity of justification.
Methods		
Test System	☐ 2 rabbits (both saline and oil extracts and controls tested on same animals) ☐✓ Other*: 3 rabbits	* Check with focal point on acceptability of test system.
Intracutaneous Injections	☐ Along the spine on one side of the back, 5 0.2 ml doses of one test extract and 5 0.2 ml doses of the control vehicle are intracutaneously injected. Similar injections of the other test article and control vehicle are injected along the other side of the back. ☐✓ Other*: 1 ml of test extract was delivered into the vagina of each animal. Dosing was repeated every day for 5 consecutive days.	* Check with focal point on acceptability of injections.
Assessment Times after Injection	☐ Required: 24h* ☐ Required: 48h* ☐ Required: 72h* ☐✓ Other*: As per 10993-10 for vaginal irritation test, animals were euthanized at 24 hours after the last treatment.	* Check with focal point if assessments do not include 24h, 48h, and 72h timepoints and/or if non-traditional assessment times are included.
Assessment Methods	☐✓ After the 72h grading is completed, individual erythema and edema scores (see grading scale below) are totaled for each test sample and vehicle blank. Each total is divided by 12 (2 animals x 3 grading periods x 2 grading categories) to obtain the overall mean treatment and control scores. The difference between the control and treatment samples needs to	* Check with focal point if non-traditional methods were used.

ISO Vaginal Irritation Report (ISO 10993-10:2002)			
	be ≤ 1to meet the requirements of this test.* <u>Erythema Scores</u> 0 = No erythema 1 = Very slight erythema (barely perceptible) 2 = Well-defined erythema 3 = Moderate erythema 4 = Severe erythema <u>Edema Scores</u> 0 = No edema 1 = Very slight edema (barely perceptible) 2 = Well-defined edema (edges definite raising) 3 = Moderate edema (raised approximately 1 mm) 4 = Severe edema (raised more than 1 mm) ☐ Other*:		
Deviations	☐ Yes*	☐✓ No	*If Yes, describe the deviation, and check with focal point on acceptability of the justification for how the deviation may impact the results of the study.
Results			
Did Study Animals Appear Normal Throughout the Study?	☐✓ Yes	☐ No*	* Check with focal point on acceptability of results.
Deaths reported?	☐ Yes*	☐✓ No	*If Yes, check with focal point to assess whether deaths are related to the use of the

ISO Vaginal Irritation Report (ISO 10993-10:2002)			
			treatment extract, or to procedural issues.
Erythema and Edema Scores in Controls and Treated Animals Different?	☐ Yes*	☐✓ No	*If Yes, check with focal point to assess whether erythema and edema scores reported suggest the extract should be considered an irritant.
Conclusion			
Irritation Potential	☐✓ Non-Irritant ☐ Irritant		*If the extract has irritation potential, check with focal point.
Other comments			
Recommendation			
☐✓ Acceptable ☐ Unacceptable If Unacceptable, please discuss what the company will need to provide to resolve this issue:			

Biocompatibility Review – Bacterial Reverse Mutation Study (Polar/Non-polar Extract)

Test Facility: (b) (4).

GLP Study Number: 17-00131-G11, Test report in L-drive.

Method: The Ames mutagenicity standard plate incorporation assay was conducted using NaCl and polyethylene glycol 400 (PEG) extracts of the test article identified as "Etonogestrel/ Ethinyl Estradiol Vaginal Rings, delivers 0.120mg/0.015 mg per day". Extraction was done at a ratio of 3 cm^2 per ml at 50^0C for 72 hours using the two extraction vehicle solvents. The condition of extracts is described as being clear and free of particulates. The test article was rendered translucent by the PEG extraction.

The tester strains used to evaluate mutagenic changes were TA98, TA100, TA1535, TA1537, and E. coli tester strain WP2uvrA. The test was performed utilizing the presence and absence of S9 metabolic activation. The S9 homogenate was prepared from Aroclor 1254-induced rat (Sprague-Dawley) rats.

The negative controls used for testing were DMSO and saline without test material. The positive controls used for the study were as follows:

Strain Designation		Positive Controls per Metabolic Activation (MA)			
		No MA		Plus MA	
		Agent	µg/mL	Agent	µg/mL
S. typhimurium	TA98	2-Nitrofluorene	10	2-Aminoanthracene	5
	TA100	Sodium Azide	100	2-Aminoanthracene	10
	TA1535	Sodium Azide	5	2-Aminoanthracene	20
	TA1537	9-Aminoacridine	800	2-Aminoanthracene	30
E. coli	WP2	4-Nitroquinoline 1-Oxide	100	2-Aminoanthracene	200

Plates were incubated at 37°C for 72 hours. Following the incubation period, spontaneous revertants from each plate were recorded. Parallel testing was also conducted with the negative and positive controls. The test article extract was tested in triplicate at one dose level (neat) along with appropriate vehicle and positive controls. All treatments were assayed against tester strains TA98, TA100, TA1535, TA1537, and E. coli tester strain WP2uvrA in the presence and absence of metabolic activation.

The test article meets the requirements of the test and is considered non-mutagenic if no statistically significant increase is found between the number of revertant colonies in the test article and in the negative control, or if this number is less than twice the number of the negative control.

Results:

- The mean number of revertants of tester strains in the presence of NaCl and PEG test article extracts and the negative control were not statistically different from each other.

- There is several-fold greater increase in the mean number of revertants of tester strains in the presence of all the various positive controls tested in the study (with and without S9) as compared with those treated with the negative control and NaCl and PEG test extracts.

- Results are summarized in the Table 4-5 of the test report.

- Historical ranges for the positive control are included in the test report (Appendix III).

Conclusion:

- Under the conditions of the assay, the NaCl and PEG extracts were considered to be non-mutagenic for all the tested strains with S9 and without S9.

Biocompatibility Review – In vitro mouse lymphoma Assay

Test Facility: (b) (4)

GLP Study Number: 17-00131-G6, Test report in L-drive.

Method: The in vitro mouse lymphoma assay was conducted using saline (polar solvent) and DMSO (non-polar) extracts of the test article identified as "Etonogestrel/ Ethinyl Estradiol Vaginal Rings, delivers 0.120mg/0.015 mg per day". Extraction was done at a ratio of 3 cm2/ml at 50^0C for 72 hours using RPMI and polyethylene glycol 400 (PEG)as extraction vehicles. The conditions of the extracts at all dilutions were clear and free of particulates. The mammalian cells exposed to the test extracts *in vitro* used in the study are L5178 TK+/-. The test was performed utilizing the presence and absence of S9 metabolic activation. The S9 homogenate was prepared from Aroclor 1254-induced adult SD rats.

The negative controls used for testing were vehicles (RPMI and PEG) without test material. EMS served as positive control article for the assay in absence of metabolic activation at a concentration of 0.5 µL/mL for the main assay and at a concentration of 0.15 µL/mL for the confirmation assay. DMBA served as the positive control article for the assay in presence of metabolic activation at a concentration of 5 and 6 µg/mL.

The test article extracts were tested in triplicate at one dose level (neat) along with appropriate vehicle and positive controls in the presence and absence of metabolic activation. Treatment variables included: untreated cultures, cultures treated with the positive controls, cultures treated with the polar extract, cultures treated with the non-polar extract, and cultures treated with the extracts alone. The assay was divided into three treatment periods; 4 hours, 4 hours with S9 activation, and 24 hours (for the detection of slower acting mutagens).

Cells were treated with the metabolic activation system for 4 and 24 hours, and then washed and maintained in the incubator for another 2 days. Cells were then cloned on the 2nd day. After completion of the 11 to 12 day incubation period, the colonies on treated plates were counted using an automatic image analyzer including software for discrimination of colony size.

A test article dose was considered acceptable for evaluation if the cloning efficiency is 80% or greater and the total viable colonies exceeds approximately 60 colonies.

Results:

- Calculated results, including cloning efficiency and mutant frequency are presented in Appendices III, IV and V of the test report. Raw data for the assay is presented in Table 3.

- Neither test article extract (either with or without metabolic activation or the extended treatment time) induced appreciable differences in cell density throughout the expression and recovery period as compared to the concurrent negative control.

- The cloning efficiencies of preparations treated with the extracts in the presence or absence of metabolic activation were within acceptable ranges.

- The group mutant frequencies of all preparations treated with the test article extracts were not materially different from those in preparations treated with the concurrent negative control.

- The IMF_{Test} Article for all conditions was less than the GEF, 126×10-6 and the $IMF_{Positive}$ for both conditions was greater than 300×10-6; the percentage of small colonies was greater than 40% in at least one condition for the positive control, confirming the validity of the assay.

- None of the test article treated groups showed biologically significant increases in mutant frequency as compared to the concurrent negative control under any condition; all mutant frequency rates were within normal negative ranges.

Conclusions:

- The negative control mutant frequencies and cloning efficiencies were within the acceptable ranges from laboratory historical data.

- The test article is considered to be nonmutagenic (non-genotoxic and non-clastogenic) in this test system.

Biocompatibility Review – Review of muscle implantation in rats (28-day)

Test Facility: (b) (4)

GLP Study Number: 17-00131-G1, Test report in L-drive.

Method: The test article, identified as "Etonogestrel/ Ethinyl Estradiol Vaginal Rings, delivers 0.120mg/0.015 mg per day" was surgically implanted intramuscularly in rats to evaluate potential local tissue response at the implantation site as well as systemic responses, per ISO 10993-6 and ISO 10993-11, respectively. A total of 10 rats were assigned to two each group (treatment and control).

The test article (vaginal ring) has a length of approximately 16 cm. As a result, 16 cm per adult female (60 kg) corresponds to ~ 0.26 cm/kg of ring surface area to body mass ratio under clinical use in humans. Based on this clinical ratio, approximately one specimen of 1 cm in length and 2 mm in diameter was

placed on either side of the spine intramuscularly in rats (with body mass of 0.35 kg). This represents an exaggerated factor of 10 x given that the calculated surface of test specimen was 0.9 cm (0.9/0.35 = 2.6 ring surface area to body mass ratio).

The steam sterilized control article was also cut to measure approximately 1 cm in length and intramuscularly implanted in the same way.

Each animal was weighed prior to implantation. The animals were maintained for a period of 28 days. During the study, all test animals were monitored for general health condition, body weight changes and food consumption. 28-days following implantation, blood samples were collected for clinical pathology parameters evaluation prior to humane euthanasia and gross necropsy. Tissues were collected and select organ weights were measured. All collected tissues were prepared for microscopic examination and evaluated. Implant sites were evaluated microscopically as well as macroscopically.

Evaluation and Statistical Analysis: Quantitative data from this study, e.g. body weights, were analyzed by appropriate statistical procedures. Any significant differences are further assessed for biological relevance by comparison to the literature and historical data. Any differences between control and treated animals are considered statistically significant only if the probability of the differences being due to chance is equal to or less than 5% ($p \sim 0.05$).

Results:

- None of the test or control animals exhibited any abnormal clinical observations and none of the animals exhibited signs of toxicity over the course of the study.

- All animals gained weight over the course of the study. The female test group was observed with statistically significant lower mean weights on Days 21, 27, and 28 and a statistically significant lower overall weight gain over the course of the study as compared to the female control group.

- The thymuses of all test animals were noted as small in size. There were no other abnormalities noted at gross necropsy for any of the test or control animals.

- The female test animals were observed with statistically significant lower red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), mean cell hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell (WBC), lymphocytes (LYMPH), and eosinophil (EOS) results as compared to the control animals. The test means for RBC cell count, hemoglobin, and hematocrit were all below the (b) (4) historical intervals while the controls means were all within the ranges.

- Clinical Chemistry: All samples for bilirubin were below the linear measurement range for the instrument and therefore, statistical analysis could not be performed.

- The female test group was observed with a statistically significant higher sodium (Na), triglycerides (TRIG), total protein (TP), glucose (GLU), albumin (ALB), calcium, and globulin (GLOB) concentrations as compared to the female control group. The female test group was observed with a statistically significant lower phosphorous (PHOS), albumin/globulin ratio (A/G), cholesterol (CHOL), alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) concentrations as compared to the control group.

- Coagulation: The female test group was observed with a statistically significant lower prothrombin time (PT) as compared to the control group.

- Organ Weights: The test group was observed with statistically significant lower absolute heart, thymus weights and statistically greater absolute ovary weights. There were histopathological findings in both the thymus (atrophic thymus with minimal inflammatory cell infiltration), heart, adrenal and ovaries (hypoplasia; decreased numbers of oocytes and corpora luteum) of the test animals. The microscopic findings in these tissues were considered an effect of the test article due to the hormones released from the vaginal rings either directly, as was likely the case for the ovaries and other findings in the ovary ducts, cervix, and uterus; or indirectly with the increased hormone exposure resulting in stress in the test animals.

- Macroscopic evaluation of the test article implant sites indicated no significant signs of inflammation, encapsulation, hemorrhage, necrosis, or discoloration at the 28-day time period.

- Microscopic assessment of the implant sites demonstrated no significant difference between the test and control implantation sites. The response to the test or control article was minimal. The Bioreactivity Ratings for the 28-day time period was 0.0, indicating no reaction as compared to the control sites.

- Main microscopic findings (systemically):

    - thymus atrophy
    - hypoplasia in the ovaries
    - hyertrophic mucosa/cytoplasmic vacuoles in the ovary ducts, hypertrophic endometrium, hypertrophic epithelium/cytoplasmic vacuoles/inflammatory cell in the cervixes
    - Microscopic findings in the thymus, spleen, ovary, oviduct, cervix, and uterus of the test animals were considered test article related
    - the degree of extramedullary hematopoiesis (EMH) in the spleen was higher in the test group than the control group

Conclusion:

- There was no evidence of systemic toxicity from the test article following subcutaneous implantation in rat for 26 weeks.

Comments:

- The animals were evaluated for local and systemic indications of toxicity related to the test article. There was no evidence of local irritation and tissue response to the test specimen. However, systemically for all parameters, animals implanted with the test article did demonstrate some differences that were considered attributable to the test article. The test animals had significant differences in weights and overall weight gains compared to the control animals. findings in the thymus, ovaries, ovary ducts, uteri, cervixes and spleens indicate an effect related to the test article when implanted in female rats for 28 days.

- Similar observations are noted in existing published literature by Cason et al (1995), where the authors have demonstrated hormonal-effect on endometrial changes including adrenal shrinkage (steroid feedback) and RBC parameters (secondary to bone marrow suppression). The observed changes are likely related to the drug effect on animals exposed to the test specimen, especially since the dose was exaggerated 10 times that of the clinical dose in humans based on the rat versus human body mass. However, the possibility that the observed systemic effects are secondary to exposure to drug-ring final, finished component needs to be ruled out. If tissue histopathological findings and systemic response to drug alone (reviewed by CDER by assessing drug pharmacology/toxicology profile and pharmaco-kinetic (PK) parameters) are different from those observed in the 28-day study on the final, finished subject device, additional sub-acute/sub-chronic systemic toxicity may be warranted with the ring component alone.

- Dosing exaggeration of 10 x in rats is acceptable.

- Intramuscular implantation as a substitute for chronic systemic toxicity testing is acceptable because of the following considerations done in the study:

    - Number of animals used for the study – 10 per group
    - Test and control specimens implanted in separate animals.
    - Dosing done represents exaggerated exposure-dose compared to that in humans during clinical use.

- Duration of exposure is clinically relevant to subacute/subchronic exposure-duration, although clinically humans are exposed to new device after 28 days and this represents repeat dose exposure.
- Exposure to test specimen represents a continuous, cumulative exposure for 28-days
- Statistical analysis done appropriately taking into consideration separate analysis of male and female groups.
- Route of exposure may not be directly relevant to the clinical route of stent exposure in the ureters, but it is not completely irrelevant considering possible exaggerated response due to increased vascularity in muscle tissue (to 4 pieces of test specimen).
- All parameters including local irritation response, hematology, clinical chemistry, organ weight, body weight, histology, and necropsy of tissues done as recommended in ISO 10993-11 for assessing systemic toxicity in animals.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)

Date:	December 6, 2017
To:	Steven Yang, Regulatory Business Project Manager OPRO/DRPMI/RBPMBII, Office of Pharmaceutical/CDER Steven.Yang@fda.hhs.gov Laurie Nelson, Consumer Safety Officer OMPT/CDER/OPQ/OPF/DIA/IABIII Laurie.Nelson@fda.hhs.gov CDER/OPQ/OPF: Junadria.Williams@fda.hhs.gov Office of Combination Products at Combination@fda.gov
Through:	Nazia Rahman, Lead Consumer Safety Officer, OC, CDRH Nazia Rahman -S 2017.12.07 11:41:48 -05'00'
From:	Therese Barber, Consumer Safety Officer, OC, CDRH
Applicant:	Amneal Pharmaceuticals 1 New England Avenue, Piscataway, New Jersey 08854 FEI# 3008861605
Application #	ANDA 210830
Consult #	ICC1700845/ICCR2017-01796
Product Name:	Etonogestrel/Ethinyl Estradiol Ring
Combination Product Intended Use:	This combination product is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.
Pre-Approval Inspection:	No
Documentation Review:	Additional Information Required
Final Recommendation:	**DELAY**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of Application ANDA 210830.

PRODUCT DESCRIPTION

The firm's Etonogestrel/Ethinyl estradiol vaginal ring is a non-biodegradable, flexible, transparent, combination contraceptive vaginal ring containing two active components, a progestin, Etonogestrel (13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one) and an estrogen, Ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol). Etonogestrel/Ethinyl estradiol vaginal ring is indicated for the prevention of pregnancy while providing menstrual cycle control. The route of administration is vaginal. Each ring is to be used for one cycle; a cycle consists of 3 weeks of ring use followed by a one-week ring-free interval. When placed in the vagina, each ring releases on average 0.120 mg/day of Etonogestrel and 0.015 mg/day of Ethynyl estradiol over a three-week period of use. The core is made of Ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate and contains 11.7 mg Etonogestrel and 2.7 mg Ethynyl estradiol. It has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.

REGULATORY HISTORY

The following facility was identified as being involved in the manufacturing and/or development of the finished combination product in Application ANDA 210830.

1. Amneal Pharmaceuticals
   1 New England Avenue, Piscataway, New Jersey 08854
   FEI# 3008861605

Responsibility – This is the applicant and manufacturer of container/close system for this CHC. Therefore, this facility is responsible for addressing the 21 CFR 820 Quality System (QS) requirements.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted 3/6/2017 to 3/20/2017. The inspection covered drug GMP and was classified NAI. NOTE: This inspection covered pre-approval inspection for three ANDAs, 208-890 Ritonavir Immediate Release Tablets, (b) (4) and 207-372 Nitrofurantoin Modified Release Capsules, under FACTS ID 11640519 and eNSpect ID 24423. The inspection also provided limited GMP coverage. As part of the limited GMP coverage, the following systems were evaluated, Quality, Laboratory Control and Production. The following areas and documents were covered: production and laboratory investigations, complaints, field

alert, corrective and preventative actions, inspection of the processing areas, laboratories and warehouse. No deficiencies were noted and no FDA-483 was issued.

Inspection Recommendation:

(1) An inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination product involving the device constituent part.
- The most recent inspection addressed drug GMP requirements and did not addressed the 21 CFR 820 QS requirements.

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR 820 Part 4 regulations for this combination product. **NOTE:** The firm did not provide any documentation that pertains to Management Control, 21 CFR 820.20; Design Controls, 21 CFR 820.30; Purchasing Controls, 21 CFR 820.50; or Corrective and Preventive Action (CAPA), 21 CFR 820.100 for review in Section 3.2.S.2., Manufacture. In this section, the firm provide numerous documents for review. However, these documents did not adequately address the 21 CFR 820 requirements. With regards to the QS requirements for Installation, 21 CFR 820.170, and Serving, 21 CFR 820.180, these requirements are not required for this combination product.

MANUFACTURING

Production and Process Controls

The sponsor did not provide a summary of the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product.

Production Flow

The sponsor did not provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process.

Acceptance Activities

The sponsor did not explain how it will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. In the response, the firm should specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. In addition, the firm should explain the acceptance/rejection criteria for the receiving

components/materials, the in-process tests and the release of the finished combination product.

Documentation Review Recommendation

This application was deficient overall. Additional information is required for an adequate documentation review.

Deficiencies to be conveyed to the applicant

The following deficiencies have been identified while doing the documentation review of Application #ANDA 210830, Etonogestrel/Ethinyl Estradiol Ring, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

1. Your firm did not adequately address the requirements for 21 CFR 820.20, Management Responsibility. Please provide a summary of how your firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4).

2. Your firm did not adequately address the requirements for 21 CFR 820.30, Design Controls. Please provide a description of your firm's design control procedures to address the requirements for design transfer. Please provide a copy or a summary of the plan used to design the combination product.

3. Your firm did not adequately address the requirements for 21 CFR 820.50, Purchasing Controls. Please provide a summary of the procedure(s) for purchasing controls. The summary should:
    a. Describe your supplier evaluation process and describe how it will determine the type and extent of control to be exercised over suppliers;
    b. Define how the records of acceptable suppliers will be maintained;
    c. Address the purchasing data approval process; and
    d. Explain how your firm will balance purchasing assessment and receiving acceptance to ensure that products are acceptable for their intended use.

    Please explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Please provide a description of how your firm will apply purchasing controls to the suppliers/contractors used in the manufacturing of the combination product.

4. Your firm did not adequately address the requirements for 21 CFR 820.100, Corrective and Preventive Actions. Please summarize the procedure(s) for your firm's Corrective and Preventive Action (CAPA) System. The CAPA system should require:
    a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
    b. Investigation of nonconformities and their causes;

c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and
d. Verification or validation of the actions taken.

5. Your firm did not adequately describe the manufacturing activities of the finished combination product. Your firm should:
    a. Provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review.
    b. Provide a summary of the procedure(s) or the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product.
    c. Explain how it will perform the acceptance activities for the receiving of components/materials to be used in the combination product; the in-process testing performed during the manufacturing/assembly; and, the final release of the combination product. In addition, the firm should explain the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product.
    d. Provide summaries or procedure(s) on the assembly of the final combination product, including packaging, sterilization and final release testing of the finished combination product.

Your firm may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm.

RECOMMENDATION

The approvability of application for the Etonogestrel/Ethinyl Estradiol Ring – Application ANDA 210380 should be delayed for the following reasons:

(1) Deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review.

(2) A pre-approval inspection is recommended for the following facility:

Amneal Pharmaceuticals

1 New England Avenue, Piscataway, New Jersey 08854.

Note: If the firm's response to the deficiencies is in compliance with the Quality System Requirements, a post- approval inspection could be recommended if the time frames for approval cannot be met due to the lack of an inspection for the device constituent part of this combination product.

Digitally signed by
Therese Barber -S
Date: 2017.12.06
17:14:29 -05'00'

Therese Barber

Prepared: TBarber: 12/4/2017

Reviewed: NRahman:

CTS No.: ICC1700845

ICCR No.: ICCR2017-01796

ANDA 210830

Review Cycle Meeting Attendance:

ANDA 210830 - ETONOGESTREL/ETHINYL ESTRADIOL RING, 0.12MG/0.015MG
by Amneal Pharmaceuticals.

IR Deficiencies:

Drug Substance

1. [redacted] (b) (4)
2.

Drug Product

1. [redacted] (b) (4)
2.
3.
4.
5.

6. (b) (4)

7.

8.

Process

1. (b) (4)

2. (b) (4)

Biopharmaceutics

1. Submit a full in vitro release method development report to the Agency for review. The report should include the following:

- Detailed description of the in vitro release test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed in vitro release method as the optimal test for your product.

- Sufficient data to support the discriminating ability of the selected method, including the complete in vitro release data (individual, mean, SD, RSD, and profile). In general, the testing conducted to demonstrate the discriminating ability of the selected method should compare the in vitro release profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected in vitro release method is able to reject batches that are not bioequivalent. Use cumulative release profiles instead of daily release to evaluate the discriminating ability.

2. You have stated that you use a ring holder to keep the ring in place during in vitro release testing. Provide details of this ring holder. You may also provide photographs of the in vitro release apparatus including the ring assembly.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210830

PROPRIETARY NAME REVIEWS

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 8, 2019
Application Type and Number:	ANDA 210830
Product Name and Strength:	Eluryng (etonogestrel and ethinyl estradiol vaginal ring) 11.7 mg/2.7 mg (delivers 0.12 mg/0.015 mg per day)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Amneal Pharmaceuticals LLC
Panorama #:	2019-32359654
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Eluryng, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A respectively. Amneal Pharmaceuticals LLC resubmitted an external name study conducted by (b) (4) previously reviewed by DMEPA, for this proposed proprietary name.[a]

1.1 REGULATORY HISTORY

Amneal Pharmaceuticals LLC previously submitted the proposed proprietary name, Eluryng on August 25, 2017. We found the name, Eluryng, conditionally acceptable in OSE Review #2017-17221700, February 9, 2018.[a] However, ANDA 210830 received a Complete Response on June 22, 2018.

Thus, Amneal Pharmaceuticals, LLC resubmitted the name, Eluryng, for review on June 11, 2019, following resubmission of ANDA 210830.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on June 11, 2019.

- Intended Pronunciation: el´ ue ring
- Active Ingredient: etonogestrel and ethinyl estradiol
- Indication of Use: prevent pregnancy
- Route of Administration: vaginal
- Dosage Form: vaginal ring
- Strength: Total drug content per ring is 11.7 mg etonogestrel/2.7 mg ethinyl estradiol (delivers 0.12 mg/0.015 mg per day)
- Dose and Frequency: insert one ring vaginally and allow to stay in place continuously for 3 weeks, followed by a one-week, ring-free interval
- How Supplied: Sold in cartons containing 3 individually-packaged (foil pouch) rings.
- Storage: Store refrigerated 2° C to 8°C. Once dispensed, product can be stored at controlled room temperature for up to 4 months
- Reference Listed Drug/Reference Product: Nuvaring, NDA 021187

[a] Fava, W. Proprietary Name Review for Eluryng (ANDA 210830). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Feb 09. Panorama No. 2017-17221700.

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Eluryng.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Eluryng would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Bone, Reproductive and Urologic Products (DBRUP) concurred with the findings of OPDP's assessment for Eluryng.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Eluryng.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proposed proprietary name[b].

2.2.2 Components of the Proposed Proprietary Name

The Applicant indicated in their submission that the proposed proprietary name, Eluryng connotes ring (vaginal ring). This proprietary name is comprised of a single word that connotes the dosage form 'ring' in its name. This naming convention follows that of the reference listed drug, Nuvaring (etonogestrel and ethinyl estradiol), NDA 021187, which is a vaginal ring and we note other approved drug products that connote their dosage form, 'ring', in their name, Estring (estradiol), NDA 020472, and Femring (estradiol acetate), NDA 021367. Additionally, this product-specific attribute is consistent with the terminology used in the product's labeling. As such, we do not anticipate that connotation of the dosage form designation 'ring' in the proposed name, Eluryng, would cause confusion or contribute to medication errors.

2.2.3 Comments from Other Review Disciplines at Initial Review

In response to the OSE, June 27, 2019 e-mail, the Division of Bone, Reproductive and Urologic Products (DBRUP) did not forward any comments or concerns relating to Eluryng at the initial phase of the review.

2.2.4 FDA Name Simulation Studies

Seventy-two practitioners participated in DMEPA's prescription studies for Eluryng. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the verbal and written prescription studies.

[b] USAN stem search conducted on June 14, 2019.

2.2.5 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Our POCA search[c] identified 61 names with the combined score of ≥55% or individual orthographic or phonetic score of ≥70%. We had identified and evaluated some of the names in our previous proprietary name review. We re-evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the name. We note that none of the product characteristics have changed and we agree with the findings from our previous review for the names evaluated previously. Therefore, we identified 6 names not previously analyzed. These names are included in Table 1 below.

2.2.6 Names Retrieved for Review Organized by Name Pair Similarity

Table 1 lists the number of names retrieved from our POCA search. These name pairs are organized as highly similar, moderately similar or low similarity for further evaluation.

Table 1. Names Retrieved for Review Organized by Name Pair Similarity

Similarity Category	Number of Names
Highly similar name pair: combined match percentage score ≥70%	0
Moderately similar name pair: combined match percentage score ≥55% to ≤ 69%	4
Low similarity name pair: combined match percentage score ≤54%	2

2.2.7 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the 6 names contained in Table 1 determined none of the names will pose a risk for confusion with Eluryng as described in Appendices C through H.

3 CONCLUSION

The proposed proprietary name, Eluryng, is acceptable.

If you have any questions or need clarifications, please contact Mammah Borbor, OSE Project Manager, at 301-796-7731.

3.1 COMMENTS TO AMNEAL PHARMACEUTICALS, LLC

We have completed our review of the proposed proprietary name, Eluryng, and have concluded that this name is acceptable.

[c] POCA search conducted on September 24, 2019 in version 4.3.

If any of the proposed product characteristics as stated in your submission, received on June 11, 2019, are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. USAN Stems (https://www.ama-assn.org/about/united-states-adopted-names-approved-stems)

USAN Stems List contains all the recognized USAN stems.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States 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* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html).

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.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: 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.) See prescreening checklist below in Table 2*. 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. [d]

[d] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥55% to ≤ 69%.

- Low similarity: combined match percentage score ≤54%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
    - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names[e]. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
    - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).

- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign

[e] Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

   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.

d. 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.

   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.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	**Y/N**	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	**Y/N**	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	**Y/N**	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	**Y/N**	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥55% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names **with** overlapping or similar strengths or doses.

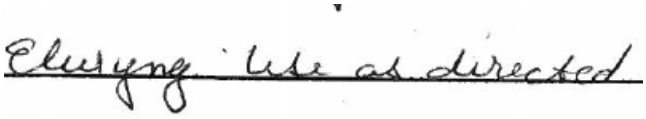
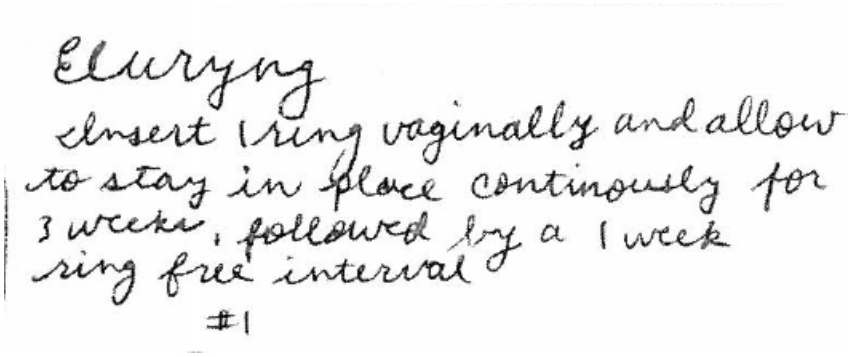
	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤54%).

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Eluryng Proprietary Name Study (Conducted on June 26, 2019)

Handwritten Medication Order/Prescription	Verbal Prescription
Medication Order:  	Eluryng – Insert 1 ring vaginally and allow to stay in place continuously for 3 weeks, followed by a 1 week ring free interval; Dispense 1
Outpatient Prescription:  	

FDA Prescription Simulation Responses (Aggregate Report)

Study Name: Eluryng
As of Date 9/23/2019

217 People Received Study
72 People Responded

Study Name: Eluryng

Total	41	12	19	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
EDURYNG	1	0	0	1
ELLURING	0	2	0	2
ELU RING	0	1	0	1
ELUIYNG	0	0	2	2
ELULYING	0	0	1	1
ELULYNG	0	0	1	1
ELURING	1	6	0	7
ELURYING	9	0	0	9
ELURYNG	28	0	14	42
ELURYNQ	0	0	1	1
ELURZNG	1	0	0	1
ELYRYNG	1	0	0	1
HELURING	0	1	0	1
LU RING	0	1	0	1
L-U-RING	0	1	0	1

Appendix C: Highly Similar Names (e.g., combined POCA score is ≥70%)

No.	**Proposed name:** Eluryng **Established name:** etonogestrel and ethinyl estradiol **Dosage form:** vaginal ring **Strength(s):** 11.7 mg/2.7 mg (delivers 0.12 mg/0.015 mg per day) **Usual Dose:** Insert one ring vaginally for 3 consecutive weeks followed by a one week ring free period before inserting a new ring	**POCA Score (%)**	**Orthographic and/or phonetic differences in the names sufficient to prevent confusion** **Other prevention of failure mode expected to minimize the risk of confusion between these two names.**
	N/A		

Appendix D: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with no overlap or numerical similarity in Strength and/or Dose

No.	Name	POCA Score (%)
	N/A	

Appendix E: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with overlap or numerical similarity in Strength and/or Dose

No.	**Proposed name:** Eluryng **Established name:** etonogestrel and ethinyl estradiol **Dosage form:** vaginal ring **Strength(s):** 11.7 mg/2.7 mg (delivers 0.12 mg/0.015 mg per day) **Usual Dose:** Insert one ring vaginally for 3 consecutive weeks followed by a one week ring free period before inserting a new ring	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
1.	Erygel	50	This name pair has sufficient orthographic and phonetic differences.
2.	(b) (4)		

No.	**Proposed name:** Eluryng **Established name:** etonogestrel and ethinyl estradiol **Dosage form:** vaginal ring **Strength(s):** 11.7 mg/2.7 mg (delivers 0.12 mg/0.015 mg per day) **Usual Dose:** Insert one ring vaginally for 3 consecutive weeks followed by a one week ring free period before inserting a new ring	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
			(vaginal ring vs tablets), route of administration (vaginal vs oral) or frequency of administration (3 consecutive weeks followed by a 1 week ring free interval vs once daily).

Appendix F: Low Similarity Names (e.g., combined POCA score is ≤54%)

No.	Name	POCA Score (%)
	N/A	

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described**.**

No.	Name	POCA Score (%)	Failure preventions
3.	Altren	58	Veterinary product.
4.	Pylorid	53	International product formerly marketed in several countries outside of the U.S.
5.			(b) (4)
6.			

Appendix H: Names not likely to be confused due to absence of attributes that are known to cause name confusion[f].

No.	Name	POCA Score (%)
	N/A	

[f] Shah, M, Merchant, L, Chan, I, and Taylor, K. Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DENISE V BAUGH
10/08/2019 05:03:15 PM

BRIANA B RIDER
10/09/2019 07:57:05 AM

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 9, 2018
Application Type and Number:	ANDA 210830
Product Name and Strength:	Eluryng (etonogestrel/ethinyl estradiol) Vaginal ring 11.7 mg/2.7 mg (delivers 0.12 mg/0.015 mg per day)
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Amneal Pharmaceuticals, LLC
Panorama #:	2017-17221700
DMEPA Safety Evaluator:	Walter Fava, RPh., MSEd.
DMEPA Team Leader:	Lolita White, PharmD.

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Eluryng, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant submitted an external name study, conducted by the (b) (4) for this product.

1.1 PRODUCT INFORMATION

The following product information is provided in the August 25, 2017 proprietary name submission.

- Intended Pronunciation: el' ue ring
- Active Ingredient: etonogestrel/ethinyl estradiol
- Indication of Use: prevention of pregnancy
- Route of Administration: vaginal
- Dosage Form: vaginal ring
- Strength: Total drug content per ring is 11.7 mg etonogestrel/2.7 mg ethinyl estradiol (delivers 0.12 mg/0.015 mg per day).
- Dose and Frequency: Insert one ring and allow to stay in place continuously for 3 weeks, followed by 1 week ring-free interval
- How Supplied: Sold in cartons containing 3 individually-packaged (foil pouch) rings.
- Storage: Store refrigerated 2° C to 8°C. Once dispensed, product can be stored at controlled room temperature for up to 4 months
- Reference Listed Drug: Nuvaring (NDA 21187)

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Bone, Reproductive, and Urologic Products (DBRUP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[a].

2.2.2 Components of the Proposed Proprietary Name

The Applicant indicated in their submission that the proposed name, Eluryng, connotes ring (vaginal ring). 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 Comments from Other Review Disciplines at Initial Review

In response to the OSE, September 18, 2017 e-mail, the Division of Bone, Reproductive, and Urologic Products (DBRUP) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

2.2.4 FDA Name Simulation Studies

Eighty-six practitioners participated in DMEPA's prescription studies. The responses did not directly overlap with any currently marketed products or any products in the pipeline.

One respondent in the voice study interpreted the proposed proprietary name, Eluryng as, 'Loring', which is a close variation to the currently marketed product 'Loryna'. We evaluated the name pair, Elurying and Loryna, further and find that there are sufficient orthographic and phonetic differences between the name pair. Orthographically, the prefixes and suffixes of this name pair ('El' vs. 'Lo' and 'ng' vs. 'na') are sufficiently different as Eluryng begins with two upstroke letters compared to one upstroke letter, 'L' at the beginning of Loryna, and ends with a downstroke letter, 'g' compared to the rounded letter, 'a' at the end of Loryna. Phonetically, the first syllable, 'el' and the second syllable, 'u' in Eluryng, sound different from the first syllable 'lo' and the second syllable, 'ryn', in Loryna. Additionally, there are no overlaps in strength (0.12 mg/day and 0.015 mg/day vs. 3 mg and 0.02 mg) between Eluryng and Loryna. Although both products have the same indication, prevention of pregnancy, there is no overlap in the usual dosage (insert one ring and allow to stay in place continuously for 3 weeks, followed by 1 week ring-free interval vs. take one tablet by mouth daily). Thus, we find there is minimal risk of name confusion for this name pair (see Appendix E). Appendix B contains the results from the verbal and written prescription studies.

2.2.5 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Our POCA search[b] identified fifty-five names with a combined phonetic and orthographic score of ≥55% or an individual phonetic or orthographic score ≥70%**.** These names are included in Table 1 below.

[a] USAN stem search conducted on (August 31, 2017).

[b] POCA search conducted on (August 31, 2017) in version 4.2.

2.2.6 Names Retrieved for Review Organized by Name Pair Similarity

Table 1 lists the number of names retrieved from our POCA search,and the (b) (4) external study. These name pairs are organized as highly similar, moderately similar or low similarity for further evaluation.

Table 1. Similarity Category	**Number of Names**
Highly similar name pair: combined match percentage score ≥70%	2
Moderately similar name pair: combined match percentage score ≥55% to ≤ 69%	53
Low similarity name pair: combined match percentage score ≤54%	33

2.2.7 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the eighty-eight names contained in Table 1 determined none of the names will pose a risk for confusion as described in Appendices C through H.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have any questions or need clarifications, please contact Mammah Borbor, OSE project manager, at 301-796-7731.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Eluryng, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your August 25, 2017 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)***

   USAN Stems List contains all the recognized USAN stems.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States 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* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html#).

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.

3. ***Electronic Drug Registration and Listing System (eDRLS) database***

The electronic Drug Registration and Listing System (eDRLS) was established to supports the FDA's Center for Drug Evaluation and Research (CDER) goal to establish a common Structured Product Labeling (SPL) repository for all facilities that manufacture regulated drugs. The system is a reliable, up-to-date inventory of FDA-regulated, drugs and establishments that produce drugs and their associated information.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: 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.) See prescreening checklist below in Table 2*. 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. [c]

[c] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥55% to ≤ 69%.
- Low similarity: combined match percentage score ≤54%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
    - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names[d]. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
    - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g.,

[d] Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).

- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

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.

d. 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.

   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.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	**Y/N**	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	**Y/N**	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	**Y/N**	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?

Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	Y/N	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥55% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg

Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names **with** overlapping or similar strengths or doses.	
	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

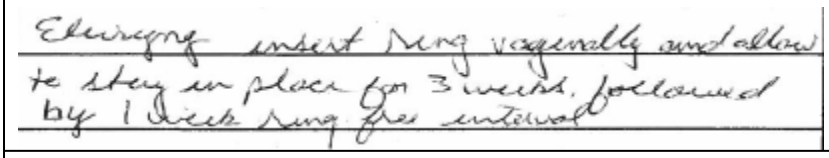
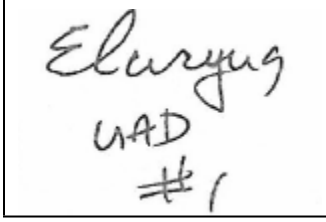
Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤54%).

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Eluryng Study (Conducted on September 29, 2017)

Handwritten Medication Order/Prescription	Verbal Prescription
Medication Order:  	Eluryng Use as directed #1
Outpatient Prescription:  	

FDA Prescription Simulation Responses

296 People Received Study

86 People Responded

Study Name: Eluryng

Total	33	25	28	
INTERPRETATION	**OUTPATIENT**	**VOICE**	**INPATIENT**	**TOTAL**
ALU-RING	0	1	0	1
BALURING	0	1	0	1
BELURING	0	1	0	1
ELARYUG	2	0	0	2
ELERYNG	0	0	1	1
ELEVYNG	0	0	1	1
ELIIRYNG	0	0	1	1

ELLURING	0	1	0	1
ELURIGYNG	0	0	1	1
ELURING	0	14	0	14
ELU-RING	0	1	0	1
ELURIRYNG	0	0	1	1
ELURUG	1	0	0	1
ELURYG	2	0	0	2
ELURYING	0	0	2	2
ELURYNG	2	0	18	20
ELURYNQ	0	0	1	1
ELURYNY	0	0	1	1
ELURYUG	20	0	0	20
ELURYUQ	2	0	0	2
ELURYUS	2	0	0	2
ELURZNG	0	0	1	1
ELURZUQ	1	0	0	1
ELUZYUG	1	0	0	1
LURING	0	1	0	1
VALURING	0	4	0	4
VALURINGS	0	1	0	1

Appendix C: Highly Similar Names (e.g., combined POCA score is ≥70%)

No.	**Proposed name: Eluryng** **Established name: etonogestrel/ethinyl estradiol** **Dosage form: Vaginal Ring** **Strength(s): 11.7 mg/2.7 mg (delivers 0.12 mg/0.015 mg per day)** **Usual Dose: Insert one ring vaginally for 3 consecutive weeks followed by a one week ring free period before inserting a new ring**	**POCA Score (%)**	**Orthographic and/or phonetic differences in the names sufficient to prevent confusion** **Other prevention of failure mode expected to minimize the risk of confusion between these two names.**
1.	Eluryng	100	Proposed proprietary name that is the subject of this review.
2.	Aleudrin	70	The name pair contains sufficient orthographic differences. Eluryng contains downstroke letters, 'y' and 'g' in the fifth and last position compared a lack of downstroke letters in the comparison name Aleudrin. Additionally, the name Aleudrin contains an upstroke letter, 'd' in the fifth position, and a bump letter 'n' in the last position. The name pair contains sufficient phonetic differences. The third syllables, 'ryng' in Eluryng has phonetic differentiation when compared to the third syllable, 'drin' in Aleudrin. Additionally, this name pair has no overlapping product characteristics including strength (0.12 mg/0.015 mg vs. 0.2 mg/mL), dosage form (vaginal ring vs. injection), route of administration (vaginal vs. intravenous), dose (insert one ring vaginally and allow to stay in place continuously for 3 weeks followed by a week ring-free period vs. infuse 0.5 mcg to 1 mg per min).

Appendix D: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with no overlap or numerical similarity in Strength and/or Dose

No.	Name	POCA Score (%)
3.	Enflurane	63
4.	Alupram	57
5.	Everone	56

Appendix E: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with overlap or numerical similarity in Strength and/or Dose

No.	**Proposed name: Eluryng** **Established name: etonogestrel/ethinyl estradiol** **Dosage form:Vaginal Ring** **Strength(s): 11.7 mg/2.7 mg (delivers 0.12 mg/0.015 mg per day)** **Usual Dose: Insert one ring vaginally for 3 consecutive weeks followed by a one week ring free period before inserting a new ring**	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
6.	Loryna	65	This name pair has sufficient orthographic and phonetic differences. Orthographically, the prefixes and suffixes of this name pair ('El' vs. 'Lo' and 'ng' vs. 'na') are sufficiently different as Eluryng begins with two upstroke letters compared to one upstroke letter, 'L' at the beginning of Loryna, and ends with a downstroke letter, 'g' compared to the rounded letter, 'a' at the end of Loryna. Phonetically, the first syllable, 'el' and the second syllable, 'u' in Eluryng, sound different from the first syllable 'lo' and the second syllable, 'ryn', in Loryna. Additionally, there are no overlaps in strength (0.12 mg/day and 0.015 mg/day vs. 3 mg and 0.02 mg) between Eluryng and Loryna. Although both products have the same indication, prevention of pregnancy, there is no overlap in the usual dosage (insert one ring and allow to stay in place continuously for 3 weeks, followed by 1 week ring-free interval vs. take one tablet by mouth daily). Thus, we find there is minimal risk of name confusion for this name pair.
7.	Saluron	64	This name pair has sufficient orthographic and phonetic differences.
8.	Ellura	63	This name pair has sufficient orthographic and phonetic differences.
9.	Elmiron	62	This name pair has sufficient orthographic and phonetic differences.

No.	**Proposed name: Eluryng** **Established name: etonogestrel/ethinyl estradiol** **Dosage form:Vaginal Ring** **Strength(s): 11.7 mg/2.7 mg (delivers 0.12 mg/0.015 mg per day)** **Usual Dose: Insert one ring vaginally for 3 consecutive weeks followed by a one week ring free period before inserting a new ring**	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
10.	Reluri	62	This name pair has sufficient orthographic and phonetic differences.
11.	Tellurium	60	This name pair has sufficient orthographic and phonetic differences.
12.	Edurant	58	This name pair has sufficient orthographic and phonetic differences.
13.	Elestrin	58	This name pair has sufficient orthographic and phonetic differences.
14.	Enduron	58	This name pair has sufficient orthographic and phonetic differences.
15.	Flurosyn	58	This name pair has sufficient orthographic and phonetic differences.
16.	Tilarin	58	This name pair has sufficient orthographic and phonetic differences.
17.	Alidrin	58	This name pair has sufficient orthographic and phonetic differences.
18.	Veraring***	54	This name pair has sufficient orthographic and phonetic differences.
19.	Enspryng***	57	This name pair has sufficient orthographic and phonetic differences.
20.	Luride	56	This name pair has sufficient orthographic and phonetic differences.

No.	**Proposed name: Eluryng** **Established name: etonogestrel/ethinyl estradiol** **Dosage form:Vaginal Ring** **Strength(s): 11.7 mg/2.7 mg (delivers 0.12 mg/0.015 mg per day)** **Usual Dose: Insert one ring vaginally for 3 consecutive weeks followed by a one week ring free period before inserting a new ring**	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
21.	Uloric	56	This name pair has sufficient orthographic and phonetic differences.
22.	(b) (4)		
23.	Estring	55	This name pair has sufficient orthographic and phonetic differences.
24.	Nuvaring	54	This name pair has sufficient orthographic and phonetic differences.

Appendix F: Low Similarity Names (e.g., combined POCA score is ≤54%)

No.	Name	POCA Score (%)
25.	Elavil	38
26.	Alophen	48
27.	Aloquin	48
28.	Alora	48
29.	Altafrin	48
30.	Atryn	48
31.	Errin	48
32.	Foltrin	48
33.	Altorant	49
34.	Asellacrin 10	49
35.	Asellacrin 2	49
36.	Ilosone	49
37.	Elastin	49
38.	Alburx	50

No.	Name	POCA Score (%)
39.	Dicloran	50
40.	Femring	50
41.	Ibuprin	50
42.	Ilozyme	50
43.	Imuran	50
44.	Sloprin	50
45.	Solodyn	50
46.	Alcortin	50
47.	Aller-Tec	52
48.	Allerfed	52
49.	Aloprim	52
50.	Iclusig	52
51.	Ilaris	52
52.	(b) (4)	52
53.	Mol-iron	52
54.	Allerfrin	54
55.	De-Chlor G	54
56.	Malarone	54

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described**.**

No.	Name	POCA Score (%)	Failure preventions
57.			(b) (4)

Appendix H: Names not likely to be confused due to absence of attributes that are known to cause name confusion[e].

[e] Shah, M, Merchant, L, Chan, I, and Taylor, K. Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

No.	Name	POCA Score (%)
58.	Alferon N	56
59.	Alkeran	58
60.	Allercon	56
61.	Allergy-12***	56
62.	Allres G	58
63.	Aluline	58
64.	Alunbrig	62
65.	Aluzine	56
66.	Dilor-G	56
67.	Florone	56
68.	Gel-Syn	59
69.	Halneuron***	58
70.	Iluvien	57
71.	Larin	58
72.	Larin 1.5/30	58
73.	Larin 1/20	58
74.	Leukeran	59
75.	Lodrane	56
76.	Lodrane 24	56
77.	Lopurin	58
78.	Lorsin	56
79.	Lorzone	56
80.	Lupron	60
81.	Lutrelin	55
82.	Lygen	55
83.	Myleran	61
84.	Onureg	58
85.	Pileran	59
86.	Rezulin	56
87.	Teldrin	58
88.	Wellbutrin	58

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

/s/

WALTER L FAVA
02/09/2018

LOLITA G WHITE
02/09/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 210830

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 12/11/2019 03:44:24 PM
To: cedwards@amneal.com
CC: adil.merchant@fda.hhs.gov
BCC:
Subject: ANDA 210830 - Approval

Hello,

Attached is the official copy of your action letter for this ANDA. Please confirm receipt of this email with the RPM (adil.merchant@fda.hhs.gov) for your ANDA.

Thanks,

Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

Please find the attached documents below:

A210830N000DPM-Approval01.pdf

ANDA 210830

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Amneal Pharmaceuticals, LLC.
50 Horseblock Road
Brookhaven, NY 11719

ATTENTION: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Ms. Edwards:

Please refer to your abbreviated new drug application (ANDA) dated and received May 17, 2019, resubmitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Etonogestrel and Ethinyl Estradiol Vaginal Ring.

We also refer to your correspondence, dated and received June 11, 2019, requesting review of your proposed proprietary name Eluryng.

We have completed our review of the proposed proprietary name, Eluryng and have concluded that it is conditionally acceptable.

If your application receives a complete response and six months or more has elapsed between the date you were notified of our decision on your proposed proprietary name and the date you respond to the application deficiencies, please submit a new request for review of your proposed proprietary name when you respond to the application deficiencies. See the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names.*[1]

If any of the proposed product characteristics as stated in your above submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Mammah Borbor-Lebbie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-7731. For any other information regarding this application, contact Adil Merchant, Regulatory Project Manager in the Office of Generic Drugs, at (240) 402-3505.

Sincerely,

{See appended electronic signature page}

Danielle Harris, PharmD, BCPS
Deputy 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DANIELLE M HARRIS
10/17/2019 07:32:26 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 06/14/2019 11:20:27 AM
To: cedwards@amneal.com
CC: adil.merchant@fda.hhs.gov
BCC:
Subject: ANDA 210830 - Amendment Acknowledgement

Please see attachment.

Please find the attached documents below:

A210830N000DPM-AcknowledgementLetter01.pdf

ANDA 210830

AMENDMENT ACKNOWLEDGEMENT
Priority
Major

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your amendment received on June 11, 2019, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II). FDA has made an initial determination that this is a major amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this priority major amendment, the GDUFA goal date for review of this priority major amendment is December 10, 2019. If FDA determines that an inspection is required to validate the information contained in this priority major amendment and a Pre-Submission Facility Correspondence was not submitted or not accepted, the GDUFA goal date for review of this priority major supplement amendment is April 10, 2020.

If you have any questions, contact Adil Merchant, Regulatory Project Manager, at (240) 402 - 3505.

Sincerely,

{See appended electronic signature page}

Adil Merchant
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Adil Merchant

Digitally signed by Adil Merchant
Date: 6/14/2019 11:15:46AM
GUID: 55ccd8f2000c18592978a9c244e1074f

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 06/14/2019 03:13:49 PM
To: steven.yang@fda.hhs.gov
CC:
BCC: CEDWARDS@AMNEAL.COM
Subject: ANDA - 210830 - Information Request

Please confirm receipt of the attached letter to steven.yang@fda.hhs.gov

Please find the attached documents below:

210830.IR.LTR.pdf

ANDA 210830

INFORMATION REQUEST

Amneal Pharmaceuticals LLC
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs
50 Horseblock Road
Brookhaven, NY 11719

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated August 25, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day.

We also refer to your May 17, 2019 submission in response to a Complete Response letter.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than 30 days, in order to continue our evaluation of your ANDA.

Comments and information requests:

A. Process

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

- (b) (4)

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Steven Yang, Regulatory Business Process Manager, at 240-402-9122.

Sincerely,

{See appended electronic signature page}

Steven Yang
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Steven Yang

Digitally signed by Steven Yang
Date: 6/14/2019 02:53:40PM
GUID: 508da70900028d408c0d8076e85ec0a4

ANDA 210830

REQUEST FOR RECONSIDERATION
REQUEST DENIED

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA), submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We also refer to your correspondence received on May 17, 2019, requesting reconsideration concerning the major classification.

I have carefully reviewed the materials you submitted in support of your request, as well as all other materials referenced herein. I have also consulted with staff in the Office of Pharmaceutical Quality.

I have completed my review of your request for reconsideration and deny your request for the following reasons.

The Agency classified your amendment received May 17, 2019, as "Major" because it included a response to a major deficiency related to the drug/device delivery system. In your request for reconsideration, you state "Amneal would like to clarify that no new toxicology data has been submitted with the response to support drug/device compatibility. Instead, Amneal has provided an (b) (4) procedure used in the toxicity studies did not lead to any false negative results. (b) (4) (b) (4) (b) (4) You have also noted in your request for reconsideration "Amneal has relisted (b) (4) as a routine commercial testing site rather than a one-time testing site. Since, (b) (4) (b) (4) as recommended by the Agency. (b) (4) is fully supported by the satisfactory inspection outcome for the facility in 2018, which has been summarized in this response along with the EIR report to aid in FDA's facile assessment of its compliance status. Thus, Amneal strongly believes that the request for reclassification from "major" to "minor" is justified." The points you have raised are unavailing with regards to the major classification. As described in Appendix A of the *Guidance for Industry ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018), Page 17, this appendix contains a non-exhaustive list of examples of deficiencies that the Agency may consider major. In this case, the deficiencies leading to the major classification

relate to insufficient data to support drug/device compatibility and sustainability for the proposed product. The review of a response to those deficiencies and the assessment of (b) (4) as a routine commercial testing facility will require, in the Agency's judgement, a substantial expenditure of the Agency's resources. Therefore, we uphold our initial decision and will still classify the May 17, 2019, amendment as major.

No change will be made to the classification of the Major Amendment discussed above.

If you have any questions, call Adil Merchant, Regulatory Project Manager at (240) 402 - 3505.

Sincerely,

{See appended electronic signature page}

Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Denise
Toyer McKan

Digitally signed by Denise Toyer McKan
Date: 6/07/2019 07:38:38AM
GUID: 5277df670008860f7e1231f730a8684c

From:	Borbor, Mammah
To:	cedwards@amneal.com
Subject:	ANDA 210830
Date:	Wednesday, June 05, 2019 4:08:00 PM
Importance:	High

Hello Ms. Edwards,

Please refer to your submission dated and received on May 17, 2019 in which you answered the CR for ANDA 210830. Please note, you did not include a request for proprietary name review which is required when answering a CR. Please kindly resubmit the proposed proprietary name for review within 7 business days

Thanks kindly,

Mammah

Mammah Sia Borbor-Lebbie, MS, MBA
Sr. Safety Regulatory Health Project Manager
Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

FDA
White Oak Complex, Bldg 22, Rm 4433
10903 New Hampshire Ave.
Silver Spring, MD 20993
Ph: 301.796.7731
Fax: 301.796.9835
Email: mammah.borbor@fda.hhs.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MAMMAH S BORBOR-LEBBIE
06/05/2019 04:15:52 PM

MEMORANDUM T O FILE- Request for Reconsideration Response

Karen Ireland/OPRO
Robert Berendt/OLDP
James Norman/OPF

ANDA No./Drug Name	210830
Applicant	Amneal Pharmaceuticals LLC
SME Decision	Denied

RESPONSE TO BE COMMUNICATED WITH THE APPLICANT

The Agency classified your amendment received May 17, 2019 as "Major" because it included a response to a major deficiency related to the drug/device delivery system. In your request for reconsideration, you state "Amneal would like to clarify that no new toxicology data has been submitted with the response to support drug/device compatibility. Instead, Amneal has provided an (b) (4) procedure used in the toxicity studies did not lead to any false negative results. (b) (4) (b) (4) (b) (4) You have also noted in your request for reconsideration "Amneal has relisted (b) (4) as a routine commercial testing site rather than a one-time testing site. Since, (b) (4) as recommended by the Agency. (b) (4) is fully supported by the satisfactory inspection outcome for the facility in 2018, which has been summarized in this response along with the EIR report to aid in FDA's facile assessment of its compliance status. Thus, Amneal strongly believes that the request for reclassification from "major" to "minor" is justified." The points you have raised are unavailing with regards to the major classification. As described in Appendix A of the *Guidance for Industry ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018), Page 17, this appendix contains a non-exhaustive list of examples of deficiencies that the Agency may consider major. In this case, the deficiencies leading to the major classification relate to insufficient data to support drug/device compatibility and sustainability for the proposed product. The review of a response to those deficiencies and the assessment of (b) (4) as a routine commercial testing facility will require, in the Agency's judgement, a substantial expenditure of the Agency's resources. Therefore, we uphold our initial decision and will still classify the May 17, 2019 amendment as major.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 05/22/2019 12:49:08 PM
To: cedwards@amneal.com
CC: adil.merchant@fda.hhs.gov
BCC:
Subject: ANDA 210830 - Request for Reconsideration Acknowledgment

Please see attachment.

Please find the attached documents below:

A210830N000DPM-ReconsiderRequestAcknowledgementLetter02.pdf

ANDA 210830

REQUEST FOR RECONSIDERATION ACKNOWLEDGEMENT

Amneal Pharmaceuticals of New York, LLC
50 Horseblock Road
Brookhaven , NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA), submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We acknowledge your correspondence received on May 17, 2019, requesting reconsideration concerning the major classification. Your request has been forwarded for review to Denise P. Toyer McKan, PharmD, Director of the Division of Project Management.

The GDUFA goal date for providing our written response is June 15, 2019.

If you have any questions, contact Adil Merchant, Regulatory Project Manager at (240) 402 - 3505.

Sincerely,

{See appended electronic signature page}

Adil Merchant
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Adil Merchant

Digitally signed by Adil Merchant
Date: 5/22/2019 11:08:05AM
GUID: 55ccd8f2000c18592978a9c244e1074f

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 05/21/2019 03:55:35 PM
To: cedwards@amneal.com
CC: adil.merchant@fda.hhs.gov
BCC:
Subject: ANDA 210830 - Amendment Acknowledgement

Please see attachment.

Please find the attached documents below:

A210830N000DPM-AcknowledgementLetter01.pdf

ANDA 210830

AMENDMENT ACKNOWLEDGEMENT
Priority
Major

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your amendment received on May 17, 2019, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II). FDA has made an initial determination that this is a major amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this priority major amendment, the GDUFA goal date for review of this priority major amendment is November 16, 2019. If FDA determines that an inspection is required to validate the information contained in this priority major amendment and a Pre-Submission Facility Correspondence was not submitted or not accepted, the GDUFA goal date for review of this priority major supplement amendment is March 16, 2020.

If you have any questions, contact Adil Merchant, Regulatory Project Manager, at (240) 402 - 3505.

Sincerely,

{See appended electronic signature page}

Adil Merchant
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Adil Merchant

Digitally signed by Adil Merchant
Date: 5/21/2019 03:51:38PM
GUID: 55ccd8f2000c18592978a9c244e1074f

GDUFA II POST FY2015 COMPLETE RESPONSE CHECKLIST**

RPM: Adil Merchant

✓ **RX or** ☐ **OTC** **ANDA #: 210830** **Applicant: Amneal Pharmaceuticals LLC** **Cohort Year: CY5**
ANDA Drug Name and Strength: Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day

Basis of Submission (RLD): 21187; Nuvaring; Organon USA Inc. **MAPP 5240.3 Priority ANDA:** ✓

(Is ANDA based on an approved Suitability Petition? ☐ *Yes* ✓ *No)*

Does the ANDA contain REMS? ☐**Yes** ✓**No** *(If YES, CR Letter must go through the Safety Review Team; clearance may take 2-3 weeks)*

Regulatory Project Manager Evaluation:		**Date: 3/29/19**	
Yes or N/A	**No**		
✓	☐	Have all submissions been reviewed and relevant disciplines finalized in CDER Informatics Platform? (date or N/A)	
		Date of Pharmaceutical Quality Review 3/27/19-MAJ Date of Bioequivalence Review 1/29/18-AQ Date of Labeling Review 1/31/19-AQ	If applicable: Date of Last Complete Response 6/22/18 Date of Clinical Review NA Date of REMS Review NA
✓	☐	Is DMF adequate and/or has the first cycle review been completed (b) (4)	
✓	☐	Are all consults complete?	
✓	☐	Are all issues resolved?	
✓	☐	Have all Policy issues (e.g., citizen petitions) been resolved? NA – Verified tracker dated 3/21/19 *If Policy issue, check with OGDP if necessary (e.g., to see whether CP blocks CR issuance).	
✓	☐	Is OSIS complete (if applicable)?	
		Notes (if applicable):	
Draft Complete Response Letter			
✓	☐	Is CR letter drafted and uploaded to "Final Decision" task?	
Review Discipline/Division Endorsements			
✓	☐	If ANDA has a pending citizen petition, did RPM notify and obtain clearance from Office of Generic Drug Policy at OGDpolicy@fda.hhs.gov? Date NA	
✓	☐	If ANDA contains REMS, did RPM notify and obtain clearance from REMS Coordinator? Date NA	
Project Close-Out			
✓	☐	Is CR checklist uploaded into "Quality Check and Close Project" task?	

***Entire Complete Response Checklist to be completed by the RPM*

Uzoma Nnebe

Digitally signed by Uzoma Nnebe
Date: 4/12/2019 01:18:20PM
GUID: 54205223000198472e8a989db47b1636

ANDA 210830

REQUEST FOR RECONSIDERATION
REQUEST DENIED

Amneal Pharmaceuticals of New York, LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA), submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We also refer to your correspondence received on October 19, 2018, requesting reconsideration concerning the major classification.

I have carefully reviewed the materials you submitted in support of your request, as well as all other materials referenced herein. I have also consulted with staff in the Office of Pharmaceutical Quality.

I have completed my review of your request for reconsideration and deny your request for the following reasons.

The decision to classify your complete response letter as "Major" was based on the June 22, 2018 complete response letter including multiple major deficiencies e.g facility deficiency, the need to identify or include critical quality attributes or methods for controlling them, insufficient data to support drug/device compatibility and sustainability for the proposed product, and inadequate due to consult-related deficiencies including, but not limited to: insufficient information submitted to address safety issues. This major classification is based on a determination by FDA that the content of the information or data provided in response to these deficiencies will require extensive assessment. In your request for reconsideration cover letter, you stated "Amneal views that the deficiencies identified in the CR letter should be reclassified as "minor" based on the following fact: Amneal is revising the proposed commercial batch size from (b) (4) as ANDA Submission Batches." We acknowledge your justification pertaining to the facility deficiency cited in the complete response letter. Therefore, with respect to the facility deficiency, this is no longer a basis to classify the amendment as major. However, as described in Appendix A of the *Guidance for Industry ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018), amendments in response to deficiencies pertaining to the need to identify or include critical quality attributes (CQAs) or methods for controlling them, insufficient data to support drug/device compatibility and sustainability for the proposed product and inadequate due to consult-related deficiencies including, but not limited to: insufficient information submitted to address safety issues may be classified as major. The assessment of the responses in its entirety will require, **in FDA's judgment**, a substantial

expenditure of FDA resources. Therefore, we uphold our initial decision and still classify the amendment received on October 19, 2018 as major.

If you have any questions, call Adil Merchant, Regulatory Project Manager at (240) 402 - 3505.

Sincerely,

{See appended electronic signature page}

Aaron W. Sigler, PharmD, BCPS, PMP, CPH
CAPT, USPHS
Acting Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Aaron Sigler

Digitally signed by Aaron Sigler
Date: 11/15/2018 03:35:02PM
GUID: 508da6fa0002827f1a9f2526d1b2cc69

From: Yokum, Ankara
To: Pham, Anh
Cc: Merchant, Adil; Shah, Priya
Subject: Re: A210830
Date: Wednesday, November 14, 2018 5:40:20 AM
Attachments: image001.png

CDRH

From: Pham, Anh <Anh.Pham@fda.hhs.gov>
Date: November 13, 2018 at 9:08:38 PM EST
To: Yokum, Ankara <Ankara.Yokum@fda.hhs.gov>
Cc: Merchant, Adil <Adil.Merchant@fda.hhs.gov>, Shah, Priya <Priya.Shah@fda.hhs.gov>
Subject: A210830

Hi Nikki

Good evening. I hope you are doing well. Sorry to bother you again. I was hoping you can assist me with a clarifying question on one of the basis of majors in this application. The highlighted section "the need to identify or include critical quality attributes (CQAs) or methods for controlling them" is this related to the CDRH consult response or is this part moreso related to the process deficiency? I m looking at the CR and applicant s response and wanted to be able to convey to our final signer what the correlation of this justification pertains to. Any guidance or advice you can provide would be helpful.

Thank You
Anh

The decision to classify your complete response letter as "Major" was based on the June 22, 2018 complete response letter including a facility deficiency that requires substantial expenditure of FDA resources to re-evaluate the facilities. In your request for reconsideration cover letter, you stated " Amneal views that the deficiencies identified in the CR letter should be reclassified as "minor" based on the following fact: Amneal is revising the proposed commercial batch size from (b) (4) (b) (4) as ANDA Submission Batches". While we agree that this would then be appropriate as a minor amendment, there is other information in your submission to sustain this as a major amendment. Consistent with the GDUFAReauthorization Performance Goals and Program Enhancement Fiscal Years 2018-2022 (GDUFA II Commitment Letter) and as described in Appendix A of the *Guidance for Industry ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018), the need to identify or include critical quality attributes (CQAs) or methods for controlling them, insufficient data to support drug/device compatibility and sustainability for the proposed product and inadequate due to consult-related deficiencies including, but not limited to: insufficient information submitted to address safety issues. Therefore, we uphold our initial decision to classify this amendment as major.

Thank You,
Anh Pham

MEMORANDUM TO FILE- Request for Reconsideration Response

Ankara Yokum/OPRO

ANDA No./Drug Name	210830
Applicant	Amneal Pharmaceuticals
SME Decision	DENIED

RESPONSE TO BE COMMUNICATED WITH THE APPLICANT

The decision to classify your complete response letter as "Major" was based on the June 22, 2018 complete response letter including a facility deficiency that requires substantial expenditure of FDA resources to re-evaluate the facilities. In your request for reconsideration cover letter, you stated " Amneal views that the deficiencies identified in the CR letter should be reclassified as "minor" based on the following fact: Amneal is revising the proposed commercial batch size from (b) (4) as ANDA Submission Batches". While we agree that this would then be appropriate as a minor amendment, there is other information in your submission to sustain this as a major amendment. Consistent with the GDUFAReauthorization Performance Goals and Program Enhancement Fiscal Years 2018-2022 (GDUFA II Commitment Letter) and as described in Appendix A of the *Guidance for Industry ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018), the need to identify or include critical quality attributes (CQAs) or methods for controlling them, insufficient data to support drug/device compatibility and sustainability for the proposed product and inadequate due to consult-related deficiencies including, but not limited to: insufficient information submitted to address safety issues. Therefore, we uphold our initial decision to classify this amendment as major.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 11/07/2018 02:28:53 PM
To: CEDWARDS@AMNEAL.COM;steven.yang@fda.hhs.gov
CC:
BCC:
Subject: ANDA - 210830 - Information Request

Please confirm receipt of the attached letter to steven.yang@fda.hhs.gov

Please find the attached documents below:

210830.IR.4.pdf

ANDA 210830

INFORMATION REQUEST

Amneal Pharmaceuticals LLC
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs
50 Horseblock Road
Brookhaven, NY 11719

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated August 25, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We also refer to your October 19, 2018 submission, containing responses to Complete Response letter.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than 1 day, in order to continue our evaluation of your ANDA.

Comments and information requests:

A. Facilities

(b) (4) (b) (4) are referenced as facilities responsible for performing mechanical properties testing in support of ANDA210830, Amneal Pharmaceuticals letter dated October 19, 2018.

1. Please provide further clarification if they perform final product testing (mechanical) for commercial product release.

2. Please submit an updated 356h form and section 3.2.P.3 with details of the mechanical tests performed by each facility.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that

a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Steven Yang, Regulatory Business Process Manager, at 240-402-9122.

Sincerely,

{See appended electronic signature page}

Steven Yang
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Steven Yang

Digitally signed by Steven Yang
Date: 11/07/2018 02:06:24PM
GUID: 508da70900028d408c0d8076e85ec0a4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 11/05/2018 07:40:37 AM
To: CEDWARDS@AMNEAL.COM
CC: adil.merchant@fda.hhs.gov
BCC:
Subject: ANDA 210830 - Request for Reconsideration - Acknowledgement

Please see attachment.

Please find the attached documents below:

A210830N000DPM-ReconsiderationAcknowledgementLetter01.pdf

ANDA 210830

REQUEST FOR RECONSIDERATION
ACKNOWLEDGEMENT

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA), submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We acknowledge your correspondence received on October 19, 2018, requesting reconsideration concerning the major classification. Your request has been forwarded for review to CAPT Aaron W. Sigler, Acting Director of the Division of Project Management.

The GDUFA goal date for providing our written response is November 17, 2018.

If you have any questions, contact Adil Merchant, Regulatory Project Manager at (240) 402 - 3505.

Sincerely,

{See appended electronic signature page}

Adil Merchant
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 11/02/2018 04:20:59 PM
To: CEDWARDS@AMNEAL.COM;steven.yang@fda.hhs.gov
CC:
BCC:
Subject: ANDA - 210830 - Information Request

Please confirm receipt of the attached letter to steven.yang@fda.hhs.gov

Please find the attached documents below:

210830.IR.3.pdf

ANDA 210830

INFORMATION REQUEST

Amneal Pharmaceuticals LLC
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs
50 Horseblock Road
Brookhaven, NY 11719

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated August 25, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We also refer to your October 19, 2018 submission, containing responses to Complete Response letter.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than 7 days, in order to continue our evaluation of your ANDA.

Comments and information requests:

A. Process

(b) (4)

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Steven Yang, Regulatory Business Process Manager, at 240-402-9122.

Sincerely,

{See appended electronic signature page}

Steven Yang
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Steven Yang

Digitally signed by Steven Yang
Date: 11/02/2018 03:45:01PM
GUID: 508da70900028d408c0d8076e85ec0a4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 10/25/2018 02:11:23 PM
To: CEDWARDS@AMNEAL.COM
CC: adil.merchant@fda.hhs.gov
BCC:
Subject: ANDA 210830 - Amendment Acknowledgement

Please see attachment.

Please find the attached documents below:

A210830N000DPM-AcknowledgementLetter01.pdf

ANDA 210830

AMENDMENT ACKNOWLEDGEMENT
Priority
Major

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your amendment received on October 19, 2018, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II). FDA has made an initial determination that this is a major amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this priority major amendment, the GDUFA goal date for review of this priority major amendment is April 18, 2019. If FDA determines that an inspection is required to validate the information contained in this priority major amendment and a Pre-Submission Facility Correspondence was not submitted or not accepted, the GDUFA goal date for review of this priority major amendment is August 17, 2019.

If you have any questions, contact Adil Merchant, Regulatory Project Manager, at (240) 402 - 3505.

Sincerely,

{See appended electronic signature page}

Adil Merchant
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Adil Merchant

Digitally signed by Adil Merchant
Date: 10/25/2018 02:05:50PM
GUID: 55ccd8f2000c18592978a9c244e1074f

ANDA 210830

POST-CRL MEETING
MEETING MINUTES

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) received for review on August 25, 2017, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We also refer to the post-complete response letter (post-CRL) meeting between the applicant and FDA on August 7, 2018. The purpose of the requested post-CRL meeting was to clarify deficiencies noted in the complete response letter issued by this office on June 22, 2018.

A copy of the official minutes of the post-CRL meeting is enclosed for your information. Please notify the Agency in writing via the Electronic Submissions Gateway of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Adil Merchant, Regulatory Project Manager at (240) 402-3505.

Sincerely,

{See appended electronic signature page}

Adil Merchant
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Post-complete response letter meeting

Meeting Date and Time: August 7, 2018; 9:30 a.m. EST

Application Number: 210830
Product Name: Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day
Applicant Name: Amneal Pharmaceuticals LLC

Meeting Recorder: Adil Merchant and Vikas Arora

FDA ATTENDEES

James Norman, Reviewer, PABV/DPAII/OPF/OPQ
Robert Berendt, Branch Chief, MRBI/DMRP/OLDP/OPQ
Jason Roberts, Reviewer, OGDB/DRGUD/ODE/CDRH
Adil Merchant, Regulatory Project Manager, DPM/ORO/OGD
Vikas Arora, Regulatory Project Manager, DPM/ORO/OGD

APPLICANT ATTENDEES

Amneal Pharmaceuticals, LLC
Candis Edwards, Senior Vice President, Regulatory Affairs
Pavan Kumar, PhD, Senior Director, Regulatory Affairs
Joseph Greer, Senior Vice President, Quality Management
Vincent Collichio, Vice President, Operations
Shreena Patel, Senior Manager, Clinical Regulatory Affairs
Ravi Harapanhalli, Senior Vice President, Global Regulatory Affairs

(b) (4)

A. BACKGROUND

The purpose of the post-complete response letter meeting was to clarify deficiencies noted in the complete response letter dated June 22, 2018.

B. DISCUSSION

Pharmaceutical Quality

1. Drug Product – CDRH Device Evaluation

Applicant's Clarifying Question for Deficiency #12

(b) (4)

(b) (4)

Discussion:
Per Amneal, no further discussion was required.

Applicant's Clarifying Question for Deficiency #13

Does Agency concur with Amneal's risk analysis plan? If the Agency does not agree, please provide additional strategy and recommendation for conducting the risk analysis.

FDA Response:

The Agency agrees with your approach to conduct the risk analysis. However, we recommend you specifically discuss (b) (4) when discussing identified risks and mitigations in your analysis of device compatibility. We also recommend you state when public information is not available concerning an identified risk, and take into account any uncertainty in your risk mitigation strategy.

Discussion:
Per Amneal, no further discussion was required.

Applicant's Clarifying Question for Deficiency #14

a. Does the Agency have any comments on the proposed formulation (b) (4)

b. Can the Agency provide specific requirements for raw data?

c. Does the Agency have any additional recommendations to assist Amneal to adapt the (b) (4) standard for its proposed vaginal ring product?

FDA Response:

(b) (4)

Discussion:
Amneal was seeking clarification whether the raw data should be submitted in .xpt or .xslx format. Per agency, .xlsx format would be acceptable.

2. Process

Applicant's Clarifying Question for Deficiency #16

a. Is Agency in agreement with Amneal's strategy? Does the Agency have any further recommendations?

b. (b) (4)

FDA Response:

(b) (4)

Discussion:
Upon approval, Amneal proposes launching its product using batch size of (b) (4) (same as the ANDA exhibit batches). Does the Agency have any further questions or concerns regarding Amneal's proposed strategy?
The Agency has no questions or concerns regarding this proposed strategy.

Amneal was making the Agency aware that they will request reclassification from Major to Minor. Agency mentioned that reclassification of CR will be reviewed separately and it should not be part of a Post CRL meeting discussion.

D. ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide Meeting Minutes	FDA	9/6/2018

Adil Merchant

Digitally signed by Adil Merchant
Date: 8/17/2018 02:42:58PM
GUID: 55ccd8f2000c18592978a9c244e1074f

ANDA 210830

POST-CRL MEETING REQUEST
PRELIMINARY RESPONSES

Amneal Pharmaceuticals of New York, LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) received for review on August 25, 2017, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

Further reference is made to our Meeting Request Granted –Teleconference letter dated July 11, 2018.

Enclosed are our preliminary responses to the questions contained in your post-complete response letter meeting request dated July 2, 2018.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, call Adil Merchant, Regulatory Project Manager at (240) 402-3505.

Sincerely,

{See appended electronic signature page}

Adil Merchant
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

QUESTIONS AND FDA PRELIMINARY RESPONSES

Pharmaceutical Quality

a. Drug Product – CDRH Device Evaluation

Applicant's Clarifying Question for Deficiency#12

(b) (4)

Applicant's Clarifying Question for Deficiency#13

Does Agency concur with Amneal's risk analysis plan? If the Agency does not agree, please provide additional strategy and recommendation for conducting the risk analysis.

FDA Response:

The Agency agrees with your approach to conduct the risk analysis. However, we recommend you specifically discuss (b) (4) when discussing identified risks and mitigations in your analysis of device compatibility. We also recommend you state when public information is not available concerning an identified risk, and take into account any uncertainty in your risk mitigation strategy.

Applicant's Clarifying Question for Deficiency#14

a. Does the Agency have any comments on the proposed formulation (b) (4)

b. Can the Agency provide specific requirements for raw data?

c. (b) (4)

FDA Response:

(b) (4)

(b) (4)

b. Process

Applicant's Clarifying Question for Deficiency#16

a. Is Agency in agreement with Amneal's strategy? Does the Agency have any further recommendations?

b. (b) (4)

FDA Response:

(b) (4)

Adil Merchant

Digitally signed by Adil Merchant
Date: 8/03/2018 03:08:32PM
GUID: 55ccd8f2000c18592978a9c244e1074f

From: Merchant, Adil
To: cedwards@amneal.com
Subject: ANDA 210830 - Post CR Meeting - Reschedule
Date: Friday, July 20, 2018 9:18:08 AM

Hi Candis,

Due to conflicts we are rescheduling the TCON date and time. Per your suggested dates (week of August 6, 2018), below are the TCON details:

Date: August 7, 2018

Time: 9:30 to 10:00 am EST

Phone Arrangements: **210-795-0506** or **877-465-7975**

Meeting number (access code): (b) (4)

CDER Participants:

James Norman – Reviewer, PABV/DPAII/OPF/OPQ

Yubing Tang – Branch Chief, PABV/DPAII/OPF/OPQ

Robert Berendt – Branch Chief, MRBI/DMRP/OLDP/OPQ

Jason Roberts - Reviewer, OGDB/DRGUD/ODE/CDRH

Sharon Andrews – Branch Chief, OGDB/DRGUD/ODE/CDRH

Adil Merchant, Regulatory Project Manager, DPM/ORO/OGD

Edward Taylor, Team Leader, Regulatory Project Manager, DPM/ORO/OGD

Vikas Arora, Regulatory Project Manager, DPM/ORO/OGD

Please note the TCON is granted only for 30 minutes.

Please confirm receipt of this email.

Kind Regards,

Adil Merchant
Center for Drug Evaluation and Research
OMPT/CDER/OGD/ORO/DPM
U.S. Food and Drug Administration
Tel: 240-402-3505
Adil.Merchant@fda.hhs.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation

ANDA210830: Amneal Pharmaceuticals Etonogestrel/Ethinyl Estradiol Ring– Device Consult

DATE: July 18, 2018

FROM: Jason Roberts, Ph.D., Biomedical Engineer
CDRH/ODE/DRGUD/OGDB

TO: Steven Yang
CDER/OPQ/OPRO/DRBPMI/RBPMBII

CC: Sharon Andrews, Branch Chief
CDRH/ODE/DRGUD/OGDB

Joyce Whang, Ph.D., Deputy Director, Science
CDRH/ODE/DRGUD

Lead Consulting Reviewer: Jason Roberts, Ph.D. Biomedical Engineer CDRH/ODE/DRGUD/OGDB

I. Purpose of Submission and Scope:

The original submission is a new drug application for the Amneal Pharmaceuticals Etonogestrel/Ethinyl Estradiol Ring. In the original consult, the initiating division asked that CDRH to identify any general concerns with a vaginal ring type product from a device perspective.

The sponsor has requested a meeting to discuss their responses to the Complete Response Letter, issued June 22, 2018. The initiating division has asked that I provide written feedback for the sponsor addressing their questions. These responses will be discussed in the teleconference with the sponsor on August 7, 2018.

In this review memo, I will provide an overview of the information provided along with my comments. Review issues will be identified and appear **in bold** in the review below.

II. Device Description:

Intended use

The Amneal Pharmaceuticals Etonogestrel/Ethinyl Estradiol Ring is an estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.

Product description

The device is a clear, flexible ethylene vinylacetate ring intended to be placed in the vagina (figure below).

The device has the following dimensional specifications:

Specification	Value
Weight	(b) (4)
Color	Colorless to nearly colorless (cloudy white)
Outer diameter	(b) (4)
Cross sectional diameter	
Surface area	
Volume	

The submission includes a single dose ring intended to delivery 0.120/0.015 mg/day Etonogestrel/Ethinyl estradiol. The ring is primarily ethylene vinylacetate, but contains the two drug products etonorgestrel and ethinyl estradiol and excipient magnesium stearate. The exact formulation is the following:

Ingredient	Quantity per ring (mg)	%w/w of total ring weight

Ethinyl estradiol	2.700	(b) (4)
Etonorgestrel	11.700	
Ethylene vinylacetate copolymer, 28% vinylacetate (b) (4) (b) (4)	(b) (4)	
Ethylene vinylacetate copolymer, 9% vinylacetate (b) (4) (b) (4)		
Magnesium stearate		
(b) (4)		

(b) (4) and are individually packaged into re-closable aluminum laminate sachets. Three sachets will be packaged per carton of product.

III. Sponsor Questions

The sponsor has proposed questions regarding FDA comments #12, #13, #14, and #16 from the CRL letter. Comments 12-14 were based upon deficiencies I raised in my original memo. Each request is listed below, followed by the sponsor's response and my review comments:

Comment #12

(b) (4)

(b) (4)

Sponsor approach/question:

With respect to this comment, the sponsor proposes to manufacture a small scale batch using the same formula and process as the ANDA batch to generate samples for testing. They also plan to test real time samples (~21 months @5±3C) from the 3 ANDA batches.

Reviewer comment:

I have no concerns with the sponsor's approach to testing newly made batches, given that they will use the same formulation and processes to make them. Further, I believe it is acceptable to utilize ANDA batches that are aged to gather mechanical data to support the shelf life.

Comment #13

(b) (4)

Sponsor approach/question:

The sponsor states they will base their risk analysis on the following:

1. Summary Basis of Approval (SBoA) for NuvaRing (NDA # N021187)
2. FDA approved labeling of NuvaRing
3. Data generated during condom compatibility testing (See FDA Comment #14)
4. Publicly available information on NuvaRing and other similar FDA approved marketed intravaginal/intrauterine devices already in use in the intended use population

Reviewer comment:

(b) (4)

Comment #14

(b) (4)

(b) (4)

(b) (4)

Sponsor response:

The sponsor proposes to conduct testing per FDA's request (b) (4) The sponsor proposes to extract the product into simulated vaginal fluid of the following formulation:

(b) (4)

The above ingredients will be (b) (4) (pH is expected to be 4.2).

The rings will be immersed in the solution under agitation for 24 hours. Further, the sponsor proposes to saturate the extract with active ingredient to represent a worst-case scenario. (b) (4) The sponsor asks whether this formula is acceptable. Further, the sponsor asks if the Agency has recommendations for raw data and any additional comments concerning their approach.

Reviewer comments:

The sponsor's formula is taken from a review on vaginal simulant fluid by (b) (4) This is acceptable. The sponsor's approach to utilize saturated active ingredient is also acceptable.

For raw data, I recommend that sponsor provide the individual measurements of (b) (4) properties of the condoms for each sample (20 samples per condom type). I would recommend these be organized by parameter and type of condom tested in table format.

With respect to the test methods, I have no further comments for the sponsor.

IV. Summary/Recommendations:

In response to the sponsor's questions, I recommend the following comments:

Response to comment #12:

The Agency has no concerns with your approach to evaluate the mechanical properties of the drug product. It is acceptable to utilize newly manufactured rings of the same formula and process to establish baseline properties, and it is acceptable to utilize real-time aged samples from the ANDA batches to support maintenance of mechanical properties throughout the shelf-life.

Response to comment #13:

The Agency agrees with your approach to conduct the risk analysis. However, we recommend you specifically discuss (b) (4) when discussing identified risks and mitigations in your analysis of device compatibility. We

also recommend you state when public information is not available concerning an identified risk, and take into account any uncertainty in your risk mitigation strategy.

Response to comment #14:

(b) (4)

Digital Signature Concurrence Table	
Reviewer Sign-Off	Jason Roberts -S 2018.07.18 08:17:29 -04'00'

Response for A210830 post-CR meeting

Process

16. During a pre-approval inspection at the drug product manufacturing site, investigators

(b) (4)

(b) (4) **If you include the automatic equipment in your complete response, provide appropriate development data collected using the installed equipment.**

Refer to the pg 8-10 of the attached PDF for the firm's response

ANDA 210830 Post CRL MR Cover Letter.

- Is Agency in agreement with this strategy? Does the Agency have any further recommendations?
- (b) (4)

Response:

(b) (4)

ANDA 210830

POST-CRL MEETING REQUEST GRANTED

Amneal Pharmaceuticals of New York, LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) received for review on August 25, 2017, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We also refer to your correspondence received on July 2, 2018, requesting a post-complete response letter meeting to clarify deficiencies noted in the complete response letter issued by this office on June 22, 2018.

Your request for a post-complete response letter meeting is granted and the teleconference is scheduled as follows:

Date:	July 31, 2018
Time:	TBD
Phone Arrangements:	TBD
CDER Participants:	TBD

Discussion points and action items will be summarized at the conclusion of the teleconference and reflected in FDA's meeting minutes.

If you need to reschedule or cancel the post-complete response letter meeting, please notify the Agency in writing via the Electronic Submissions Gateway.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact Adil Merchant, Regulatory Project Manager, at (240) 402 - 3505.

Sincerely,

{See appended electronic signature page}

Adil Merchant
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Adil Merchant

Digitally signed by Adil Merchant
Date: 7/11/2018 05:06:08PM
GUID: 55ccd8f2000c18592978a9c244e1074f

From:	Taylor, Edward
To:	Patel, Nitin K. (CDER/OGD)
Cc:	Merchant, Adil
Subject:	RE: ANDA 210830 Comparative Analysis Consult Response Document
Date:	Friday, June 22, 2018 9:55:31 AM

Hi Nitin,

It would be good to have the review be consistent and have the "N/A (Review is Adequate)" box checked. There are 47 documents in the project so I am afraid that even if we upload your email, it will get lost amongst everything else in there. The goal date is Sunday and therefore needs to be signed today so we are going to go ahead and send this to Denise to work on but we would appreciate if you could get it updated and archived as soon as possible.

Thank you,

Edward (Andrew) Taylor

From: Patel, Nitin K. (CDER/OGD)
Sent: Friday, June 22, 2018 9:48 AM
To: Taylor, Edward <Edward.Taylor@fda.hhs.gov>
Cc: Merchant, Adil <Adil.Merchant@fda.hhs.gov>; Patel, Nitin K. (CDER/OGD) <Nitin.Patel@fda.hhs.gov>
Subject: RE: ANDA 210830 Comparative Analysis Consult Response Document

Hi Andrew,

This is to confirm that the outcome is Adequate and there are no comments to be conveyed to the applicant. The reviewer made an error when they checked the 'Minor" classification on page 1.
However, it does say to see Section 4 for the Recommendation, where the conclusion is that there are no comments.
Will my email suffice or do you think that a new revised document needs to be uploaded by the review team?
Please let me know, after which I will archive the document.
Thanks for bringing this to my attention.

Nitin

From: Taylor, Edward
Sent: Thursday, June 21, 2018 4:58 PM
To: Patel, Nitin K. (CDER/OGD) <Nitin.Patel@fda.hhs.gov>
Cc: Merchant, Adil <Adil.Merchant@fda.hhs.gov>
Subject: ANDA 210830 Comparative Analysis Consult Response Document

Hi Nitin,
This in reference to the document in the task below
http://panorama.fda.gov/task/view?ID=5a3188570001ab5ae099ad7a0b8798e1

Since you say the outcome is adequate, should the N/A (Review is Adequate) box be checked instead of Minor in the "Deficiency Classification" section? Also, after you have confirmed that, could you please archive the file?

Thank you,

Edward (Andrew) Taylor, PharmD, CAPM
Regulatory Project Manager Team Leader
Office of Generic Drugs
Food and Drug Administration
WO75 Room 3706
10903 New Hampshire Avenue
Silver Spring, MD 20993
240-402-6094

GDUFA II POST FY2015 COMPLETE RESPONSE CHECKLIST**

RPM: Adil Merchant

✓ **RX or** ☐ **OTC** **ANDA #: 210830** **Applicant: Amneal Pharmaceuticals LLC** **Cohort Year: CY5**
ANDA Drug Name and Strength: Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day

Basis of Submission (RLD): 21187; Nuvaring; Organon USA Inc's **MAPP 5240.3 Priority ANDA:** ☐

(Is ANDA based on an approved Suitability Petition? ☐ *Yes* ✓ *No)*

Does the ANDA contain REMS? ☐ **Yes** ✓ **No** *(If YES, CR Letter must go through the Safety Review Team; clearance may take 2-3 weeks)*

Regulatory Project Manager Evaluation:		**Date: 6/21/18**	
Yes or N/A	**No**		
✓	☐	Have all submissions been reviewed and relevant disciplines finalized in CDER Informatics Platform? (date or N/A)	
		Date of Pharmaceutical Quality Review 6/21/18-MAJ Date of Bioequivalence Review 1/29/18-AQ Date of Labeling Review 4/23/18-Min	If applicable: Date of Last Complete Response NA Date of Clinical Review NA Date of REMS Review NA
✓	☐	Is DMF adequate and/or has the first cycle review been completed (b) (4)	
✓	☐	Are all consults complete?	
✓	☐	Are all issues resolved?	
✓	☐	Have all Policy issues (e.g., citizen petitions) been resolved? NA – Verified tacker dated 6/18/18 *If Policy issue, check with OGDP if necessary (e.g., to see whether CP blocks CR issuance).	
✓	☐	Is OSIS complete (if applicable)?	
		Notes (if applicable):	
Draft Complete Response Letter			
✓	☐	Is CR letter drafted and uploaded to "Final Decision" task?	
Review Discipline/Division Endorsements			
✓	☐	If ANDA has a pending citizen petition, did RPM notify and obtain clearance from Office of Generic Drug Policy at OGDpolicy@fda.hhs.gov? Date NA	
✓	☐	If ANDA contains REMS, did RPM notify and obtain clearance from REMS Coordinator? Date NA	
Project Close-Out			
✓	☐	Is CR checklist uploaded into "Quality Check and Close Project" task?	

***Entire Complete Response Checklist to be completed by the RPM*

OFFICE OF PHARMACEUTICAL QUALITY

OPQ Consult Template

Topic (select from dropdown): (b) (4)

Primary Contact Name/Division/Office: Desai, Pinaki | DMRP/OLDP/OP

(Enter the name of the chemistry reviewer as it appears in Outlook)

---

1. **Application/Supplement Number:** 210830
   or DMF Number _____ **and Referencing ANDA Number** _____

2. **Target Action Date:** 06/24/2018

3. **Consult Due Date** 05/11/2018
   (Regular Consult: 3 months from consult request date / Fast Track: 5 weeks from consult request date):

4. **Request Expedited Consult Review: Yes:** ■ **No:** ☐
   If yes, the request must fit one of the following criteria:
   - ☐ **First Generic**
   - ☐ **Drug shortage**
   - ☐ **Patent Expiration within 6 months; Forfeiture Date** _____
   - ☐ **Expedited review granted**
   - ■ **GDUFA Goal Date is within** 3.5 **months**

5. **Request Fast Track Consult Review: Yes:** ☐ **No:** ■
   (Fast Track is only for specific questions related to genotoxicity or product use.)
   If yes, the request must fit one of the following requests:

   ☐ **AMES data review (complete package)**
   Do the AMES data and methods support the firm's conclusion that the impurity in question is not Genotoxic? See attached package in section 10

   ☐ **MDD calculation in support of M7 TTC**
   What is the maximum daily dose (MDD) for the listed RLD. (RLD name or #) _____
   See attached RLD Approved labeling in section 10.

   ☐ **Request for Duration of Use Calculation in support of M7 TTC**
   What is the maximum duration of treatment for the drug product considering all indications listed on the label? Please note that "off label" use does not apply.

☐ **Confirmation of term 'Advanced' cancer as the only indication**

The firm is requesting exclusion of PGI limit requirements claiming that the drug product is used for advanced cancer treatments ONLY. Please confirm that this is correct. Please note that "off label" use does not apply.

☐ **Clarification of product use** (population, duration, frequency)

The use instructions for the RLD are unclear (see RLD label in section 10. Please provide the following information about product use

6. **Reason for consult:** (This section should be a brief paragraph. Additional information can be provided under item10. Describe the concerns about the level or presence of an ingredient or impurity/ product use/ label instructions/ specific differences from RLD that may have clinical effect/ tablet or capsule size/ other concerns.
Provide a brief history of comments to and from the applicant regarding the issue.)

The OPQ/OLDP/DMRP/Branch-I is requesting OGD/DCR review to evaluate the proposed (b) (4) levels in Ethylene Vinyl Acetate Copolymers 9% (b) (4) and 28% (b) (4) in raw material specifications associated with ANDA 210830. The applicant (Ameal Pharmaceuticals LLC) is proposing to control (b) (4) for both EVA 9% and 28%. The applicant is not monitoring the levels of (b) (4) in finished drug product.

The Ethinyl Estradiol and Etonogestrel Vaginal Ring is indicated for Prevention of Pregnancy. The product contains 2.7 mg Ethinyl Estradiol and 11.7 mg Etonogestrel

7. **Specific request**: (chose one)
(For Fast Track consults, see section 5 above and leave this section blank.)

☒ **a. Is the ☐ Maximum Daily Intake ☒ Specification Limit (chose one)] of** [redacted] (b) (4) _____

acceptable in the product based on the MDD, route of administration and proposed product use?

☐ **b. Is the size of the generic tablet/capsule safe for the intended use and population?**

☐ **c. Are the use instructions in section _____ of the product label for the generic product ☐ accurate ☐ appropriate (chose one)?**

☐ **d. Other consult request**
(Add a clear request for an opinion on the issue of concern)

8. **Maximum Daily Intake/Exposure Calculation** (Insert the calculation of Maximum Daily Intake (MDI) of an inactive ingredient or Total Daily Intake (TDI) of an impurity based on the MDD.)

Calculation:

[redacted] (b) (4)

Calculation guide
Inactive ingredient (mg/unit) x # units in MDD = MDI
Impurity limit (ppm or %) x MDD = TDI in mg or mcg
[redacted] (b) (4) limit (ppm or %) x MDD = TDI in mg/day

MDD is usually in mcg, mg or g
(MDD x %)/100 or (MDD x ppm)/1,000,000 = TDI in mcg, mg or g
For liquids, convert w/v or v/v into weight/dose x number doses.
Transdermal Systems may be stated as weight/patch.

9. **RLD application number:** N21187 **,**
and product name: Nuvaring®

10. **Additional background information** (Include relevant RLD information or other information that supports the consult request or explains the concern. For concerns about an impurity, describe the type of impurity, chemical structure and level reported in the RLD. For concerns about size, include a comparison of the RLD and generic.)

RLD also uses similar grades of EVA Copolymers. The referencing DMF for EVA Copoly

11. **Location and submission date of referenced information** (Provide the specific section(s) in eCTD submission or pages in paper submissions. For paper submissions, scanned copies of relevant pages should be included in section 14.)

    a. **Location:** Section 3.2.P.4.1 Specifications for EVA Copolymer 28% and 9%

    b. **Date:** 11/29/17

12. **Chemistry Reviewer Name** Pinaki Desai
    Date: 03/14/2018

13. **BC/QAL/TL concurrence with the consult:** ■
    BC/QAL/TL Name Robert Berendt

14. **Attachments:** (This section may be left blank if the location is in eCTD and clearly stated under item 11. For paper submission, 5 include information other than the referenced documents cited in item 6 such as written summaries, data from other references, cross-references, reference to previous consults. These can be pasted at the end of the template.) **Attachment**

Intercenter Consult Requests (ICCRs) ▸ ICCR Forms: ICCR2018-02958

Print this page

Problems with or questions on this form or the ICCR process?
Access the ICCR Intranet Page for additional resources.
**** This form works best in Internet Explorer. Do not use Firefox or Chrome. ****

Improvements and updates to the ICCR form were made on May 21, 2018. For a summary of changes, click here.

ICCR2018-02958
Submitted

Intercenter Consult Request (ICCR)

TIER AND CONTACT INFORMATION

Lead Center: *The Center with which the individual submitting the ICCR is affiliated*	CDER
Consulted Center: *The Center to which the individual receiving the ICCR is affiliated*	CDRH
Consult Tier Information: *If you have questions on whether an ICCR is Routine (Tier 2) or Non-Routine (Tier 3) or appropriate Consulted Center Receivers, contact your Center's Product Jurisdiction Officer:* Click to Contact CDER Product Jurisdiction	Routine ("Tier 2") *Tier cannot be changed once the ICCR is submitted. If consult tier is incorrect, copy this form to a new ICCR, withdraw this form, and resubmit the new ICCR with corrected tier.* **Facilities inspections consults for a CDER application (e.g., identifying the neec** *Consult Type*
Lead Center Consult Requester: *The individual in the Lead Center who fills out and submits an ICCR form and serves as the contact for the ICCR*	**Yang, Steven** *Lead Center Requester Office/Division:* **OPQ/OPRO**
Lead Center Submission Contact: *The individual in the Lead Center who takes responsibility for the submission or file*	**Nelson, Laurie**
Consulted Center Receiver: *Identified person or inbox designated to receive ICCRs*	**CDRH_OC_Combination Products** ***CLICK HERE** for a list of contacts in each Center.*
Others Notified ***[Optional]:*** *Include others to receive e-mail notification that are NOT already identified above.*	
Contact Details ***[Optional]:*** *Clarify how contacts above are related to review (e.g., which of above is lead reviewer/PM/ scientific reviewer) or provide other information on review team.*	

CONSULTED CENTER ACTION ITEMS

Assigned Consulted Reviewer(s): *Consulted center reviewer who is assigned to complete an ICCR*	*Assigned Reviewer Office/Division:*
Reviewer Supervisor(s): ***[Optional]***	
Project Manager (PM/RPBM/SRPM): ***[Optional]***	
Consulted Center Tracking Number(s) ***[Optional]*** *PANORAMA, CTS, or Other Center-Specific Tracking]*	

SAVE DISABLED - ICCR cannot be saved as REVIEWER ASSIGNED until reviewer entered above. All Required (Red) Fields in Form must also be filled.

PRODUCT INFORMATION:

Product Name:	**ELURYNG (ETONOGESTREL/ETHINYL ESTRADIOL) RING**	
Applicant/Sponsor:	**AMNEAL PHARMACEUTICALS LLC**	
Indications for Use:	**It is estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.**	
Combo Product Details:	**Drug-Device** (b) (4)	
Device Constituent Details:	*Device Type:* *Notes:*	
Drug Constituent Details:	*Dosage Form:* *Notes:*	
Biologic Constituent Details:	*Biologic Type:* *Notes:*	

SUBMISSION INFORMATION:

Application/Submission Information:	**ANDA** *Submission Type*	**210830** *Application/Submission Number*
Submission Dates:	**8/25/2017** *Received Date ("Date Stamped" Date)*	**6/24/2018** *FDA Action Date (e.g., MDUFA/PDUFA Goal Date)*
Reason for Submission:	**Other**	
	Submission Notes: Need CDRH review of 483, EIR and 483 response. The 483 is currently uploaded in CMS under the Amneal FEI 3008861605. We are still awaiting the EIR from the DO. We have spoken with the DO and they are aware we are waiting on this, so we need this for my review too. As soon as we receive the EIR we will pass it on but it will also be uploaded in CMS along with the 483 response.	
Other Relevant Submissions: *Include Master Files and previous submissions related to review.*		
Documentation Location:	**Other**	
Documentation Details: ***Include specific location of information*** *(volumes, pages, or other assistance to reviewer in locating content relevant to ICRR request).*	Information will be provided once we receive it.	

DESCRIPTION OF THE INTERCENTER CONSULT REQUEST:

CONSULT DUE DATE:	***6/5/2018*** *If you want to also document intermediate milestones during the review cycle, scroll down to interim milestones/ deliverables Section below.*
Previous/Requested Reviewer(s) [OPTIONAL]:	**Barber, Therese**

Request Details:
*Provide **specific** direction to reviewer on scope and output of request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the reviewer.*

As per CDRH-OC:

In my amended review dated April 23, 2018, I recommended a post-approval inspection for this combination product. However, now that the inspection has been completed and the investigator(s) found several deficiencies (that could apply to 21 CFR 820 requirements), a new ICCR SharePoint consult should be submitted to review the information from the inspection (the EIR (when it is ready for review by CDRH and CDER) from the district office and the firm's response). Based on my quick review of the FDA Form 483, the six observations all pertain to design controls, manufacturing process controls, and management review (which could apply to both drug and device requirements).

Lead Center Tracking Number(s): ***[Optional]*** *PANORAMA, CTS, or Other Center-Specific Tracking #]*	

Interim milestones/deliverables, list below with projected dates. Text field only. [OPTIONAL]

Save edits but DOES NOT change status. No notifications are sent.

Copy product information and submission information from this form to a new ICCR and sends you an e-maill notification with link.

WITHDRAW an active ICCR and notify involved staff. You will be prompted to add a reason for withdrawal.

ICRR Tracking Dates (these will be filled automatically)

Tier 2 & Tier 3 Sub-consults	Submitted	5/22/2018	Reviewer Assigned	Completed

This ICCR Last Updated 5/22/2018 *by Steven.Yang@fda.hhs.gov*

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 03/01/2018 08:34:58 PM
To: CEDWARDS@AMNEAL.COM;steven.yang@fda.hhs.gov
CC:
BCC:
Subject: INFORMATION REQUEST ANDA 210830

Please confirm receipt of the attached letter to steven.yang@fda.hhs.gov

Please find the attached documents below:

210830.IR.2.pdf

ANDA 210830

INFORMATION REQUEST

Amneal Pharmaceuticals LLC
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs
50 Horseblock Road
Brookhaven, NY 11719

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated August 25, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We also refer to your November 29, 2017 submission, containing responses to an information request letter.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than 30 days, in order to continue our evaluation of your ANDA.

Comments and information requests:

A. Drug substance

Drug Substance – Ethinyl Estradiol

1. (b) (4)

Drug Substance – Etonogestrel

1. (b) (4)

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

2 page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

5. (b) (4)

6.

7.

D. Biopharmaceutics

1. You manufactured five batches with different thickness of ring membrane to conduct discriminatory power study of the proposed dissolution method. However, you did not report if these five batches (b) (4) Submit the (b) (4) information of the following five batches to the Agency for review:

   Batch G16K058057P (80 µm)

   Batch G16K058057T (90 µm)

   G16K058057J (100 µm)-Target

   Batch G16K058057U (110 µm)

   Batch G16K058057Q (120 µm)

   Also, provide the (b) (4) in each formulation of the above five batches.

2. Based on the data provided, your proposed specifications are not appropriate. We request that you acknowledge your acceptance of the following specifications for your proposed products:

Etonogestrel

Ethinyl Estradiol

It should be noted that for Days 8-14, daily release rate should be used to determine if it meets the above the specifications. Acceptance Table 1 of USP <724> should be used to determine whether the acceptance criteria are met at different stages.

Acknowledge your acceptance of the above dissolution specifications and update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

3. Clarify if you have manufactured any commercial (scale-up) batches. If yes, submit the complete dissolution data (individual, mean, SD, RSD, profiles) to the Agency for review.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Steven Yang, Regulatory Business Process Manager, at 240-402-9122.

Sincerely,

{See appended electronic signature page}

Steven Yang
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Steven Yang

Digitally signed by Steven Yang
Date: 3/01/2018 08:31:54PM
GUID: 508da70900028d408c0d8076e85ec0a4

Print this page

ICCR2018-02410
Submitted

Intercenter Consult Request (ICCR)

TIER AND CONTACT INFORMATION

Lead Center: *The Center with which the individual submitting the ICCR is affiliated*	CDER
Consult Tier Information: *Tier 1* No consult required based on agreed upon list between Centers; *Tier 2* Consults leveraging existing working relationships or where scope is limited and well-defined; *Tier 3* Consults that do not fall in Tier 1 or 2	Tier 2 *Tier cannot be changed once the ICCR is submitted. If consult tier is incorrect, copy this form to a new ICCR, withdraw this form, and resubmit the new ICCR with corrected tier.* Facilities inspections consults for a CDER application (e.g., identifying the need for *Tier 2 Consult Agreement* facilities *Consult Expertise/Keywords* *Use this field to describe the particular expertise, etc, being requested in the consult(e.g., "Engineering," "Biocompatibility," "Clinical," "CMC," "PharmTox," "Human Factors," "Facilities," "cGMP")*
Lead Center Consult Requester: *The individual in the Lead Center who fills out and submits an ICCR form and serves as the contact for the ICCR*	Yang, Steven *Lead Center Requester Office/Division:* OPQ/OPRO
Lead Center Submission Contact: *The individual in the Lead Center who takes responsibility for the submission or file*	Nelson, Laurie
Consulted Center: *The Center to which the individual receiving the ICCR is affiliated*	CDRH
Consulted Center Receiver: *Identified person or inbox designated to receive ICCRs*	CDRH_OC_Combination Products *CLICK HERE for a list of contacts in each Center.*
Others Notified [Optional]: *Include others to receive e-mail notification that are NOT already identified above.*	Berendt, Robert; Williams, Juandria
Contact Details [Optional]: *Clarify how contacts above are related to review (e.g., which of above is lead reviewer/PM/ scientific reviewer) or provide other information on review team.*	

CONSULTED CENTER ACTION ITEMS

Assigned Consulted Reviewer(s): *Consulted center reviewer who is assigned to complete an ICCR*	*Assigned Reviewer Office/Division:*
Reviewer Supervisor(s): [OPTIONAL]	
SAVE DISABLED - ICCR cannot be saved as REVIEWER ASSIGNED until reviewer entered above. All Required (Red) Fields in Form must also be filled.	
Consulted Center Tracking Number(s) *[OPTIONAL - PANORAMA, CTS, or Other Center-Specific Tracking]*	

PRODUCT INFORMATION:

Product Name:	ETONOGESTREL/ETHINYL ESTRADIOL,	
Applicant/Sponsor:	AMNEAL PHARMACEUTICALS LLC	
Indications for Use:	It is estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy	
Combo Product Details:	Drug-Device (b) (4)	
Device Constituent Details:	*Device Type:* *Notes:*	
Drug Constituent Details:	*Dosage Form:* *Notes:*	
Biologic Constituent Details:	*Biologic Type:*	

	Notes:	

SUBMISSION INFORMATION:

Application/Submission Information:	**ANDA** *Submission Type*	**210830** *Application/Submission Number*
Submission Dates:	**8/25/2017** *Received Date ("Date Stamped" Date)*	**6/24/2018** *FDA Action Date (e.g., MDUFA/PDUFA Goal Date)*
Reason for Submission:	**Other**	
	Submission Notes: Applicant has responded to comments from original consult (ICC1700845/ICCR2017-01796). Responses need to be reviewed by CDRH-OC.	
Other Relevant Submissions: *Include Master Files and previous submissions related to review.*		
Documentation Location:	**Available Electronically**	
Documentation Details: ***Include specific location of information*** *(volumes, pages, or other assistance to reviewer in locating content relevant to ICRR request).*	Documents located in DARRTS. Supporting document 8, eCTD 0008 dated 2/16/18.	

DESCRIPTION OF THE INTERCENTER CONSULT REQUEST:

CONSULT DUE DATE:	***4/25/2018*** *If you want to also document intermediate milestones during the review cycle, scroll down to interim milestones/ deliverables Section below.*
Previous/Requested Reviewer(s) [OPTIONAL]:	**Barber, Therese**

Request Details:
*Provide **specific** direction to reviewer on scope and output of request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the reviewer.*

Let me know if you are unable to access the files from DARRTS.

Lead Center Tracking Number(s): *[OPTIONAL - PANORAMA, CTS, or Other Center-Specific Tracking #]*	

Interim milestones/deliverables, list below with projected dates. Text field only. [OPTIONAL]

Save edits but DOES NOT change status. No notifications are sent.

Copy product information and submission information from this form to a new ICCR and sends you an e-maill notification with link.

WITHDRAW an active ICCR and notify involved staff. You will be prompted to add a reason for withdrawal.

ICRR Tracking Dates (these will be filled automatically)

Tier 2 & Tier 3 Sub-consults	Submitted	2/22/2018	Reviewer Assigned	Completed

This ICCR Last Updated 2/22/2018 *by Steven.Yang@fda.hhs.gov*

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 210830

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Amneal Pharmaceuticals, LLC.
50 Horseblock Road
Brookhaven, NY 11719

ATTENTION: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Ms. Edwards:

Please refer to your Abbreviated New Drug Application (ANDA) dated and received August 25, 2017, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Etonogestrel and Ethinyl Estradiol Vaginal Ring.

We also refer to your correspondence, dated and received August 25, 2017, requesting review of your proposed proprietary name, Eluryng.

We have completed our review of the proposed proprietary name, Eluryng and have concluded that it is conditionally acceptable.

If your application receives a complete response and six months or more has elapsed between the date you were notified of our decision on your proposed proprietary name and the date you respond to the application deficiencies, please submit a new request for review of your proposed proprietary name when you respond to the application deficiencies. 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

If any of the proposed product characteristics as stated in your above submissions 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 Mammah Borbor-Lebbie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-7731. For any other information regarding this application, contact Adil Merchant, Regulatory Project Manager in the Office of Generic Drugs, at (240) 402-3505.

Sincerely,

{See appended electronic signature page}

Todd Bridges, 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/

AZEEM D CHAUDHRY
02/12/2018

DANIELLE M HARRIS on behalf of TODD D BRIDGES
02/13/2018

ANDA Review Pre-Screening Checklist*

Primary Reviewer	Diana Vivian, Ph.D.		Potential Consult Needed? ☐YES ☒NO
ANDA No.	210830	Drug Product Name	Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day
Date Assigned	10/24/2017	Assignment Type	Original, submitted 8/25/2017

No.	Question	Yes/No/NA	Comments
1	Is the product a drug-device combination?	☒YES ☐NO	
2	Is the product a complex drug product? (Check Complex Product Database)	☒YES ☐NO	
3	Is there a product-specific guidance for this drug product? (Check Product-Specific Guidances for Generic Drug Development)	☒YES ☐NO ☐NA	
4	Is the product-specific guidance for this drug product in development or under revision? (Check BE Guidances Under Development)	☐YES ☒NO ☐NA	
5	Does the product-specific guidance need to be revised to meet the current BE standards (e.g., recommend a fed BE study)?	☐YES ☒NO ☐NA	
6	Does the firm's study design (in vivo or in vitro) deviate from the design recommended in the product-specific guidance?	☐YES ☒NO ☐NA	
7	Is the statistical design or approach different than a typical statistical analysis handled by the Divisions of Bioequivalence?	☐YES ☒NO ☐NA	
8	Are there any serious adverse events?	☐YES ☒NO ☐NA	
9	Is there a difference in adverse event profiles between the test and reference products that may pose a safety concern?	☐YES ☒NO ☐NA	
10	Is there a meaningful difference in the T_{max} between the test and reference products?	☐YES ☒NO ☐NA	
11	Is there a meaningful difference in the T_{lag} between the test and reference products?	☐YES ☐NO ☒NA	

Please note, this checklist is only intended to be used internally as a preliminary assessment by the Divisions of Bioequivalence to prioritize the requests for consults and early identification of information requests (IRs). Some answers to the questions presented in the checklist may change during the review process, and the answers are not representative of a completed review of the assignment. (Current draft version edited Sep 20, 2017)

ANDA Review Pre-Screening Checklist*

12	Does one or more supporting metabolite(s) have point estimates outside of 0.80-1.25?	☐YES ☐NO ☒NA	
13a	Is there an inactive ingredient that exceeds the limit currently present in FDA-approved drug products based on the maximum daily dose?	☐YES ☒NO	
13b	Has the firm submitted Pharm/Tox data?	☐YES ☐NO ☒NA	
14	Is there a formulation difference between the test and reference products that may impact bioequivalence or safety for products eligible for a waiver of in vivo BE studies? [For products for which we waive in vivo BE study requirements under 21 CFR 320.22(b) or BCS]	☐YES ☐NO ☒NA	
15	Did the firm submit IVRT and/or IVPT studies to support bioequivalence?	☐YES ☐NO ☒NA	
16a	Is NG/G/J tube administration listed in the most recent RLD label?	☐YES ☐NO ☒NA	
16b	Did the firm submit NG/G/J tube studies if necessary?	☐YES ☐NO ☒NA	
17	Does the application need to go to the BCS committee? (Check BCS I Classified Products)	☐YES ☐NO ☒NA	
18	Has Integrity Services entered all sites responsible for conducting pivotal BE studies into GDRP?	☒YES ☐NO ☐NA	

Please note, this checklist is only intended to be used internally as a preliminary assessment by the Divisions of Bioequivalence to prioritize the requests for consults and early identification of information requests (IRs). Some answers to the questions presented in the checklist may change during the review process, and the answers are not representative of a completed review of the assignment. (Current draft version edited Sep 20, 2017)

Information Request (IR)

ANDA No.	210830
Drug Product Name	Etonogestrel/Ethinyl Estradiol Vaginal Ring
Strength(s)	0.120 mg/0.015 mg per day
Applicant Name	Amneal Pharmaceuticals LLC
Applicant Address	50 Horseblock Road Brookhaven, NY 11719
US Contact Name and US Mailing Address	Candis Edwards, Senior Vice President, Regulatory Affairs 50 Horseblock Road Brookhaven, NY 11719
US Contact Telephone Number	631-974-7949
US Contact Fax Number	631-527-3523
Original Submission Date(s)	08/25/2017
Submission Date(s) of Amendment(s) Under Review	--
Primary Reviewer	Diana Vivian, Ph.D.
Secondary Reviewer	Dongmei Lu, Ph.D.

The deficiencies presented below represent an *INFORMATION* REQUEST identified during the full ANDA review and the current ANDA review cycle will remain open. The following comment should be communicated to the firm.

1. In your submitted dataset 'adpp' for in vivo study # BE/16/373, the same PK parameters were listed for both etonogestrel and ethinyl estradiol. Please submit your pharmacokinetic parameters data of the BE study in SAS Transport format (.xpt) by including the following columns for each individual subject for each analyte:

SUB	SEQ	PER	GRP	TRT	TMAX	CMAX	AUCT	AUCI	KE	THALF

Where SUB= subject ID, SEQ= sequence, GRP= group, TRT= treatment

2. In your bioequivalence summary tables for in vivo study # BE/16/373, two clinical study sites were mentioned: (1) Raptim Research Ltd. Clinical Pharmacology Unit (A-226), T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai – 400701, India, and (2) Sai Snehdeep Hospital, Plot No. 12/13, Sector No-20, Kopar Khairane, Navi Mumbai-400 709, India. Please clarify how the study sites were used (e.g. whether study subjects were split into the two sites, etc.).

Please respond within five business days.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 01/19/2018 01:59:22 PM
To: CEDWARDS@AMNEAL.COM; Steven.Yang@fda.hhs.gov; Qinghua.Ge@fda.hhs.gov
CC:
BCC:
Subject: ANDA 210830 INFORMATION REQUEST

Please confirm receipt of this attachment to Steven.Yang@fda.hhs.gov and Qinghua.Ge@fda.hhs.gov

Thanks,
Qinghua Ge

Please find the attached documents below:

210830 IR.pdf

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 210830

INFORMATION REQUEST

Amneal Pharmaceuticals LLC
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs
50 Horseblock Road
Brookhaven, New York 11719

Dear Madam:

Please refer to your Abbreviated New Drug Application dated August 25, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than 30 days in order to continue our evaluation of your ANDA.

Facility

The following deficiencies have been identified while doing the documentation review of Application #ANDA 210830, Etonogestrel/Ethinyl Estradiol Ring, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

1. Your firm did not adequately address the requirements for 21 CFR 820.20, Management Responsibility. Please provide a summary of how your firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4).

2. Your firm did not adequately address the requirements for 21 CFR 820.30, Design Controls. Please provide a description of your firm's design control procedures to address the requirements for design transfer. Please provide a copy or a summary of the plan used to design the combination product.

3. Your firm did not adequately address the requirements for 21 CFR 820.50, Purchasing Controls. Please provide a summary of the procedure(s) for purchasing

controls. The summary should:

a. Describe your supplier evaluation process and describe how it will determine the type and extent of control to be exercised over suppliers;
b. Define how the records of acceptable suppliers will be maintained;
c. Address the purchasing data approval process; and
d. Explain how your firm will balance purchasing assessment and receiving acceptance to ensure that products are acceptable for their intended use.

Please explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Please provide a description of how your firm will apply purchasing controls to the suppliers/contractors used in the manufacturing of the combination product.

4. Your firm did not adequately address the requirements for 21 CFR 820.100, Corrective and Preventive Actions. Please summarize the procedure(s) for your firm's Corrective and Preventive Action (CAPA) System. The CAPA system should require:
    a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
    b. Investigation of nonconformities and their causes;
    c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and
    d. Verification or validation of the actions taken.

5. Your firm did not adequately describe the manufacturing activities of the finished combination product. Your firm should:
    a. Provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review.
    b. Provide a summary of the procedure(s) or the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product.
    c. Explain how it will perform the acceptance activities for the receiving of components/materials to be used in the combination product; the in-process testing performed during the manufacturing/assembly; and, the final release of the combination product. In addition, the firm should explain the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product.
    d. Provide summaries or procedure(s) on the assembly of the final combination product, including packaging, sterilization and final release testing of the finished combination product.

Your firm may find useful information regarding the types of documents to provide in the document called "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff" (2003). This document may be found at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

If you do not submit a complete response by February 17, 2018 the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Steven Yang, Regulatory Business Process Manager, at 240-402-9122.

Sincerely,

{See appended electronic signature page}

Steven Yang
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Steven Yang

Digitally signed by Steven Yang
Date: 1/19/2018 01:42:38PM
GUID: 508da70900028d408c0d8076e85ec0a4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 01/09/2018 01:08:57 PM
To: CEDWARDS@AMNEAL.COM
CC: nitin.patel@fda.hhs.gov
BCC: karyn.berry@fda.hhs.gov
Subject: INFORMATION REQUEST Original ANDA 210830

ANDA 210830
INFORMATION REQUEST
Original ANDA
Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards

Dear Candis Edwards::

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 25, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

Please see the attached Information Request letter.

DO NOT RESPOND TO THIS EMAIL ADDRESS – IT IS A SEND-ONLY ACCOUNT. For questions, please contact the Regulatory Project Manager assigned to your application.

Please find the attached documents below:

ANDA 210830 IR for Comparative Analysis.pdf

ANDA 210830

INFORMATION REQUEST

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards

Dear Candis Edwards::

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 25, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

Your submission remains under review, and we require additional information in order to complete our Clinical Consultation review.

Specifically, FDA has insufficient information to determine whether your proposed product can be substituted for the reference listed drug (RLD) without the intervention of a health care provider and/or without additional training prior to use. We refer you to FDA's draft guidance entitled Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (January 2017) (available at http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm536959.pdf), which provides recommendations on the identification and assessment of differences in the design of the user interface for a proposed generic combination product when compared to its RLD. Please provide the Agency with the results of the three threshold analyses (e.g., comparative labeling analysis, comparative task analyses, comparison in the design of the delivery device constituent), as well as your overall assessment of any identified differences for your proposed product when compared to the RLD.

Should you find that these analyses suggest that any identified differences in the designs of your presentation(s) are minor, we request that you provide this data for FDA's review and concurrence.

However, please note that the Agency may view the design differences for your proposed presentation(s) as not being minor if any aspect of the analyses suggests that, when your product is substituted for the RLD, they may impact a critical task that can affect patient use or caregiver administration of the product. In such cases, additional information and/or data, such as data from comparative human factors studies, may be warranted to further assess whether the differences identified in the

user interface impact the clinical effect or safety profile of your proposed product when compared to its RLD. We strongly encourage you to consult with the Agency if such design differences are identified.

The requested information should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

We request a complete written response no later than January 22 , 2018 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
CLINICAL
REFERENCE # 20186182

If you do not submit a complete written response by January 22 , 2018, the listed information requests may be incorporated in a complete response letter.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact the Clinical Project Manager, at Nitin.Patel@fda.hhs.gov.

Please also confirm receipt of this letter.

Sincerely,

Nitin K. Patel, Pharm.D.
Clinical Project Manager
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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: December 15, 2017

TO: Dale Conner, Pharm.D.
Director
Office of Bioequivalence
Office of Generic Drugs

FROM: Li-Hong Yeh, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE, OSIS

SUBJECT: Routine inspection of Raptim Research Ltd., Navi Mumbai, Maharashtra, India.

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of Studies (b) (4) **BE-15-237** (**ANDA 210602**) and **BE-17-183 (ANDA 203083)** conducted at Raptim Research Ltd., Navi Mumbai, Maharashtra, India.

No significant deficiencies were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I found the data from the audited studies (b) (4) **BE-15-237, and BE-17-183** reliable. Thus, I recommend that the data from these studies and other studies of similar design (see attachment 1) be accepted for further Agency review.

Application	Study	Sponsor	Study Site	Recommendation	Classification
(b) (4)			Raptim Research Ltd., Navi Mumbai, India	Accept all data	**NAI**
ANDA 210602	BE-15-237	THINQ Pharma-CRO Pvt. Ltd.			
ANDA 203083	BE-17-183	AptaPharma Inc., U.S.A.			

Inspected Studies:

(b) (4)

ANDA 210602

Study Number: **BE-15-237**

Study Title: "Bioequivalence Study of Ibuprofen Oral Suspension 100 mg/5 mL in Normal, Healthy, Adult, Human Subjects Under Fed Condition."

Dates of Study Conduct: 12/07/2016 – 12/15/2016

ANDA 203083

Study Number: **BE-17-183**

Study Title: "An Open-Label, Balanced, Randomized, Two-Treatment, Two-Sequence, Four-Period, Single Oral Dose, Fully Replicate Crossover Bioequivalence Study of Lansoprazole Delayed Release Capsules 30 mg of Hetero Labs Limited, India with PREVACID® (Lansoprazole)

Delayed Release Capsules 30 mg of Takeda Pharmaceuticals America, Inc. Deerfield, IL 60015, Sprinkled over Applesauce, in Normal, Healthy, Adult Human Subjects under Fasting Condition."

Dates of Study Conduct: 05/07/2017 – 05/21/2017

Clinical site: Raptim Research Ltd.
A-226 Near Mahape Depot, TTC Industrial Area
Navi Mumbai, Maharashtra, India

ORA Investigator Joseph L Despins (DBIMO-I) inspected Raptim Research Ltd., Navi Mumbai, Maharashtra, India from 11/06/2017 - 11/10/2017.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

At the conclusion of the inspection, Investigator Despins did not observe any objectionable findings and did not issue Form FDA 483 to the clinical site.

Conclusion:

After reviewing the inspectional findings, I found the data from the audited studies (Studies (b) (4), **BE-15-237, and BE-17-183**) to be reliable. Thus, I recommend that the data from Studies (b) (4), **BE-15-237, and BE-17-183** and other studies of similar design be accepted for further Agency review. In addition, the data from studies submitted to pending applications (**Attachment 1**) should be accepted for further Agency review without an inspection.

Li-Hong Yeh, Ph.D.
Chemical Engineer
DNDBE/OSIS

Final Classification:
Clinical site
NAI- Raptim Research LLC, Navi Mumbai, Maharashtra, India
(FEI: 3007267856)

CC:
OTS/OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller/Johnson
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Yeh
OTS/OSIS/DGDBE/Cho/Kadavil/Skelly/Choi/Au

Draft: PY 12/08/2017
Edits: RCA 12/09/2017 12/15/2017

ECMS:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881362556

BE File #: BE 7686 ((b) (4)), BE 7738 (ANDA 203083) and BE 7685 (ANDA 210602).

FACTS: 11757928

Lihong P. Yeh -S
Digitally signed by Lihong P. Yeh -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lihong P. Yeh -S, 0.9.2342.19200300.100.1.1=1300155526
Date: 2017.12.15 10:55:58 -05'00'

Li-Hong Yeh

Lihong P. Yeh -S
Digitally signed by Lihong P. Yeh -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lihong P. Yeh -S, 0.9.2342.19200300.100.1.1=1300155526
Date: 2017.12.15 10:56:23 -05'00'

On behalf of Ruben Ayala

Arindam Dasgupta -S
Digitally signed by Arindam Dasgupta -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0012329705, cn=Arindam Dasgupta -S
Date: 2017.12.15 11:04:24 -05'00'

Arindam Dasgupta

Attachment 1
List of additional Studies

Application # (BE #)	Study #	Drug Name(s)	Dates of conduct
ANDA 210347 (BE 7572)	BE-16-246 BE-16-247	Piroxicam	01/09/2017-01/27/2017 02/16/2017-03/06/2017
ANDA 210402 (BE7573)	BE-17-017	Dimethyl Fumarate	02/18/2017-03/07/2017
ANDA 210500 (BE7574)	BE-17-003 BE-17-004	Dimethyl Fumarate	02/04/2017-02/27/2017 02/12/2017-03/18/2017
ANDA 210577 (BE7575)	BE-16-196 BE-16-197	Hydroxychloroquine sulfate	11/17/2016-11/21/2016 11/23/2016-11/27/2016
			(b) (4)
ANDA 210859 (BE7686)	BE-17-161 BE-17-162	Ezetimibe	05/05/2017-05/21/2017 05/09/2017-05/25/2017
ANDA 211060 (BE7687)	BE-17-047 BE-17-048	Silodosin	03/19/2017-04/02/2017 03/25/2017-04/08/2017
			(b) (4)
ANDA 209366 (BE7738)	BE-14-206 BE-14-207	Acyclovir	02/18/2016-02/28/2016 11/24/2015-12/04/2015
ANDA 210628 (BE7577)	BE-15-153 BE-15-154	Celecoxib	08/11/2016-08/26/2016 09/16/2016-10/02/2016
ANDA 210675 (BE7635)	BE-16-209 BE-15-074 BE-15-075	Doxepin Hydrochloride	10/21/2016-11/08/2016 08/02/2015-08/22/2015 09/14/2015-10/04/2015
ANDA 210733 (BE7636)	BE-15-230	Potassium Chloride	04/12/2017-04/29/2017
			(b) (4)
ANDA 210830 (BE7638)	BE-16-373	Ethinyl estradiol and etonogestrel vaginal ring	02/23/2017-04/27/2017

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Division of Clinical Review (DCR) Office of Bioequivalence (OB)/Office of Generic Drugs	Division of Clinical Review (DCR) Office of Bioequivalence (OB)/Office of Generic Drugs

DATE	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/13/2017		210830	Original ANDA	8/25/2017

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day			3/13/2018

NAME OF FIRM: Amneal Pharmaceuticals LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER: _Comparative Analysis review___

II. BIOMETRICS

- ☐ TYPE A OR B NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER _____
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER _____

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Please conduct a comparative evaluation of the user interface with the RLD since this is a drug-device combination product.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check all that apply)
Nitin K. Patel	☒ PANORAMA ☐ EMAIL ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 12/06/2017 02:29:55 PM
To: CEDWARDS@AMNEAL.COM
CC: julie.call@fda.hhs.gov; adil.merchant@fda.hhs.gov
BCC:
Subject: DISCIPLINE REVIEW LETTER ANDA 210830

Hello,

Please find attached the Discipline Review Letter for your pending ANDA 210830.

Provide a complete response to these deficiencies as soon as possible but no later than December 20, 2017. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING
REFERENCE # 19399139

If you do not submit a complete response by December 20, 2017, the review may be closed and the listed deficiencies may be incorporated in a COMPLETE RESPONSE correspondence. Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application As contemplated in the GDUFA II Commitment Letter, these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review.

If you have questions regarding these deficiencies or would like acknowledgement of receipt of your amendment upon submission, please contact the Labeling Project Manager, Julie Call, at julie.call@fda.hhs.gov.

Sincerely,

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Please find the attached documents below:

A210830N000DLR_DRL-Amneal.pdf

ANDA 210830

DISCIPLINE REVIEW LETTER

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719

Attention: Candis Edwards
U.S. Agent

Dear Ms. Edwards:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 25, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We have completed the Labeling review of this ANDA and have the following preliminary thoughts on possible deficiencies:

1. GENERAL COMMENTS
   a. We note that you have submitted a proprietary name for this product. It will be reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Safety and Epidemiology. Additional labeling comments may be forthcoming after review of the name by DMEPA.
   b. We recommend revising the established name (b) (4) (b) (4) to read “etonogestrel and ethinyl estradiol vaginal ring” on your labels and labeling. (b) (4)

2. CONTAINER LABEL
   a. (b) (4)
   b.

3. CARTON LABELING
   a. (b) (4)
   b.

4. PRESCRIBING INFORMATION
   16 HOW SUPPLIED: Remove (b) (4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review-cycle, we request a complete written response no later than December 20, 2017. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING
REFERENCE # 19399139

If you do not submit a complete written response by December 20, 2017, these possible deficiencies may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application As contemplated in the GDUFA II Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review.

[1] The term "GDUFA II Commitment Letter" refers to the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact Julie Call, Labeling Project Manager, at julie.call@fda.hhs.gov or 240-402-8598.

Sincerely,

{See appended electronic signature page}

Julie Call, PharmD
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Julie Call

Digitally signed by Julie Call
Date: 12/06/2017 02:28:19PM
GUID: 525d9e9d00038c406bce70608a211ab1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 11/21/2017 11:06:25 AM
To: CEDWARDS@AMNEAL.COM
CC:
BCC: eva.chan@fda.hhs.gov, adil.merchant@fda.hhs.gov
Subject: INFORMATION REQUEST: ANDA 210830

Dear Mrs. Edwards:

Please see the attached information request.

Sincerely,

Eva Chan, Pharm.D.
OFFICE OF GENERIC DRUGS
OFFICE OF BIOEQUIVALENCE
Center for Drug Evaluation and Research

Please find the attached documents below:

A210830N000DB-InformationRequest02-11212017.pdf
http://panorama.fda.gov/document/download?ID=5a144d9f000eace4b829c0626d0e763d

ANDA 210830

INFORMATION REQUEST

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719

Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Mrs. Edwards:

This letter is in reference to your abbrebiated new drug application (ANDA) received for review on August 25, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We are reviewing the bioequivalence section of your submission and have the following information requests.

1. In your submitted dataset 'adpp' for in vivo study # BE/16/373, the same PK parameters were listed for both etonogestrel and ethinyl estradiol. Please submit your pharmacokinetic parameters data of the BE study in SAS Transport format (.xpt) by including the following columns for each individual subject for each analyte:

SUB	SEQ	PER	GRP	TRT	TMAX	CMAX	AUCT	AUCI	KE	THALF

Where SUB= subject ID, SEQ= sequence, GRP= group, TRT= treatment

2. In your bioequivalence summary tables for in vivo study # BE/16/373, two clinical study sites were mentioned: (1) Raptim Research Ltd. Clinical Pharmacology Unit (A-226), T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai – 400701, India, and (2) Sai Snehdeep Hospital, Plot No. 12/13, Sector No-20, Kopar Khairane, Navi Mumbai-400 709, India. Please clarify how the study sites were used (e.g. whether study subjects were split into the two sites, etc.).

We request a complete written response no later than November 28, 2017 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
DISCIPLINE
REFERENCE # 19117853

If you do not submit a complete written response by November 28, 2017, the listed information requests may be incorporated in a complete response letter.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact Eva Chan, Bioequivalence Project Manager, at eva.chan@fda.hhs.gov or 240-402-9648.

Sincerely,

Eva Chan, Pharm.D.
OFFICE OF GENERIC DRUGS
OFFICE OF BIOEQUIVALENCE
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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: 11/9/2017

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: ANDA 210733
ANDA 210675
(b) (4)
ANDA 210830

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

Nicola Fenty-stewart -S

Digitally signed by Nicola Fenty-stewart -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001347020, cn=Nicola Fenty-stewart -S
Date: 2017.11.09 21:34:43 -05'00'

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: 11/13/2017

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct biopharmaceutical inspection**

RE: ANDA 210830

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) declines to conduct a biopharmaceutical inspection for the site specified below.

Rationale

Although OSIS has no inspection history for the below site, the review of the submission determined that only test and reference product placement (ring insertion activities) were conducted at the site. The remaining clinical activities were conducted at another clinical site.

.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Sai Snehdeep Hospital	Plot No. 12/13, Sector No. 20, Kopar Khairane, Navi Mumbai, Maharashtra, India

Nicola Fenty-stewart -S

Digitally signed by Nicola Fenty-stewart -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001347020, cn=Nicola Fenty-stewart -S
Date: 2017.11.13 14:34:30 -05'00'

Print this page

TBD (Assigned when Submitted)
Submitted

Intercenter Consult Request (ICCR)

TIER AND CONTACT INFORMATION

Lead Center: *The Center with which the individual submitting the ICCR is affiliated*	CDER
Consult Tier Information: *Tier 1* No consult required based on agreed upon list between Centers; *Tier 2* Consults leveraging existing working relationships or where scope is limited and well-defined; *Tier 3* Consults that do not fall in Tier 1 or 2	Tier 2 *Tier cannot be changed once the ICCR is submitted. If consult tier is incorrect, copy this form to a new ICCR, withdraw this form, and resubmit the new ICCR with corrected tier.* Vaginal Ring/IUD Consults to CDRH *Tier 2 Consult Agreement* Engineering and biocompatibility consult *Consult Expertise/Keywords* *Use this field to describe the particular expertise, etc, being requested in the consult(e.g., "Engineering," "Biocompatibility," "Clinical," "CMC," "PharmTox," "Human Factors," "Facilities," "cGMP")*
Lead Center Consult Requester: *The individual in the Lead Center who fills out and submits an ICCR form and serves as the contact for the ICCR*	Yang, Steven
	Lead Center Requester Office/Division: OPQ/OPRO
Lead Center Submission Contact: *The individual in the Lead Center who takes responsibility for the submission or file*	Desai, Pinaki; Berendt, Robert
Consulted Center: *The Center to which the individual receiving the ICCR is affiliated*	CDRH
Consulted Center Receiver: *Identified person or inbox designated to receive ICCRs*	DAGRID ICC *CLICK HERE for a list of contacts in each Center.*
Others Notified [Optional]: *Include others to receive e-mail notification that are NOT already identified above.*	
Contact Details [Optional]: *Clarify how contacts above are related to review (e.g., which of above is lead reviewer/PM/ scientific reviewer) or provide other information on review team.*	Robert Berendt - ATL; Pinaki Desai - Reviewer; Steven Yang - RBPM

CONSULTED CENTER ACTION ITEMS

Assigned Consulted Reviewer(s): *Consulted center reviewer who is assigned to complete an ICCR*	
	Assigned Reviewer Office/Division:
Reviewer Supervisor(s): [OPTIONAL]	
SAVE DISABLED - ICCR cannot be saved as REVIEWER ASSIGNED until reviewer entered above. All Required (Red) Fields in Form must also be filled.	
Consulted Center Tracking Number(s) *[OPTIONAL - PANORAMA, CTS, or Other Center-Specific Tracking]*	

PRODUCT INFORMATION:

Product Name:	ETONOGESTREL/ETHINYL ESTRADIOL RING	
Applicant/Sponsor:	AMNEAL PHARMACEUTICALS LLC	
Indications for Use:	It is estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.	
Combo Product Details:	Drug-Device Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)	
Device Constituent Details:	*Device Type:* *Notes:*	Other Contraceptive Vaginal Ring
Drug Constituent Details:	*Dosage Form:* *Notes:*	Other Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0 015 mg per day

Biologic Constituent Details:	*Biologic Type:* *Notes:*	

SUBMISSION INFORMATION:

Application/Submission Information:	**ANDA** *Submission Type*	**210830-orig-1** *Application/Submission Number*
Submission Dates:	**8/25/2017** *Received Date ("Date Stamped" Date)*	**12/20/2017** *FDA Action Date (e.g., MDUFA/PDUFA Goal Date)*
Reason for Submission:	**Original Submission**	
	Submission Notes: Requesting a reviewer assignment for a team review of the quality of the proposed generic vaginal ring product. The generic formulation is qualitatively and quantitatively similar to the Referenced Listed Drug (NDA 21187 - NuvaRing). Further, the quality controls (tests and acceptance criterion) and manufacturing processes are similar to the RLD (NDA 21187 - NuvaRing). We are requesting this consult to identify any general concerns CDRH reviewers may have with a vaginal ring type product from a device perspective (We have drug-product samples in house that can be provided once a reviewer is assigned).	
Other Relevant Submissions: *Include Master Files and previous submissions related to review.*	**CDRH consults for other proposed NuvaRing generic products ANDA 204305 (ICCR submitted on April 28, 2016) and ANDA 207577 (ICCR submitted on May 09, 2016) may be helpful references.**	
Documentation Location:	**Available Electronically**	
Documentation Details: ***Include specific location of information*** *(volumes, pages, or other assistance to reviewer in locating content relevant to ICRR request).*	\\cdsesub1\evsprod\anda210830\0001\m3\33-lit-ref\3-3-literature-reference.pdf All quality control tests, manufacturing process descriptions, and specifications are providcd in Module 3 of the ANDA 210830. Polymers (Two Ethylene Vinyl Acetate Copolymers) are referenced from (b) (4)	

DESCRIPTION OF THE INTERCENTER CONSULT REQUEST:

CONSULT DUE DATE:	***12/25/2017*** *If you want to also document intermediate milestones during the review cycle, scroll down to interim milestones/ deliverables Section below.*
Previous/Requested Reviewer(s) [OPTIONAL]:	**Mackey, Cheryl**

Request Details:

*Provide **specific** direction to reviewer on scope and output of request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the reviewer.*

See "reason for submission" section above.

Lead Center Tracking Number(s): *[OPTIONAL - PANORAMA, CTS, or Other Center-Specific Tracking #]*	

Interim milestones/deliverables, list below with projected dates. Text field only. [OPTIONAL]

Save edits but DOES NOT change status. No notifications are sent.

Copy product information and submission information from this form to a new ICCR and sends you an e-maill notification with link.

WITHDRAW an active ICCR and notify involved staff. You will be prompted to add a reason for withdrawal.

ICRR Tracking Dates (these will be filled automatically)

Tier 2 & Tier 3 Sub-consults	Submitted	10/30/2017	Reviewer Assigned	Completed

This ICCR Last Updated 10/30/2017 *by Steven.Yang@fda.hhs.gov*

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 10/30/2017 01:22:17 PM
To: CEDWARDS@AMNEAL.COM;steven.yang@fda.hhs.gov
CC:
BCC:
Subject: INFORMATION REQUEST ANDA 210830

Please confirm receipt of the attached letter to steven.yang@fda.hhs.gov

Please find the attached documents below:

210830 IR Ltr.pdf
http://panorama.fda.gov/document/download?ID=59f751d100237c4a0ccbaebc04ebb0c3

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 210830

INFORMATION REQUEST

Amneal Pharmaceuticals LLC
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs
50 Horseblock Road
Brookhaven, NY 11719

Dear Madam:

Please refer to your Abbreviated New Drug Application dated August 25, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Drug substance:

1. (b) (4)

2.

B. Drug Product

1 page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

8. (b) (4)

C. Process

1. (b) (4)

2.

D. Biopharmaceutics

1. Submit a full in vitro release method development report to the Agency for review. The report should include the following:

    a. Detailed description of the in vitro release test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed in vitro release method as the optimal test for your product.
    b. Sufficient data to support the discriminating ability of the selected method, including the complete in vitro release data (individual, mean, SD, RSD, and profile). In general, the testing conducted to demonstrate the discriminating ability of the selected method should compare the in vitro release profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected in vitro release method is able

to reject batches that are not bioequivalent. Use cumulative release profiles instead of daily release to evaluate the discriminating ability.

2. You have stated that you use a ring holder to keep the ring in place during in vitro release testing. Provide details of this ring holder. You may also provide photographs of the in vitro release apparatus including the ring assembly.

If you do not submit a complete response by November 29, 2017 the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Steven Yang, Regulatory Business Process Manager, at 240-402-9122.

Sincerely,

{See appended electronic signature page}

Steven Yang
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Steven Yang

Digitally signed by Steven Yang
Date: 10/30/2017 01:16:57PM
GUID: 508da70900028d408c0d8076e85ec0a4

Print this page

ICCR2017-01796
Submitted

Intercenter Consult Request (ICCR)

TIER AND CONTACT INFORMATION

Lead Center: *The Center with which the individual submitting the ICCR is affiliated*	CDER
Consult Tier Information: *Tier 1* No consult required based on agreed upon list between Centers; *Tier 2* Consults leveraging existing working relationships or where scope is limited and well-defined; *Tier 3* Consults that do not fall in Tier 1 or 2	Tier 2 *Tier cannot be changed once the ICCR is submitted. If consult tier is incorrect, copy this form to a new ICCR, withdraw this form, and resubmit the new ICCR with corrected tier.* Vaginal Ring/IUD Consults to CDRH *Tier 2 Consult Agreement* facilities, CGMP *Consult Expertise/Keywords* *Use this field to describe the particular expertise, etc, being requested in the consult(e.g., "Engineering," "Biocompatibility," "Clinical," "CMC," "PharmTox," "Human Factors," "Facilities," "cGMP")*
Lead Center Consult Requester: *The individual in the Lead Center who fills out and submits an ICCR form and serves as the contact for the ICCR*	Yang, Steven *Lead Center Requester Office/Division:* OPQ/OPF
Lead Center Submission Contact: *The individual in the Lead Center who takes responsibility for the submission or file*	Nelson, Laurie
Consulted Center: *The Center to which the individual receiving the ICCR is affiliated*	CDRH
Consulted Center Receiver: *Identified person or inbox designated to receive ICCRs*	CDRH_OC_Combination Products *CLICK HERE for a list of contacts in each Center.*
Others Notified [Optional]: *Include others to receive e-mail notification that are NOT already identified above.*	Berendt, Robert; Desai, Pinaki; Williams, Juandria
Contact Details [Optional]: *Clarify how contacts above are related to review (e.g., which of above is lead reviewer/PM/ scientific reviewer) or provide other information on review team.*	Robert Berendt - ATL; Pinaki Desai - DP reviewer; Juandria Williams - OPF facilities secondary reviewer.

CONSULTED CENTER ACTION ITEMS

Assigned Consulted Reviewer(s): *Consulted center reviewer who is assigned to complete an ICCR*	*Assigned Reviewer Office/Division:*
Reviewer Supervisor(s): [OPTIONAL]	
SAVE DISABLED - ICCR cannot be saved as REVIEWER ASSIGNED until reviewer entered above. All Required (Red) Fields in Form must also be filled.	
Consulted Center Tracking Number(s) *[OPTIONAL - PANORAMA, CTS, or Other Center-Specific Tracking]*	

PRODUCT INFORMATION:

Product Name:	ETONOGESTREL/ETHINYL ESTRADIOL RING	
Applicant/Sponsor:	AMNEAL PHARMACEUTICALS LLC	
Indications for Use:	It is estrogen/progestin combination hormonal contraceptive (CHC) indicated for use by women to prevent pregnancy.	
Combo Product Details:	Drug-Device Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)	
Device Constituent Details:	*Device Type:* *Notes:*	Other Contraceptive Vaginal Ring
Drug Constituent Details:	*Dosage Form:* *Notes:*	Other Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0 015 mg per day

Biologic Constituent Details:	*Biologic Type:* *Notes:*	

SUBMISSION INFORMATION:

Application/Submission Information:	**ANDA** *Submission Type*	**210830-orig-1** *Application/Submission Number*
Submission Dates:	**8/25/2017** *Received Date ("Date Stamped" Date)*	**12/20/2017** *FDA Action Date (e.g., MDUFA/PDUFA Goal Date)*
Reason for Submission:	**Original Submission**	
	Submission Notes:	
Other Relevant Submissions: *Include Master Files and previous submissions related to review.*		
Documentation Location:	**Available Electronically**	
Documentation Details: ***Include specific location of information*** *(volumes, pages, or other assistance to reviewer in locating content relevant to ICRR request).*	\\cdsesub1\evsprod\anda210830\0001\m3\33-lit-ref\3-3-literature-reference.pdf	

DESCRIPTION OF THE INTERCENTER CONSULT REQUEST:

CONSULT DUE DATE:	***12/1/2017*** *If you want to also document intermediate milestones during the review cycle, scroll down to interim milestones/ deliverables Section below.*
Previous/Requested Reviewer(s) [OPTIONAL]:	

Request Details:

*Provide **specific** direction to reviewer on scope and output of request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the reviewer.*

Please identify and evaluate the relevant device constituent manufacturing facilities and determine acceptability to support the current application.

Lead Center Tracking Number(s): *[OPTIONAL - PANORAMA, CTS, or Other Center-Specific Tracking #]*	

Interim milestones/deliverables, list below with projected dates. Text field only. [OPTIONAL]

Save edits but DOES NOT change status. No notifications are sent.

Copy product information and submission information from this form to a new ICCR and sends you an e-maill notification with link.

WITHDRAW an active ICCR and notify involved staff. You will be prompted to add a reason for withdrawal.

ICRR Tracking Dates (these will be filled automatically)

Tier 2 & Tier 3 Sub-consults	Submitted	10/26/2017	Reviewer Assigned	Completed

This ICCR Last Updated 10/26/2017 by Steven.Yang@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 10/06/2017 05:36:31 PM
To: CEDWARDS@AMNEAL.COM
CC: andafiling@fda.hhs.gov
BCC: rhonda.rowell@fda.hhs.gov; truong-vinh.phung@fda.hhs.gov; evelyn.molen@fda.hhs.gov
Subject: ANDA 210830 CORRESPONDENCE

ANDA 210830

Dear Candis Edwards:

Please see the attached correspondence.

Best Regards,

Division of Filing Review
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DO NOT RESPOND TO THIS EMAIL ADDRESS – IT IS A SEND-ONLY ACCOUNT. For questions, please contact the Regulatory Project Manager assigned to your application.

Please find the attached documents below:

A210830N000DFR_ACK.pdf
http://panorama.fda.gov/document/download?ID=59d7f61e00a018e7a9bf4a000fa88199

ANDA 210830

ACKNOWLEDGEMENT
ANDA RECEIPT

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards

Dear Candis Edwards:

This is in reference to your abbreviated new drug application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Food and Drug Administration (FDA) has made a threshold determination that this ANDA is substantially complete. This ANDA is received for review.

NAME OF DRUG: Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day

DATE OF APPLICATION: August 25, 2017

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: August 25, 2017

This application is subject to the provisions of the Generic Drug User Fee Amendments of 2012 (GDUFA). The GDUFA goal date for review of this application is June 24, 2018.

Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Dat Doan, Project Manager Team Leader, at Dat.Doan@FDA.HHS.GOV[1] or 240-402-8926. Sign up for Generic Drug e-mail updates.[2]

Sincerely,

{See appended electronic signature page}

Vinh Phung, Pharm.D.
Team Leader
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] A secure email address is recommended for applicants to utilize when communicating with the Agency. If you have not already established a secure email with FDA, you may send a request for a secure email address to

SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. Formal regulatory submissions must be submitted according to FDA regulations and current guidances.
[2] https://service.govdelivery.com/accounts/USFDA/subscriber/new?topic_id=USFDA_476

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Vinh Phung

Digitally signed by Vinh Phung
Date: 10/06/2017 01:05:24PM
GUID: 542052230001983c274c8695c2ed2db4

ANDA FILING CHECKLIST

(Post June 20, 2014)

ANDA: **210830**
APPLICANT: **Amneal Pharmaceuticals LLC**
RELATED APPLICATION(S): Related Applications

DRUG PRODUCT NAME: **Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day**

LETTER (356h) DATE: **August 25, 2017**
RECEIVED DATE: **August 25, 2017**
GDUFA GOAL DATE: June 24, 2018

Type II DMF #: (b) (4)

BASIS OF SUBMISSION:

(If reference standard is an ANDA, complete right column)

NDA/ANDA:	**21187**	**NDA:**	NDA
RLD/Ref.Std.:	**Nuvaring**	**RLD:**	RLD
FIRM:	**Organon USA Inc's**	**Firm:**	FIRM

Completion Signature	Recommendation:
10/3/2017 X [redacted] Filing Reviewer Signed by: Molen, Evelyn	☒ **FILE** ☐ **REFUSE to RECEIVE**

1. ☒ Confirm that appropriate **Application Specific Inspection Criteria** have been checked
2. ☒ QC Application Information Task Completed (Update Product Information, Patent and Policy in Project and Program Level) *(any corrections should be sent to CDERInformatics)*
3. ☒ GDUFA Obligations Met (Filing Fee, Type II DMF Fee, and Facility Fee)- (internal notation-if not met contact: cder-gdufa-applications@fda.hhs.gov)
4. ☒ DMF Complete Assessment
5. ☐ Confirm OSIS Consult (Issue) was created (for clinical endpoints)
6. ☐ Review Recommendation in Platform
7. ☐ Policy Alert List ANDA – check for updates prior to issuing IR/action letter
8. ☒ This is a combination product as defined under 21 CFR 3 (e.g., drug/device, drug/biologic)
9. ☒ All documents submitted in eCTD Format (see next page)

a. No security settings
b. Fonts embedded or standard fonts used

c. Font sizes ranging from 9 to 12 point (including scanned images)
d. Correct page orientation
e. Scanned documents are text searchable
f. Easily legible
g. Adequate bookmarks (if > 5 pages)
h. Descriptive bookmarks
i. Bookmarks set to inherit zoom
j. Hyperlinks (especially if there's a Table of Contents; > 5 pages)
k. Hyperlinks set to inherit zoom
l. Hyperlinks open in a new window
m. Navigation tab open to Bookmarks Panel and Page (unless there are no bookmarks)
n. Page Layout and Magnification set to Default
o. Descriptive Leaf Titles

DEVIATIONS FROM GUIDANCE RECOMMENDATIONS:

Note any deviations within the ANDA submission affecting BE/OPQ review:

ADDITIONAL COMMENTS:

Applicant contact information (U.S. Agent information)

Request for proprietary name

*Amneal is submitting a separate electronic amendment to this ANDA application (Refer to Sequence # 0002) labeled "Proprietary Name Request" at initial time of filing for requesting the Proprietary Name for Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day.

Per cover letter dated 08/25/2017(sequence 0002) , applicant is **requesting a proprietary name review.**
Please read below:

(b) (4)

[redacted]

Control correspondence

Control correspondence C13-0561:
Applicant makes mention of control # C13-0561 that was submitted to the Agency on 07/10/2013 to determine if their proposed formulation is q1/q2 to the rld formulation. The Agency responded on 05/21/2014 stating none of their formulation were qualitatively the same as the rld.

Applicant's inquiry:

2 page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Ethinyl Estradiol and Etonogestrel Vaginal Ring, 0.015 mg/0.12 mg

Amneal Pharmaceuticals
Attention: Candis Edwards
85 Adams Avenue
Hauppauge, NY 11788

MAY 21 2014

Reference Number: OGD # C13-0561

Dear Ms Candis Edwards:

This letter is in response to your correspondence dated on July10, 2013. You requested that the Office of Generic Drugs (OGD) to confirm the acceptability of formulations for filing an Abbreviated New Drug Application (ANDA) for your test product, Ethinyl Estradiol and Etonogestrel Vaginal Ring, 0.015 mg/0.12 mg. OGD provides the following comments:

1. The Division of Bioequivalence I (DBI) considers that the proposed formulation #1 you submitted for Ethinyl Estradiol and Etonogestrel Vaginal Ring, 0.015 mg/0.12 mg is **NOT quantitatively (Q2)** the same as NuvaRing® (ethinyl estradiol and etonogestrel) Vaginal Ring, 0.015 mg/0.12 mg, manufactured by Organon USA Inc., with respect to Magnesium Stearate.

2. The Division of Bioequivalence I (DBI) considers that the proposed formulation #2 you submitted for Ethinyl Estradiol and Etonogestrel Vaginal Ring, 0.015 mg/0.12 mg is **NOT Q2** the same as NuvaRing® (ethinyl estradiol and etonogestrel) Vaginal Ring, 0.015 mg/0.12 mg, manufactured by Organon USA Inc., with respect to Ethylene Vinyl Acetate Copolymer (28% vinyl acetate), Ethylene Vinyl Acetate Copolymer (9% vinyl acetate), and Magnesium Stearate.

3. The Division of Bioequivalence I (DBI) considers that the proposed formulation #3 you submitted for Ethinyl Estradiol and Etonogestrel Vaginal Ring, 0.015 mg/0.12 mg is **NOT Q2** the same as NuvaRing® (ethinyl estradiol and etonogestrel) Vaginal Ring, 0.015 mg/0.12 mg, manufactured by Organon USA Inc., with respect to Magnesium Stearate.

Control # 42491:

Applicant makes mention of control # C42491 that was submitted to the Agency on 11/10/2014 to determine if their proposed formulation is q1/q2 to the rld formulation. The Agency responded on 12/16/2014 stating **formulation 3** is q1/q2 the same as the RLD.

Applicant's inquiry

2 page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Correspondence Receipt Date: 10-Nov-14
Correspondence Response Date: 16-Dec-14
Correspondence Control: 42491

Title of Inquiry: Q1/Q2 formulation review for Ethinyl Estradiol/Etonogestrel Vaginal Ring

Amneal Pharmaceuticals, LLC
Attention: Candis Edwards
85 Adams Avenue, Hauppauge, NY, 11788
(b) (4)

Dear Candis Edwards,

This letter is in regard to your correspondence submitted to the Office of Generic Drugs (OGD), U.S. Food and Drug Administration; control number 42491.

OGD provides the following comments:

Based on the information provided, the following conclusions are made: Your proposed formulation 1 is Q1 the same, but not Q2 the same as the RLD product, Nuvaring® (Etonogestrel/Ethinyl Estradiol) Vaginal Ring, 0.015MG/24HR; 0.12MG/24HR by Organon USA Inc., with regard to magnesium stearate. Your proposed formulation 2 is Q1 the same, but not Q2 the same as the RLD product, Nuvaring® (Ethinyl Estradiol/Etonogestrel) Vaginal Ring, 0.015MG/24HR; 0.12MG/24HR by Organon USA Inc., with regard to magnesium stearate. Your proposed formulation 3 is Q1 and Q2 the same as the RLD product, Nuvaring® (Ethinyl Estradiol/Etonogestrel) Vaginal Ring, 0.015MG/24HR; 0.12MG/24HR by Organon USA Inc.

This response closes out the above controlled correspondence.

If you have additional inquiries regarding this issue, please submit a new request for information, and include both the control number for this submission, as well as a copy of this letter, in that new request.

Note: Review of ANDA shows applicant's proposed formulation is q1/q2 to the RLD formulation. See section 3.2.P.1

Control # 45810 :

Applicant makes reference to control # 45810 that was submitted to the Agency on 12/18/2014 in regards to the batch size.

The agency responded on 02/04/2015.

Applicant's inquiry

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Correspondence Receipt Date: 18 DEC 14
Correspondence Response Date: 04 FEB 15
Correspondence Control: 45810

Title of Inquiry: Etonogestrel and ethinyl estradiol vaginal ring, 0.120 mg and 0.015 mg per day- Batch Size Review

Amneal Pharmaceuticals
Attention: Meghana Patel
1 New England Ave
Piscataway, NEW JERSEY 08854
732-645-3030 Ext. 6036

Dear Meghana Patel,

This letter is in regard to your correspondence submitted to the Office of Generic Drugs (OGD), U.S. Food and Drug Administration; control number 45810.

The Agency provides the following comments:

Question:
You have proposed exhibit batch sizes for an etonogestrel/ethinyl estradiol vaginal ring product and seek for the Agency's concurrence that the batch sizes are adequate for an ANDA submission. You were concerned that the Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products – Questions and Answers does not explicitly address vaginal ring products in its batch size recommendations.

Response:
As a general principle, the primary batch (or ANDA submission batch) size(s) should be large enough to allow confidence that unit operations and environmental conditions actually simulate the full production environment. So 10% of the commercial batch size may be sufficient or bigger batch sizes may be needed following such a principle. Therefore, the Agency cannot determine the appropriateness of the proposed batch sizes based on the limited information provided. Please evaluate whether your proposed batch sizes are adequate to simulate the full production environment, and justify your conclusions in your ANDA submission

This response closes out the above controlled correspondence.

Page 1 of 2

Control number 50893:

Applicant makes mention of control number 50893 that was submitted to the Agency on March 10, 2015 to determine if their approach to utilize one lot of each of the ethylene vinylacetate copolymer to manufacture 3 ANDA exhibit batches is acceptable.

The Agency responded on 04/14/2015 stating they do not agree with Applicant's approach to utilize one lot of each of the ethylene vinylacetate copolymer.
Agency **recommended using 3 discrete lots of each of the 28% EVA and 9% EVA to manufacture the 3 exhibit batches.**

Controlled Correspondence for Request for Requirement on Multiple-lots of Polymer Excipients

On March 10, 2015, Amneal had submitted the controlled correspondence (CC # **50893**) requesting agency's assistance in determining if Amneal's approach to utilize one lot of each of these Ethylene Vinylacetate Copolymer, 28% Vinylacetate (EVA 28 %) and Ethylene Vinylacetate Copolymer, 9% vinylacetate (EVA 9%) to manufacture three (3) ANDA (Exhibit) batches is acceptable for this product. Please refer to **Module 3.2.R.1.P.1** for the copy of controlled correspondence (#**50893**), submitted to the Agency.

On April 14, 2015, Agency responded to Amneal's controlled correspondence (#**50893**), and did not agree to Amneal's proposal to utilize one lot of each of this Ethylene Vinylacetate Copolymer, 28% Vinylacetate (EVA 28 %) and Ethylene Vinylacetate Copolymer, 9% vinylacetate (EVA 9%) to manufacture three (3) ANDA (Exhibit) batches. Additionally, Agency recommended using three discrete lots of each of the 28% EVA and 9% EVA to manufacture three (3) ANDA (Exhibit) batches. Please refer to **Module 3.2.R.1.P.1** for OGD's response to controlled correspondence (#**50893**).

Applicant's inquiry

Food and Drug Administration
Silver Spring, MD 20993

Correspondence Receipt Date: 10 Mar 2015
Correspondence Response Date: 14 APR 15
Correspondence Control: 50893

Title of Inquiry: Controlled Correspondence - Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day

Amneal Pharmaceuticals
Attention: Pavan Kumar
85 Adams Avenue
Hauppauge, NEW YORK 11788
631-952-0214 Ext. 331

Dear Pavan Kumar,

This letter is in regard to your correspondence submitted to the Office of Generic Drugs (OGD), U.S. Food and Drug Administration; control number 50893.

The Agency provides the following comments:

Question 1

You would like to confirm with the agency if your approach to utilize one lot of each of these EVA polymers (28% VA & 9% VA) to manufacture three (3) ANDA (Exhibit) batches is acceptable for this product.

Response

No, Agency does not agree with your proposal to utilize one lot of each EVA polymers (28% VA & 9% VA) to manufacture three (3) ANDA (exhibit) batches. We recommend using three discrete lots of each of the EVA polymers (28% VA & 9% VA) to manufacture three (3) ANDA (Exhibit) batches.

This response closes out the above controlled correspondence.

If you have additional inquiries regarding this issue, please submit a new request for information, and include both the control number for this submission, as well as a copy of this letter, in that new request.

Sincerely,

Note: Primary Review of ANDA shows Applicant used 3 discrete lots of the Ethylene Vinylacetate Copolymer 28% vinylacetate and 3 discrete lots of Ethylene Vinylacetate Copolymer, 9% Vinylacetate to manufacture the 3 exhibit batches(they followed the Agency's recommendation). See below:

(b) (4)

Control 549549

On July 02, 2015, Agency responded to Amneal's controlled correspondence (#**549549**), and did not agree to Amneal's proposal to utilize one lot of each of this Ethylene Vinylacetate Copolymer, 28% Vinylacetate (EVA 28 %) and Ethylene Vinylacetate Copolymer, 9% vinylacetate (EVA 9%) to manufacture three (3) ANDA (Exhibit) batches. Agency recommended using three discrete lots of each of the 28% EVA and 9% EVA to manufacture three (3) ANDA (Exhibit) batches. Please refer to **Module 3.2.R.1.P.1-Appendix 4** for the OGD's response to controlled correspondence (#**549549**).

Agency's response:

Correspondence Receipt Date: 28 May 2015
Correspondence Response Date: 02 Jul 2015
Correspondence Control: 549549

Title of Inquiry: Response to Control Correspondence - Etonogestrel and Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day

Amneal Pharmaceuticals
Attention: Pavan Kumar
85 Adams Avenue
Hauppauge, NEW YORK 11788
631-952-0214 ext 331

Dear F Pavan Kumar,

This letter is in regard to your correspondence submitted to the Office of Generic Drugs (OGD), U.S. Food and Drug Administration; control number 549549.

The Agency provides the following comments:

Question 1
You would like to re-confirm with the agency if your approach to utilize one lot of each of these EVA polymers (28% VA & 9% VA) to manufacture three (3) ANDA (Exhibit) batches is acceptable for this product.

Response
We recommend using three discrete lots of each of the EVA polymers (28% VA & 9% VA) to manufacture three (3) ANDA (Exhibit) batches. The rational for this recommendation is to evaluate the effect of critical excipient lot-to-lot variability on the drug product's quality and performance.

This response closes out the above controlled correspondence.

If you have additional inquiries regarding this issue, please submit a new request for information, and include both the control number for this submission, as well as a copy of this letter, in that new request.

Sincerely,

Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Control

Applicant makes mention of the control correspondence that was submitted to the Agency to request

bioequivalence recommendation for generic version of NuvaRing.

Controlled Correspondence for Request for Bioequivalence Recommendation:

On March 7, 2013, Amneal had submitted controlled correspondence requesting Agency's recommendation for Request for Bioequivalence Recommendation for generic version of NuvaRing®. Please refer to **Appendix 1 of this Cover Letter** for the copy of controlled correspondence, submitted to the Agency. Please note that Amneal has not received the response from the Agency on this Controlled Correspondence. Instead, USFDA has updated the product specific bioequivalence recommendation on USFDA Site.

Control correspondence 14417557:

(b) (4)

The Agency responded on 06/05/2017 stating this was acceptable.

Amneal Pharmaceuticals LLC — Etonogestrel/ Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day

Original ANDA eCTD Submission — ANDA # 210830 (Sequence # 0001)

(b) (4)

Applicant's inquiry

2 page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Correspondence Receipt Date: 11-Apr-17
Correspondence Response Date: 5-Jun-17
Correspondence Control: 14417557

Title of Inquiry: Etonogestrel/ Ethinyl Estradiol Vaginal Rings RLD N021187 - Optional Applicator

Amneal Pharmaceuticals
Attention: Arlin Frias-Medina
50 Horseblock Road
Brookhaven, NY 11719
(b) (6)

Dear Ms. Frias-Medina,

This letter is in regard to your correspondence submitted to the Office of Generic Drugs (OGD), U.S. Food and Drug Administration; control number 14417557.

OGD provides the following comments:

The Division of Labeling Review (DLR) has reviewed your Controlled Correspondence asking if it would be acceptable to file the ANDA (b) (4) (b) (4)

DLR notes that Amneal has made a business decision (b) (4) (b) (4) as in the RLD, and therefore, (b) (4) (b) (4)

ANDAs must have the same labeling as their reference listed drugs (RLDs), except for permissible differences because the generic drug product and the RLD are produced or distributed by different manufacturers. 21 CFR 314.127(a)(7). Given that the RLD includes the applicator as an optional alternative to manually inserting the product, (b) (4) (b) (4) the RLD under 21 CFR 314.127(a)(7). (b) (4)

This response closes out the above controlled correspondence.

(b) (4)

GDUFA DMF COMPLETENESS ASSESSMENT CHECKLIST

For evaluation of initial COMPLETENESS for review of a Type II Drug Master File which has paid the required GDUFA DMF fee.

(b) (4)

[redacted]

Primary Reviewer: Jayani Perera Date: 06/09/2015	Review Recommendation for Initial Completeness Assessment ☑ COMPLETE ☐ INCOMPLETE

1. Has the GDUFA fee been paid? Enter date paid: 04/02/2015 Payment ID: 8009433

☑ Yes ☐ No

2. Is the DMF active?

☑ Yes ☐ No

If no, DMF is INCOMPLETE per policy. Issue Incomplete Letter to DMF holder.

3. Has the DMF been reviewed, after November 30, 2007, for chemistry, manufacturing and controls (CMC) by FDA in the context of a review of a prior application?

☐ Yes ☒ No

If "yes," the DMF is COMPLETE per policy. If "no," review DMF with checklist.

ADDITIONAL COMMENTS REGARDING THE DMF:

(b) (4)

[redacted]

ANDA #:	ANDA #:
Contact Person:	Contact Person:
Phone Number:	Phone Number:
Email:	Email:

RV1: Complete as per this review.

Reference ID: 3804465

(b) (4)

[redacted]

GDUFA DMF COMPLETENESS ASSESSMENT CHECKLIST

For evaluation of initial COMPLETENESS for review of a Type II Drug Master File which has paid the required GDUFA DMF fee.

(b) (4)

[redacted]

Primary Reviewer: Evelyn Hong Date: **11/2/2012**	Review Recommendation for Initial Completeness Assessment: ☒ **COMPLETE** ☐ **INCOMPLETE**

1. Has the GDUFA fee been paid? Enter date paid: 10/26/2012

☒ Yes ☐ No

2. Is the DMF active?

☒ Yes ☐ No

If no, DMF is INCOMPLETE per policy. Issue Incomplete Letter to DMF holder.

3. Has the DMF been reviewed, after November 30, 2007, for chemistry, manufacturing and controls (CMC) by FDA in the context of a review of a prior application?

☒ Yes ☐ No

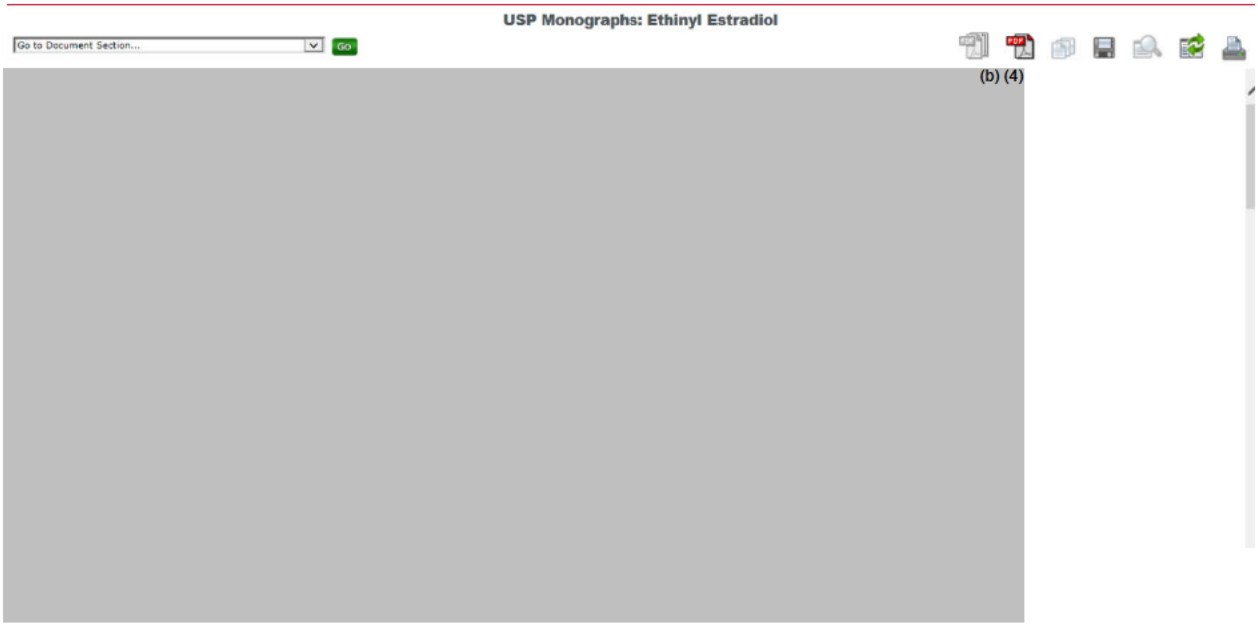
If "yes," the DMF is COMPLETE per policy.
If "no," review DMF with checklist.

ADDITIONAL COMMENTS REGARDING THE DMF:

CA during limbo period, no User Fee ID #.

Reference ID: 3212123

USP, if applicable
Drug substance is USP, but not drug product(for Ethinyl Estradiol).



Bioequivalence Guidance with date
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

Contains Nonbinding Recommendations

Draft Guidance on Ethinyl Estradiol; Etonogestrel

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 ingredient: Ethinyl Estradiol; Etonogestrel

Form/Route: Ring/Vaginal

Recommended studies: 1 study

Type of study: Bioequivalence (BE) Study with Pharmacokinetic (PK) Endpoints
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 0.015 mg/24 hr; 0.12 mg/24 hr
Subjects: Nonpregnant, nonsmoking healthy females aged 18 to 45 years of age and without any contraindication for contraceptive steroids.
Additional comments:

1. If the test product in not Q1/Q2 to the Reference Listed Drug (RLD) an additional clinical study or studies to identify any increased risk posed by the differing inactive ingredients or formulation differences between the test product and the RLD may be necessary.

2. Depending upon the specific clinical study or studies recommended, e.g., vaginal safety study, a test drug product that is not Q1/Q2 to the RLD may need to be submitted in a NDA to the Office of New Drugs.

Analytes to measure (in appropriate biological fluid): Ethinyl estradiol in plasma and etonogestrel in plasma

Bioequivalence based on (90% CI): Ethinyl estradiol and etonogestrel

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times: Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. 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. Specifications will be determined upon review of the application.

Recommended Apr 2013

Dissolution method

Dissolution Methods

About this Database | Back to Search Page

Search Results for: "ethinyl estradiol"

CSV | Excel

Filter:

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Desogestrel/Ethinyl Estradiol	Tablet			Refer to USP			11/04/2008
Drospirenone/Ethinyl Estradiol	Tablet			Refer to USP			07/28/2016
Drospirenone/Ethinyl Estradiol/Levomefolate Calcium	Tablet	II (Paddle)	50	Phosphate buffer pH 6.8, saline with 0.03 % ascorbic acid	900	5, 10, 15, 20 and 30	07/28/2016
Ethinyl Estradiol	Tablet			Refer to USP			09/22/2011
Ethinyl Estradiol/Ethynodiol Diacetate	Tablet	II (Paddle)	75	0.25% Sodium Lauryl Sulfate (SLS) in Water	600	10, 20, 30 and 45	07/14/2008
Ethinyl Estradiol/Etonogestrel	Vaginal Ring			Develop a method to characterize in vitro release			01/31/2013
Ethinyl Estradiol/Levonorgestrel	Tablet			Refer to USP			02/19/2008
Ethinyl Estradiol/Levonorgestrel (AB)	Tablet			Refer to USP			02/19/2008
Ethinyl Estradiol/Levonorgestrel (AB2)	Tablet			Refer to USP			11/04/2008
Ethinyl Estradiol/Norethindrone	Tablet			Refer to USP			07/15/2009

Showing 1 to 10 of 18 entries

Previous 1 2 Next

MODULE 1: ADMINISTRATIVE

1.1	1.1.2	**Rx** **Signed and Completed Application Form (356h)** (Rx / OTC Status) (original signature) **YES** **Electronic, Fillable Copy** (if a signed, scanned copy is provided) Refer to the links provided for the newly revised form 356h and updated instructions. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf Comments
		YES ***Form FDA 3794 (PDF)*** *GDUFA* Comments
1.2	*	**YES** **Cover Letter** **NO** **Is the drug product subject to REMS requirements?** http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm Comments
	1.2.1	**B** **Form FDA 3674 (PDF)** 42 U.S.C. 282(j)(5)(B) **YES** **Electronic, Fillable Copy** (if a signed, scanned copy is provided) Comments
*	*	**Select** **Table of Contents** (paper submission only)
1.3	1.3.1	**Contact/Sponsor/Applicant Information** **N/A** **1.3.1.2 U.S. Agent Appointment Letter** 21 CFR §314.50(a)(5) If the applicant identifies a U.S. Agent on the 356h, a U.S. Agent Appointment letter should be provided. Comments
	1.3.2	**YES** **Field Copy Certification** 21CFR §314.94(d)(5) (For paper applications only, Original Signature) Comments
	1.3.3	**Debarment Certification** from **Applicant** Generic Drug Enforcement Act (GDEA)/ Other: FD&C Act §306(k), §306(a) and (b) (21 U.S.C. 335a(k), 335(a) and (b)) (no qualifying statement) **YES** 1. Debarment Certification (original signature) **YES** 2. List of Convictions statement (original signature) Comments
	1.3.4	**Financial Certifications** 21 CFR §54 | 21 CFR §54.2(e) | 21 CFR §314.94(a)(13) **YES** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) **Select** Disclosure Statement (Form FDA 3455) Comments
	1.3.5	**Patent and exclusivity** **1.3.5.1 Patent Information** 21 CFR §314.94(a)(12) | FD&C Act 505(j)(2)(A)(vii) Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 21 CFR §314.94(a)(12)(i)(A)(1) through (4) or §314.94(a)(12)(iii) 1. Patent number(s) Paragraph: (Check all certifications that apply)

	Certification	Patents
☐	No Relevant Patents	
☐	MOU	
☐	PI	
☐	PII	
☒	PIII	**"581(04/08/2018)**
☐	PIV	

Statement of Notification (21 CFR §314.95 \| 505(j)(2)(B)) ☐

N/A 2. Pediatric Extension

a. Expiration of Pediatric Extension? Pediatric Extension Date

1.3.5.3 Exclusivity Claim

YES Exclusivity Statement: State marketing intentions?

N/A Pediatric Exclusivity (NPP, PED)

N/A PEPFAR NCE-1 Wavier of Exclusivity

☒ Receipt date of ANDA submission after the approval date per Orange Book

Comments

Copy and Paste Orange Book screen shots (ensure that all patents are addressed for each proposed strength)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Home | Modify Search

Search Results for Proprietary Name, Active Ingredient or Application Number: *etonogest*

3 records returned

☑ RX ☑ OTC ☑ DISCN

CSV | Excel

Display 50 records per page

Search for text in the table:

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	ETHINYL ESTRADIOL; ETONOGESTREL	NUVARING	N021187	RING	VAGINAL	0.015MG/24HR; 0.12MG/24HR		RLD	RS	ORGANON USA INC
RX	ETONOGESTREL	NEXPLANON	N021529	IMPLANT	IMPLANTATION	68MG/IMPLANT		RLD	RS	ORGANON USA INC
DISCN	ETONOGESTREL	IMPLANON	N021529	IMPLANT	IMPLANTATION	68MG/IMPLANT				ORGANON USA INC
Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder

Showing 1 to 3 of 3 entries

Previous 1 Next

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Product Details for NDA 021187

NUVARING (ETHINYL ESTRADIOL; ETONOGESTREL)
0.015MG/24HR;0.12MG/24HR

Marketing Status: Prescription

Active Ingredient: ETHINYL ESTRADIOL; ETONOGESTREL
Proprietary Name: NUVARING
Dosage Form; Route of Administration: RING; VAGINAL
Strength: 0.015MG/24HR;0.12MG/24HR
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N021187
Product Number: 001
Approval Date: Oct 3, 2001
Applicant Holder Full Name: ORGANON USA INC
Marketing Status: Prescription
Patent and Exclusivity Information

- Patent listings published prior to August 18, 2003, only identify method-of-use claims. The listed patents may include drug substance and/or drug product claims that are not indicated in the listing.
- As of December 5, 2016, an NDA holder submitting information on a patent that claims both the drug substance and the drug product (and is eligible for listing on either basis) is required only to specify that it claims either the drug substance or the drug product. Orange Book users should not rely on an Orange Book patent listing, regardless of when first published, to determine the range of patent claims that may be asserted by an NDA holder or patent owner.

Patent and Exclusivity for: N021187

Product 001
ETHINYL ESTRADIOL; ETONOGESTREL (NUVARING) RING 0.015MG/24HR;0.12MG/24HR

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
001	5989581	Apr 8, 2018				

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration

There is no unexpired exclusivity for this product in the Orange Book database.

View a list of all patent use codes
View a list of all exclusivity codes

Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.
Language Assistance Available: Español | 繁體中文 | Tiếng Việt | 한국어 | Tagalog | Русский | العربية | Kreyòl Ayisyen | Français | Polski | Português | Italiano | Deutsch | 日本語 | فارسی | English

PIII: “581(04/08/2018)

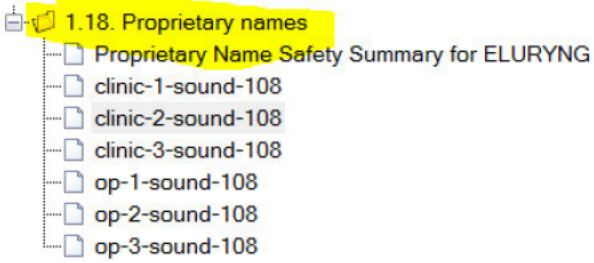
Exclusivity statement

Copy and Paste the RLD. If the RLD is an ANDA, then trace back to NDA on which the ANDA was based. A screenshot of section 1.12.11 Basis for Submission from the RLD ANDA should be provided.

1.4	1.4.2	**Statement of right of references** 21 CFR §314.50(g)(1) DMF Written Statement of authorization for reference (copy of LoA received from DMF holders) **YES** 1. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient 2. Type II DMF# (b) (4) **YES** 3. Type III DMF authorization letter(s) for container closure
		(b) (4) 28. Cross References (List related BLAs, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, M Type II DMF: (Drug Substance) (b) (4) Type III DMF: (Packaging Material) (b) (4) Type IV DMF: (Inactive Ingredient) Please refer to Module 1.4.2 of Sequence # 0001 for Letters of Authorization.
1.12	1.12.4	**YES** **Request for Comments and Advice** – Proprietary name requested If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing **YES** 1. Yes 2. No – contact the firm to submit the request as a separate electronic amendment
		Applicant is requesting a proprietary name review per sequence 0002(dated 08/25/2017)

(b) (4)

Information on proprietary name has been placed in section 1.18



1.12.11

Basis for Submission 21 CFR §314.94(a)(3)

Applicant identifies the following:

YES 1. NDA/ANDA # 021187

YES 2. Ref Listed Drug NuvaRing

YES 3. Firm Organon USA Inc

N/A **ANDA suitability petition required?** 21 CFR §10.20 | 21 CFR §10.30 | 21 CFR §314.93

If Yes, Petition number Petition Number

N/A Copy of FDA's correspondence approving the petition (21 CFR §314.94(a)(3)(iii))

N/A **ANDA Citizen's Petition required?** 21 CFR §10.25(a) | 21 CFR §10.30 | 21 CFR §314.122

If Yes, Petition number Petition Number

N/A Copy of petition

Comments

1.12.12

Comparison between Generic Drug and RLD 505(j)(2)(A) | 21 CFR §314.94(a)(4) to (6)

SAME AS RLD 1. Conditions of Use

SAME AS RLD 2. Active Ingredients

		SAME AS RLD 3. Inactive Ingredients (21 CFR §314.94(a)(9)(ii)) **SAME AS RLD** 4. Route of Administration **SAME AS RLD** 5. Dosage Form **SAME AS RLD** 6. Strength Comments
	1.12.14	**Environmental Analysis** from **Applicant** 21 CFR §25.31 and §25.15(d), if applicable **Select** Environmental Assessment (EA) (21 CFR §25.20) **Select** If applicable, Environmental Impact Statement (EIS) (21 CFR 25.22) **YES** Claim of Categorical Exclusion (21 CFR §25.30 or 21 CFR §25.31) **YES** **Statement:** "to the applicant's best of knowledge no extraordinary circumstances exist" Comments
	1.12.15	**Request for Waiver** 21 CFR 320.22 | 320.24(b)(6) **N/A** Request for Waiver of In-Vivo BA/BE Study(ies) Comments
1.14	**1.14.1**	**Draft Labeling** (Multi Copies N/A for E-Submissions) 21 CFR 314.94(a)(8)(ii) (if applicant provides "Final Labeling," the labeling information should be provided in Module 1.14.2.) **1.14.1.1 Draft carton and container labels** **YES** Electronic copy (each strength and container) -OR- **Select** 4 copies of draft for paper submission only (each strength and container) **1.14.1.2 Annotated draft labeling text** 21 CFR §314.94(a)(8)(iv) **YES** Side by side labeling comparison of container(s) and carton(s) for each strength with all differences visually highlighted and annotated **1.14.1.3 Draft labeling text (Does not apply to OTC)** **YES** 1 package insert (content of labeling) in PDF and WORD format, and SPL submitted electronically **1.14.1.4 Labeling Comprehension Studies** **N/A** Refer to Pharmacy Bulk Package Sterility Assurance Table (for PBP's only) See link below for table: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM352612.pdf **Supplied as:** **Etonogestrel/Ethinyl Estradiol Vaginal Ring- delivers 0.120 mg/0.015 mg per day(carton of 3 pouches, individual pouch).**
	1.14.3	**Listed Drug Labeling** **1.14.3.1 Annotated comparison with listed drug** 21 CFR §314.94(a)(8)(iv) **YES** Side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated a. Container Closure system (if different from what's approved for the RLD) **Select** i. Vial or ampule vs. prefilled syringe **Select** ii. Vial vs. ampule **Select** iii. Delivery device that's different from the RLD, e.g. inhalers **Select** iv. Bottles vs blisters ("calendarized" packaging) **Select** v. Unit of use (dispensable bottle) vs. multiple use bottles (pharmacy bottle) **Select** b. Drug product packaged in an IV bag **YES** **1.14.3.3 Labeling text for reference listed drug** 21 CFR §314.94(a)(8)(iv) RLD package insert, 1 RLD container label, and if applicable, 1 RLD outer container label Comments

Copy and Paste Side by Side Comparison of the "How Supplied" section from the Package Insert

RLD is individually packaged in a reclosable aluminium laminate sachet consisting of 3 layers from outside to inside (polyester, aluminium foil and low density polyethylene).

Proposed generic is individually packaged in a reclosable aluminium laminate pouch consisting of 4 layers from outside to inside(polyester, LDPE-EAA coex(low density polyethylene/ethylene acrylic acid copolymer coextrudate laminate, aluminiym foil and EAA-LLDPE coex(ethylene acrylic acid copolymer/low density polyethylene coextrudate laminate).

16 HOW SUPPLIED/STORAGE AND HANDLING Each NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) is individually packaged in a reclosable aluminum laminate sachet consisting of three layers, from outside to inside: polyester, aluminum foil, and low-density polyethylene. The ring should be replaced in this reclosable sachet after use and discarded in a waste receptacle out of the reach of children and pets. It should not be flushed down the toilet.	Trade name removed. RLD product speicifc information replaced with Amneal's.	(b) (4)

(b) (4)

Comparison between rld and proposed generic

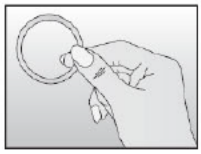
Pg.9: Per control correspondence # 14417557 in which the Agency responded on 6/5/17:information regarding the (b) (4)

Merck & Co., Inc., Package Insert Rev. 08-2017 NuvaRing (Etonogestrel/Ethinyl Estradiol) Vaginal Ring, 0.120 mg/0.015 mg per day	Comments	Amneal's Proposed Package Insert Rev. 08-2017-00 Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day
2 DOSAGE AND ADMINISTRATION **2.1 How to Use NuvaRing** To achieve maximum contraceptive effectiveness, NuvaRing must be used as directed *[see Dosing and Administration (2.2)]*. One NuvaRing is inserted in the vagina. **The ring is to remain in place continuously for three weeks.** It is removed for a one-week break, during which a withdrawal bleed usually occurs. A new ring is inserted one week after the last ring was removed. The user can choose the insertion position that is most comfortable to her, for example, standing with one leg up, squatting, or lying down. The ring is to be compressed and inserted into the vagina. An optional alternative is to insert the ring using the applicator for NuvaRing *[see Applicator for NuvaRing Instructions for Use]*. The exact position of NuvaRing inside the vagina is not critical for its function. The vaginal ring must be inserted on the appropriate day and left in place for three consecutive weeks. This means that the ring should be removed three weeks later on the same day of the week as it was inserted and at about the same time.	Trade name replaced with generic name. Trade name replaced with generic name. RLD product specific information removed, as per FDA Correspondence Response Letter dated 06/05/2017. Trade name replaced with generic name.	(b) (4)

Pg.79, 97, 98, 100, 101,

Merck & Co., Inc., Package Insert Rev. 08-2017 NuvaRing (Etonogestrel/Ethinyl Estradiol) Vaginal Ring, 0.120 mg/0.015 mg per day	Comments	Amneal's Proposed Package Insert Rev. 08-2017-00 Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day
This leaflet summarizes the most important information about NuvaRing. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NuvaRing that is written for health professionals. For more information on NuvaRing and the applicator for NuvaRing, go to www.nuvaring.com or call 1-877-NUVARING (1-877-688-2746). **What are the ingredients in NuvaRing?**	Trade name replaced with generic name. RLD company specific information replaced with Amneal's. Trade name replaced with generic name.	(b) (4)

Pg.88

Merck & Co., Inc., Package Insert Rev. 08-2017		Amneal's Proposed Package Insert Rev. 08-2017-00
NuvaRing (Etonogestrel/Ethinyl Estradiol) Vaginal Ring, 0.120 mg/0.015 mg per day	Comments	Etonogestrel/Ethinyl Estradiol Vaginal Ring, 0.120 mg/0.015 mg per day
• Hold NuvaRing between your thumb and index finger and press the sides of the ring together **(See Figures D and E)**.	Trade name replaced with generic name.	(b) (4)
  **Figure D** **Figure E**		
Step 4. Insert NuvaRing into your vagina.		
• Insert the folded NuvaRing into your vagina and gently push it further up into your vagina using your index finger **(See Figure F and G).** Alternatively, the applicator for NuvaRing (available separately) may be used to help you insert the ring *[see Applicator for NuvaRing Instructions for Use]*.	Trade name replaced with generic name. RLD product specific information removed, as per FDA Correspondence Response Letter dated 06/05/2017.	
• When you insert NuvaRing it may be in different positions in your vagina, but NuvaRing does not have to be in an exact position for it to work (See	Trade name replaced with generic name. Trade name replaced with generic name.	

How supplied: RLD

16 HOW SUPPLIED/STORAGE AND HANDLING

Each NuvaRing (etonogestrel/ethinyl estradiol vaginal ring) is individually packaged in a reclosable aluminum laminate sachet consisting of three layers, from outside to inside: polyester, aluminum foil, and low-density polyethylene. The ring should be replaced in this reclosable sachet after use and discarded in a waste receptacle out of the reach of children and pets. It should not be flushed down the toilet.

Box of 3 sachets NDC 0052-0273-03

16.1 Storage

Prior to dispensing to the user, store refrigerated 2-8°C (36-46°F). After dispensing to the user, NuvaRing can be stored for up to 4 months at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Avoid storing NuvaRing in direct sunlight or at temperatures above 30°C (86°F).

For the Dispenser: When NuvaRing is dispensed to the user, place an expiration date on the label. The date should not exceed either 4 months from the date of dispensing or the expiration date, whichever comes first.

MODULE 2: CTD SUMMARIES

2.3 QUALITY OVERALL SUMMARY (QOS)

2.3

YES **E-Submission: PDF**

YES **MS Word**

Additional information regarding QbR may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120971.htm

YES **Question based Review (QbR)**

(b) (4)

YES **2.3.S Drug Substance (Active Pharmaceutical Ingredient)**

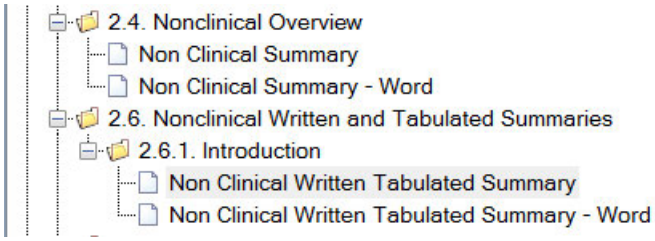
- 2.3.S.1 General Information
- 2.3.S.2 Manufacture
- 2.3.S.3 Characterization
- 2.3.S.4 Control of Drug Substance
- 2.3.S.5 Reference Standards
- 2.3.S.6 Container Closure System
- 2.3.S.7 Stability

Comments

YES **2.3.P Drug Product**

- 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 **Oral Solids**: Immediate Release or Modified Release (Matrix Technology or Compressed Film Coated Components) tablet scoring data per Draft *Guidance for Industry, Tablet Scoring: Nomenclature, Labeling and Data for Evaluation* (if applicable)
  - 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 and Materials
- 2.3.P.7 Container Closure System
- 2.3.P.8 Stability

Information on nonclinical written and tabulated summaries can be found in module 2.4 and 2.6



MODULE 3: QUALITY

3.2.S DRUG SUBSTANCE (Active Pharmaceutical Ingredient)

3.2.S.1

YES **General Information** (May not refer to DMF)

3.2.S.1.1 Nomenclature

3.2.S.1.2 Structure

3.2.S.1.3 General Properties

(b) (4)

3.2.S.2.1

YES **Manufacturer**

Drug Substance (Active Pharmaceutical Ingredient)

Must correlate to the establishment information submitted in annex to Form FDA 356h

1. Name and Full Address(es) of the Facility(ies)
2. Contact name, phone and fax numbers, email address
3. U.S. Agent's Name (if applicable)
4. Specify function or responsibility
5. Type II DMF number(s) for API(s)
6. CFN, FEI, or DUNS number (if available)
7. Additional sources of API and information (1 through 6, if applicable)

Comments

3.2.S.3

YES **Characterization**

All potential impurities should be listed in tabular format as given below:

IUPAC Chemical Name	Code #	Chemical Structure	Process/ Degradation Impurity	Source/ Mechanism

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf

Comments

3.2.S.4 Control of Drug Substance (Active Pharmaceutical Ingredient)

3.2.S.4.1

YES **Specification**

Testing specifications and data from drug substance manufacturer(s)

Comments

3.2.S.4.2

YES **Analytical Procedures**

Comments

3.2.S.4.3

YES **Validation of Analytical Procedures**

(API that is USP or reference made to DMF, **MUST** provide verification of USP or DMF procedures)

YES 1. Spectra and chromatograms for **reference standards** and **test samples** *(ref. std. can be located in 3.2.S.5)*

YES 2. Samples-Statement of Availability and Identification (21 CFR §314.50(e)(1))

a. Name of Drug Substance

(b) (4)

(b) (4)

[redacted]

3.2.S.4.4

Batch Analysis

YES 1. COAs specifications and test results from DS manufacturer(s)

YES 2. Drug Product manufacturer's Certificates of analysis

API lot numbers API lot numbers

Comments

3.2.S.4.5

Justification of Specifications

(Provide data in tabular format):

YES **Specified Identified Impurities:**

Chemical Name	Code #	MDD	QT (%)	QT (TDI)	Regulatory QT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory QT Threshold (%)

N/A **Specified Unidentified Impurities:**

Relative Retention Time	Code #	MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory IT Threshold (%)

YES **Unspecified Impurities:**

MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	**Not acceptable** if proposed AC (%) > Regulatory IT Threshold (%)

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf

(b) (4)

(b) (4)

For specified identified impurities: proposed AC is less than regulatory QT
Specified unidentified impurities: n/a
Unspecified impurities: proposed AC is the same as regulatory IT

3.2.S.5	YES **Reference Standards or Materials** (Do NOT refer to DMF) Comments
3.2.S.6	YES **Container Closure Systems** Comments
3.2.S.7	**Stability** YES 1. Retest date or expiration date of API(s) (b) (4)

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3.2.P DRUG PRODUCT

3.2.P.1		**Description and Composition of the Drug Product**
	YES	1. Unit composition with indication of the function of the inactive ingredient(s)
	YES	2. Inactive ingredients and amounts are appropriate per IIG (per/dose, unit, or MDD justification) (provide justification in a tabular format)
		3. Formulation
	N/A	Oral Tablet and Oral Capsules: % to mg/dosage unit
	N/A	Oral suspensions and oral solutions: % to mg/dose
	N/A	Parenterals: same unit of measure as RLD
	N/A	4. Elemental iron: provide daily elemental iron calculation pursuant to 21 CFR 73.1200 (calculation of elemental iron intake based on **maximum daily dose (MDD)** of the drug product is preferred if this section is applicable)
	N/A	5. Injections: If the reference listed drug is packaged with a drug specific diluent, then the diluent must be Q1/Q2 and must be provided in the package configuration
		Product is a vaginal ring.

(b) (4)

[redacted]

1 page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Copy and Paste Reviewer's IID Justification

Copy and Paste RLD Formulation, if applicable

Note: Applicant is carving out the applicator from their labeling per control # **14417557:**

RLD formulation from REV-QUALITY-03(General Review) dated 03/25/2002

CHEMIST REVIEW #1
Supplement

1. **ORGANIZATION:** HFD-580
2. **NDA Number:** 21-187
3. **SUPPLEMENT NO/DATES:** SCS-001
   Letter Date: 28-Nov-2001
   Stamp Date: 29-Nov-2001
   Due Date: 29-Mar-2002
4. **AMENDMENTS/REPORTS DATES:**
   Letter Date: 25-Jan-2002
   Stamp Date: 28-Jan-2002
5. **RECEIVED BY CHEMIST:** 30-Nov-2001

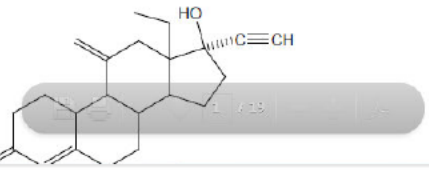
6. **SPONSOR NAME AND ADDRESS**
Organon Inc.
375 Mount Pleasant Avenue
West Orange, NJ 07052

7. **DRUG PRODUCT NAME:** NuvaRing

8. **NONPROPRIETARY NAME:** Etonogestrel/ethinyl estradiol vaginal ring

9. **DRUG SUBSTANCES NAMES/STRUCTURES**

Etonogestrel: 13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17-pregn-4-en-20-yn-3-one



B. DRUG PRODUCT

1/2 Components / Composition

The sponsor proposes to scale-up the manufacturing scale from a 32 kg premix amount to a commercial scale size of 940 kg premix. The composition of the NuvaRing is the same, as described in the Table below. See chemistry review #1 of the original NDA for additional information about the quality of the components and the tests/specifications used to characterize them.

Composition of NuvaRing

Ingredient	Formulation (mg/ring)	Amount per (b) (4)
(b) (4)		
• Ethylene vinylacetate copolymer, 28% m/m vinylacetate	(b) (4)	(b) (4)
• Etonogestrel	11.7	
• Ethinyl estradiol	2.7	
• Magnesium stearate	(b) (4)	
(b) (4)		
• Ethylene vinylacetate copolymer, 9% m/m vinylacetate		
	(b) (4)	

RLD FORMULATION FROM REV-QUALITY(General Review) supplement 19 dated 6/21/2012(same formulation as above).

FORMULATION

NuvaRing® is made of ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol. NuvaRing® is latex-free. NuvaRing® has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. Tables 1 show the components and composition for Nuvaring.

Table 1. Composition Statement for NuvaRing

Composition of NuvaRing		
Ingredient	Formulation (mg/ring)	Amount per (b) (4)
(b) (4) • Ethylene vinylacetate copolymer, 28% m/m vinylacetate • Etonogestrel • Ethinyl estradiol • Magnesium stearate	(b) (4) 11.7 2.7 (b) (4)	(b) (4)
(b) (4) • Ethylene vinylacetate copolymer, 9% m/m vinylacetate (b) (4)	(b) (4)	

Drug Release Rate Method and Acceptance Criteria

The drug release rate method and acceptance criteria[2,3,4] that are currently being used to release clinical batches and to test samples under long-term stability studies for Nuvaring are summarized below:

Q1/Q2 justification (Excel calculator), if applicable

(b) (4)

Active ingredient: Proposed generic contains the same active ingredient as the rld and in the same amount.

Inactive ingredients: Proposed generic contains the same inactive ingredients as the rld and in the same amount.

(b) (4)

Proposed generic formulation by Amneal is q1/q2 to the rld formulation.

3.2.P.2		YES **Pharmaceutical Development Report**
		Comments
3.2.P.3		**Manufacture**
	3.2.P.3.1	YES **Drug Product Manufacturer(s)** Must correlate to the establishment information submitted in annex to Form 356h for the finished dosage manufacturer and all outside contract testing laboratories. 1. Name and Full Address(es) of the Facility(ies) 2. Contact name, phone and fax numbers, email address 3. U.S. Agent's name (if applicable) 4. Specify function or responsibility 5. cGMP Certification from **Applicant** 6. CFN, FEI, or DUNS numbers (if available)
		Ensure function of (b) (4) **in form 356h matches 3.2.P.3.1**
	3.2.P.3.2	YES **Batch Formula** Largest Intended Commercial Batch Size
		Comments

3 page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

	3.2.P.3.3	**Description of Manufacturing Process and Process Controls** YES 1. Description of the Manufacturing Process and (for aseptic fill products) Facility YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3. Master Packaging Records for intended marketing container(s) 4. If sterile product **Select** YES 5. Reprocessing Statement (cite 21 CFR 211.115) from **Applicant**
		Comments
	3.2.P.3.4	YES **Controls of Critical Steps and Intermediates**
		Comments
	3.2.P.3.5	**Process Validation and/or Evaluation** 1. Terminally Sterilized Product N/A • Is this pharmacy bulk? (Go to 1.14.1.4) 2. Aseptically Filled Product N/A • Validation (bacterial retention studies) of sterilizing grade filter(s) N/A • Is this pharmacy bulk? (Go to 1.14.1.4)
		Comments

Copy and Paste Bacterial Retention Filter Validation table

3.2.P.4		**Controls of Excipients (Inactive Ingredients)**
	*	**Select** Source of Inactive Ingredients Identified
		Comments
	3.2.P.4.1	**Specifications** YES 1. Testing specifications (including identification and characterization)

		YES 2. Supplier's COA (specifications and test results)
		Comments
	3.2.P.4.2	YES **Analytical Procedures**
		Comments
	3.2.P.4.3	YES **Validation of Analytical Procedures**
		Comments
	3.2.P.4.4	**Justification of Specifications** (as applicable)
		YES 1. Applicant COA
		Comments
		Controls of Drug Product
	3.2.P.5.1	YES **Specification(s)**
		Comments
	3.2.P.5.2	YES **Analytical Procedures**
		Comments
3.2.P.5	3.2.P.5.3	YES **Validation of Analytical Procedures** (if using USP procedure, must provide verification of USP procedure) Samples - Statement of Availability and Identification (21 CFR §314.50(e)(1)) YES Finished Dosage Form
		(b) (4) 
	3.2.P.5.4	**Batch Analysis** YES Certificates of Analysis for Finished Dosage Form Lot numbers and strength of Drug Products List of lot numbers and strength of drug products
		Comments
	3.2.P.5.5	YES **Characterization of Impurities**

All potential degradation products should be listed in a tabular format as given below:

IUPAC Chemical Name	Code #	Chemical Structure	Degradation Product	Source/ Mechanism

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf

Comments

3.2.P.5.6

Justification of Specifications

(Provide data in tabular format):

YES **Specified Identified Degradation Products (Shelf Life):** **proposed AC is less than regulatory QT for ethinyl estradiol and etonogestrel.**

Chemical Name	Code #	MDD	QT (%)	QT (TDI)	Regulatory QT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory QT Threshold (%)

N/A

Specified Unidentified Degradation Products:

Relative Retention Time	Code #	MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory IT Threshold (%)

YES

Unspecified Degradation Products:

MDD	IT (%)	IT (TDI)	Regulatory IT Threshold (%)	Proposed AC (%)	**Not acceptable** if proposed AC (%) > Regulatory IT Threshold (%)

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf

Unspecified Degradation Products: **proposed AC is less than regulatory QT for ethinyl estradiol and etonogestrel.**

3.2.P.7

Container Closure System

YES 1. Summary of Container/Closure System (data should be provided for each resin)
YES 2. Components Specification and Test Data
YES 3. Packaging Configurations and Sizes
4. Container/Closure Testing (recommended additional testing for **all plastic**)
N/A a. Solid Orals: water permeation, light transmission
N/A b. Liquids: leachables, extractables, light transmission
N/A i. Injectables with rubber stoppers: extractables
YES 5. Source of supply and suppliers address

Product is a vaginal ring.
Applicant provided USP testing report(Roll stock and zipper), extraction and leachable study,
In addition, other studies was conducted: pg.12-15.

In addition to the above studies: Amneal has also performed the following Biocompatibility Studies for Amneal's Generic Drug Product, Etonogestrel/Ethinyl Estradiol Vaginal Ring, delivers 0.120 mg/0.015 mg per day. Please refer to **Tabel below** for more details.

(b) (4)

(b) (4)

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			Stability
3.2.P.8	3.2.P.8.1		**Stability Summary and Conclusion (Finished Dosage Form)**
		YES	1. Stability Protocol Submitted
			2. Expiration Dating Period for Marketed Packaging Expiration date
			3. Expiration Dating Period for Bulk packaging (if applicable) Expiration date
	3.2.P.8.2		**Post-Approval Stability Protocol and Stability Commitment**
		YES	1. Post-Approval Protocol and Commitment from **Applicant** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120979.pdf
			Comments
	3.2.P.8.3		**Stability Data** (Refer to the Final Guidance for Industry *ANDAs: Stability Testing Drug Substances and Products*, dated June 2013)
		YES	1. 3 batches?
		YES	a. Two API lots used? (provide the page number in the EBR that identifies the API lot in the **comment** box below)
		YES	b. All presentations of container closure systems amongst the 3 batches?
		Select	2. Additional stability data to support additional API sources (if applicable)
			3. Data- At minimum, 6 months **and** 3 time points
		YES	a. Accelerated
		N/A	1. Significant change occurred
		N/A	2. If yes, 6 months intermediate stability data
		YES	b. Long term storage (Room Temperature)
		YES	4. Batch numbers on stability records the same as the test batch
			5. Stability study initiated
		YES	a. Accelerated
		N/A	b. Intermediate (if applicable)
		YES	c. Long Term
			6. Date stability sample removed from stability chamber for each testing time point
		YES	a. Accelerated
		N/A	b. Intermediate (if applicable)
		YES	c. Long Term
		N/A	7. For liquid and semi-solid products, upright and inverted/horizontal storage orientation
			Note: Product is a vaginal ring* **

Copy and paste screenshot to show 2 APIs were used. (If the applicant provides a table to show that they have used at least 2 APIs for the 3 batches, this can be provided. If not, the API batch map tool should be used and a copy should be provided.)

Ethinyl Estradiol: 2 API lot from section 3.2.S.4.3

3.2.R REGIONAL INFORMATION

21 CFR §314.50(d)(1)(ii)(b)

REGIONAL INFORMATION (DRUG PRODUCT)

3.2.R.P Drug Product

3.2.R.1.P

1. Executed Batch Records

YES Copies of Executed Batch Records with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures)

(Refer to batch size and packaging information that meet the minimum threshold amount for specified dosage forms, i.e., solid oral dosage forms, oral powders/solutions/suspensions, parenteral drug products, ophthalmic/otic drug products, transdermal patches, topicals (i.e., creams, lotions, gels, inhalation solutions, nasal sprays, etc.). Refer to the Final Guidance for Industry *ANDAs: Stability Testing Drug Substances and Products, Questions and Answers*. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM366082.pdf)

a. Two (2) Pilot Scales and one (1) small scale
   OR
b. Three (3) Pilot scales

Comments

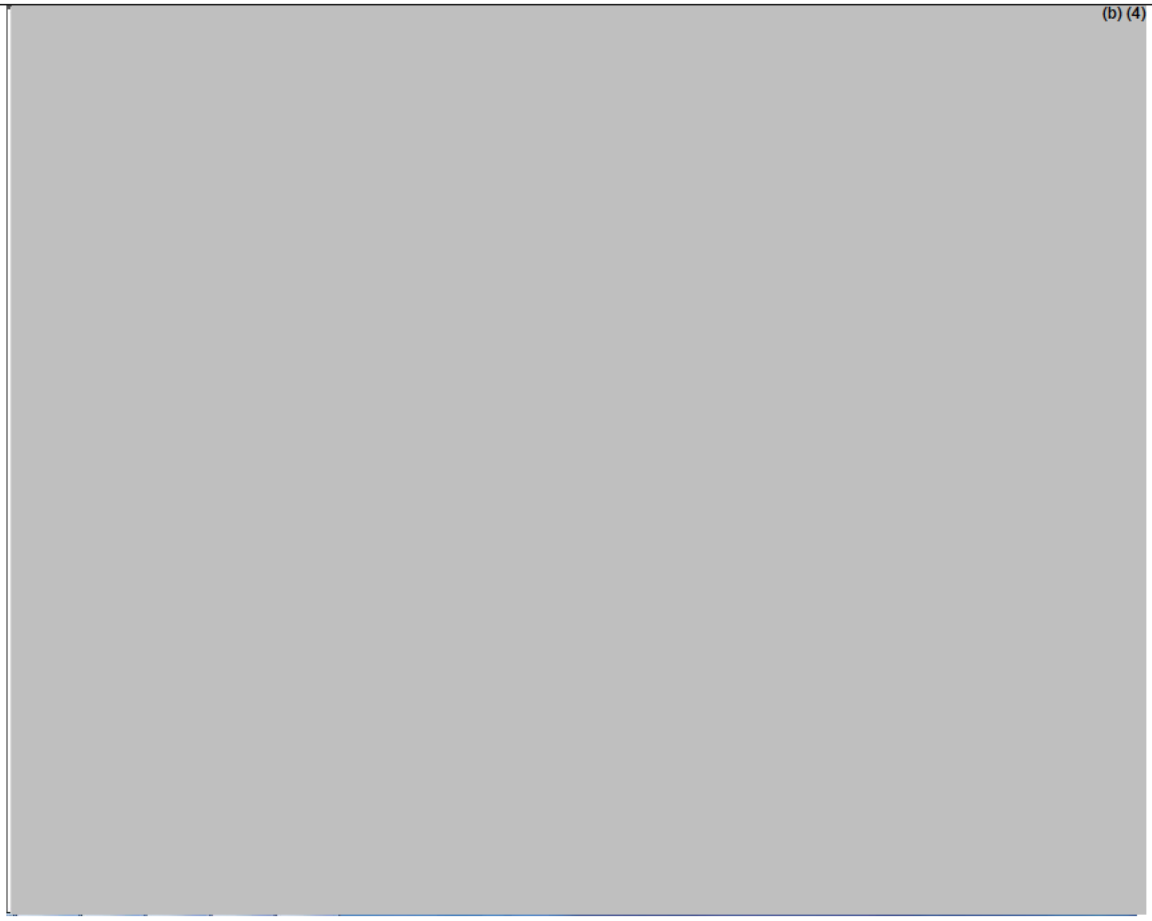
YES Batch Reconciliation and Label Reconciliation

a. Theoretical Yield Theoretical Yield
b. Actual Yield Actual Yield
c. Packaged Yield Packaged Yield

Pg.4 to 12

(b) (4)

[redacted]

		(b) (4) 
		Bulk Package Reconciliation for all bulk packaging considered a commercial container is recommended if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections: **Select** a. Bulk Package Label (1.14.1) **Select** b. Bulk Package Stability (3.2.P.8) **Select** 1. If bulk is to be shipped, provide accelerated stability data at 0,3,6 months **Select** 2. If bulk is only warehoused for repackaging, provide RT stability data at 0,3,6 months **Select** c. Bulk Package Container and Closure information (3.2.P.7)
		Comments
		YES 2. Information on Components *Name(s) and Address(es) of the Active Pharmaceutical Ingredient (API), inactive ingredient(s), and containers and closures in **tabular format**. Hyperlinks are sufficient.*
		Comments
	3.2.R.3.P	**YES Methods Validation Package** Methods Validation Package (3 copies for paper and **N/A for E-Submissions**) (Required for Non-USP drugs)
		Note: **Information on toxicology was provided in module 4**

MODULE 5: CLINICAL STUDY REPORTS

5.2		**YES** **Tabular Listing of Clinical Studies** http://www.fda.gov/ucm/groups/fdagov-public/%40fdagov-drugs-gen/documents/document/ucm073290.pdf Comments
5.3	5.3.1	**Bioavailability/Bioequivalence** 1. **Formulation data same?** **N/A** a. Comparison of all Strengths (proportionality of multiple strengths) **Select** b. Parenterals, Ophthalmics, Otics and Topicals (21 CFR 314.94 (a)(9)(iii)-(v)) 2. **Lot Numbers and strength of Products used in BE Study(ies)** **Test product (batch # PW-ST-16056A vs RLD(batch # MO36725).** 3. **In-Vivo PK study(ies)** 4. **In-Vivo BE study(ies) with Clinical Endpoint(s)** 5. **In-Vivo BE study(ies) with PD endpoints (pilot and pivotal vasoconstrictor)** 6. **In-Vitro Binding study(ies)** 7. **Nasal Products** 8. **BCS** (Continue with the appropriate study type box below) **Product is a vaginal ring**
Study Type		**MISCELLANEOUS** **Select** 1. Quantitative capsule rupture testing (liquid-filled capsule products) **Select** a. Study Report **Select** b. Release profile per the drug product specific guidance (demonstrates the time points at which 80% of the drug is released from the capsule) **Select** c. Apparatuses and the respective parameters as recommended per the drug product specific guidance **Select** 2. In-vitro release tests (specifically for Acyclovir ointment and some Ophthalmic Susp) **Select** a. 90% CI within 75-133% for 8th and 29th (first stage) **Select** b. 90% CI within 75-133% for 100th and 215th (second stage, if first stage failed) **Select** c. Study Report **Select** d. Chromatograms/Histograms **Select** e. Raw Data **Select** 3. In-vitro comparative physicochemical data **Select** 4. In-vitro microbial kill test

Effective as of April 25, 2017

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm
For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
Draft Guidance for Industry ANDA Submissions – Content and Format of Abbreviated New Drug Applications:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400630.pdf

BE Guidance recommends BE study with PK Endpoint.

YES **PK Studies**

2.7 Clinical Summary

2.7

Clinical Summary (Bioequivalence) Model BE Data Summary Tables
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf

YES **E-Submission: PDF**
YES **MS Word**

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

2.7.1.1 Background and Overview

YES Table 1. Submission Summary
YES Table 4. Bioanalytical Method Validation
YES Table 6. Formulation Data
YES Table 10. Study Information
- YES LTSS data location and hyperlink

YES Table 11. Product Information
N/A Table 17. Comparative Physiochemical Data of Ophthalmic Solution Products

Applicant conducted BE studies: study # BE/16/373 comparing their test product (batch # PW-ST-16056A vs RLD(batch # MO36725).

2.7.1.2 Summary of Results of Individual Studies

YES Table 5. Summary of In Vitro Dissolution
- YES Comparative In Vitro Dissolution Data (individual)
- N/A Multimedia Dissolution (if applicable)
- N/A Alcohol Dose Dumping Dissolution (if applicable)
- N/A ½ Tablet Dissolution (if applicable)
- YES COA for Test and Reference Products of the BE Strength (should include potency, assay, content uniformity, date of manufacture and lot number)

YES Table 9. Reanalysis of Study Samples
YES Table 12. Dropout Information
YES Table 13. Protocol Deviation
YES Table 14. Summary of Standard Curve and QC Data for BE Sample Analysis

Comments

2.7.1.3 Comparison and Analyses of Results Across Studies

YES Table 2. Summary of Bioavailability (BA) Studies
Table 3. Statistical Summary of the Comparative BA Data:
- YES 1. Unscaled Average – Table A
- Select 2. Reference-scaled Average BE Studies – Tables A **and** B BE Studies

N/A Table 16. Composition of Meal Used in Fed Bioequivalence Study

Comments

2.7.1.4 Appendix

YES Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples

Comments

2.7.4 Summary of Clinical Safety

2.7.4.1.3 Demographic and Other Characteristics of Study Population

YES Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study

Comments

2.7.4.2.1.1 Common Adverse Events

	YES Table 8. Incidence of Adverse Events in Individual Studies
	Comments

Dissolution Guidance from USP or FDA webpage
Copy and Paste Table 17, if applicable

BE Guidance recommends BE study with PK Endpoint.
It appears applicant conducted BE studies **with PK endpoint comparing their test product (batch # PW-ST-16056A vs RLD(batch # MO36725).**

Table 3:
90% CI is between 80-125%(for ethinyl estradiol and etonogestrel)

(b) (4)

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Desogestrel/Ethinyl Estradiol	Tablet			Refer to USP			11/04/2008
Drospirenone/Ethinyl Estradiol	Tablet			Refer to USP			07/28/2016
Drospirenone/Ethinyl Estradiol/Levomefolate Calcium	Tablet	II (Paddle)	50	Phosphate buffer pH 6.8, saline with 0.03 % ascorbic acid	900	5, 10, 15, 20 and 30	07/28/2016
Ethinyl Estradiol	Tablet			Refer to USP			09/22/2011
Ethinyl Estradiol/Ethynodiol Diacetate	Tablet	II (Paddle)	75	0.25% Sodium Lauryl Sulfate (SLS) in Water	600	10, 20, 30 and 45	07/14/2008
Ethinyl Estradiol/Etonogestrel	Vaginal Ring			Develop a method to characterize in vitro release			01/31/2013
Ethinyl Estradiol/Levonorgestrel	Tablet			Refer to USP			02/19/2008
Ethinyl Estradiol/Levonorgestrel (AB)	Tablet			Refer to USP			02/19/2008
Ethinyl Estradiol/Levonorgestrel (AB2)	Tablet			Refer to USP			11/04/2008
Ethinyl Estradiol/Norethindrone	Tablet (Chewable)	II (Paddle)	75	0.09% Sodium Lauryl Sulfate in 0.1 N HCl	500	10, 15, 20, 30 and 45	01/14/2008

Applicant conducted **dissolution studies** comparing their test product(batch # PW-ST-16056A) vs RLD(batch # M036725) in the following media: pg.13-25.

1. Acetate buffer(pH 4.2)

(b) (4)

They also conducted **dissolution studies** comparing their test product(batch # PW-ST-16052A, PW-ST-16055A) vs RLD(batch # M036725) in the following media:

Acetate buffer(pH 4.2)

Please see pg.13-25

5.3.1.2 and 5.3.1.4

YES	**BE Study(ies) per the Recommendations in the Individual Product BE Guidance**
Applicant conducted BE studies: study # BE/16/373	
	Clinical Report
YES	Fasting
Select	Fed
Select	Other
Comments	
	Individual and Mean Data
YES	Fasting
Select	Fed
Select	Other
Comments	
	Graphs, Linear, & Ln
YES	Fasting
Select	Fed
Select	Other
Comments	
	SAS Datasets
YES	Fasting
Select	Fed
Select	Other
Comments	
	Statistical Report (including SAS Output)
YES	Fasting
Select	Fed
Select	Other
Comments	
	Method Validation Report

YES	Fasting
Select	Fed
Select	Other
Comments	
	LTSS Data
YES	Fasting
Select	Fed
Select	Other
Comments	
	Study Bioanalytical or Analytical Report
YES	Fasting
Select	Fed
Select	Other
Comments	
	Chromatograms, 20%
YES	Fasting
Select	Fed
Select	Other
Comments	
	Raw Numerical Data
YES	Fasting
Select	Fed
Select	Other
Comments	

N/A **Clinical Endpoint(s)**

2.7 Clinical Summary

Clinical Endpoint Summary Tables
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM400548.pdf

Select E-Submission: PDF
Select MS Word

2.7	**Select**	Table 1.	Submission Summary
	Select	Table 2.	Summary of Clinical Endpoint Bioequivalence Studies
		Table 3.	Summary of Skin Irritation/sensitization/adhesion study(ies)
	Select		#1 Skin irritation/sensitization/adhesion study(ies)
	Select		#2 Adhesion data from PK study
	Select		#3 Adhesion Study
	Select	Table 4.	Study Center Information
	Select	Table 5.	Study Inclusion/Exclusion Criteria
	Select	Table 6.	Prohibited Concomitant Medication List
	Select	Table 7.	Product Information
	Select	Table 8.	Study Schedule (for example)
	Select	Table 9.	Study Populations (General)
	Select	Table 10.	Subject Populations (specific for Nasal Spray Products)
	Select	Table 11.	Subject Populations (specific for Skin irritation/sensitization/adhesion studies)
	Select	Table 12.	Summary of Protocol Deviations
	Select	Table 13.	Summary of Patient Discontinuation/Early Termination from the study
	Select	Table 14.	Demographic Characteristics at Baseline for the Safety Population, (M)ITT Population, and Per Protocol (PP) Population
	Select	Table 15.	Primary Endpoint Analysis result for a clinical endpoint bioequivalence study
		Table 16.	Non-inferiority Analysis result for a skin irritation/sensitization/adhesion study
	Select		A. Irritation and adhesion scores
	Select		B. Sensitization analysis
		Table 17.	Frequency Tables (specific for skin irritation/sensitization/adhesion studies)
	Select		A. Irritation Scores(combined irritation and other effect scores) for Per Protocol population
	Select		B. Adhesion scores for Per Protocol Population
	Select		C. Irritation scores (combined irritation and other effect scores) for Per Protocol Population during Challenge Period/Re-challenge Period
	Select	Table 18.	Patch removal or move date due to significant skin irritation (specific for skin irritation/sensitization/adhesion studies)
	Select	Table 19.	Proportion of subjects with adhesion score of 2 or more and 3 or more per treatment (specific for skin irritation/sensitization/adhesion studies)
	Select	Table 20.	Summary of Adverse Events
	Select	Table 21.	Formulation
	Select		a. For a waiver of bioequivalence study requirements or for a test product that requires qualitative and quantitative sameness to the RLD
	Select	Table 22	OGD Excipient/Impurity Toxicology Data Table

Comments

5.3.1.2 and 5.3.1.4

Select	All Studies **(#Study Number)**
Comments	
Select	Study Report
Comments	
Select	Protocol (original and amendments)
Comments	
Select	Placebo Formulation
Comments	
Select	Date of Data Unblinded
Comments	
Select	Date of Data Locked
Comments	
Select	Clinical Site(s) and Study Investigator(s) list (if no U.S. sites used, ask for justification whether the sponsor's study population is representative of the disease state in the U.S. population)
Select	Study Investigator(s) CVs
Comments	
Select	Statistical Analysis Plan
Comments	
	IRB Approval
Select	Approval letters for protocol
Select	Approved consent/assent forms (IRB letter/memo with stamped date of approval and/or IRB letterhead with date showing approval)
Comments	
Select	Consent Forms
Comments	
Select	All Case Report Forms (at minimum, should have for all patients who were dropped from the analysis population, demonstrated protocol deviations, demonstrated protocol violations, experienced serious adverse events, and a random sample of 10% of all enrolled patients)
Comments	
Select	Data definition file (describes the variables in each data set)
Comments	
Select	Provides all SAS programs and list of all programs (Used to generate the analysis datasets and efficacy results)
Comments	
	SAS Dataset (XPT)
Select	Randomization Schedule
Select	Demographic Data
Select	Reasons for discontinuation from the study if discontinued
Select	Adverse Events
Select	Concomitant Medications
Select	Individual subject's scores/data per visit
Select	Protocol Deviations
Select	Raw Data (NO-LOCF)
Select	LOCF Data
Select	Summary Data (usually it is the ADSL.xpt dataset with efficacy measures or the combined dataset of ADSL.xpt and efficacy dataset)
Select	Identification of the mITT population
Select	Reasons for Exclusion
	If transdermal,
Select	Identification of Adhesion population
Select	Reason for Exclusion

Select	Identification of the PP population
Select	Reasons for Exclusion
	If transdermal,
Select	Identification of Irritation population
Select	Reasons for Exclusion
	When applicable,
Select	Identification of Sensitization population
Select	Reasons for Exclusion
Comments	

Clinical Endpoint Study (#Study Number)

	Primary Endpoint
Select	Defined (within BE limits)
Select	Superiority over placebo
Comments	
	Secondary Endpoint
Select	Defined (within BE limits)
Select	Superiority over placebo
Comments	

Non-Transdermal Study (#Study Number)

	SAS Dataset (XPT)
Select	Subject's measurements/visits/dates
Select	Data to evaluate treatment compliance
Comments	

Irritation/Sensitization Study (#Study Number)

Select	Applicant indicates no worse skin irritation and sensitization properties of the test product compared to that of the RLD (within non-inferiority limit, T-[1.25X R] < 0)
Comments	
	SAS Dataset (XPT)
Select	Subject's irritation measurements (i.e., time points, scores, visit #, dates)
Select	Subject's sensitization measurements (if applicable) (i.e., time points, scores, visit #, dates)
Comments	

Adhesion Study (#Study Number)

Select	Applicant indicates no worse skin adhesion properties of the test product compared to that of the RLD (within non-inferiority limit, T-[1.25X R] < 0)
Comments	
	SAS Dataset (XPT)
Select	Adhesion measurements per patch (i.e., time points, scores, visit #, dates)
Comments	

Copy and Paste Table for 5.2

N/A **PD endpoints**

(e.g., topical corticosteroid pilot and pivotal vasoconstrictor assay studies, MDI, Acarbose, Orlistat, Megletol)

2.7 Clinical Summary

2.7

Topical Dermatologic Corticosteroids in Vivo Bioequivalence Study Summary Tables and SAS Transport Formatted Tables for Dataset Submission

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM379421.pdf

Select E-Submission: PDF
Select MS Word

I. Pre-Study Method Validation

- **Select** Table 1. Chroma Meter Validation
- **Select** Table 2. Skin Site Validation
- **Select** Table 3. Intra-Subject and Inter-Site Validation
- **Select** Table 4. Operator Validation

Comments

II. Summary of Studies

- **Select** Table 5. Summary of the Pilot Dose Duration-Response Study
- **Select** Table 6. Summary of the Pivotal Bioequivalence Study
- **Select** Table 7. Summary of the Pivotal Bioequivalence Study (PD Parameters, AUC, etc.)
- **Select** Table 8. Listing of Relevant SOP for Pre-Study Method Validation and Pilot Dose Duration-Response and Pivotal BE Studies

Comments

III. Pilot Dose Duration-Response Study

- **Select** Table 9. Study Information
- **Select** Table 10. Product Information
- **Select** Table 11. Demographics Profile of Subjects Completing the Pilot Dose Duration-Response Study Product Information
- **Select** Table 12. Dropout Information, Pilot Dose Duration-Response Study
- **Select** Table 13. Study Adverse Events, Pilot Dose Duration-Response Study
- **Select** Table 14. Protocol Deviations, Pilot Dose Duration-Response Study
- **Select** Table 15. ED_{50} and Emax Values Calculated

Comments

IV. Pivotal Bioequivalence Study

- **Select** Table 16. Study Information
- **Select** Table 17. Product Information
- **Select** Table 18. Demographics Profile of Subjects Completing the Pivotal BE Study
- **Select** Table 19. Dropout Information, Pivotal BE Study
- **Select** Table 20. Study Adverse Events, Pivotal BE Study
- **Select** Table 21. Protocol Deviations, Pivotal BE Study
- **Select** Table 22. Area Under the Effect Curve and 90% Confidence Intervals
- **Select** Table 22. Test Product Formulation

Comments

5.3.1.2 and 5.3.1.4

Select	Pilot and Pivotal Studies Submitted
Comments	

Select	**BE Study(ies) per the Recommendations in the Individual Product BE Guidance**
Comments	
	Clinical Report
Select	Pilot Dose Duration-Response Study
Select	Pivotal Bioequivalence Study
Select	Other
Comments	
	Individual and Mean Data
Select	Pilot Dose Duration-Response Study
Select	Pivotal Bioequivalence Study
Select	Other
Comments	
	Graphs, Linear
Select	Pilot Dose Duration-Response Study
Select	Pivotal Bioequivalence Study
Select	Other
Comments	
	Statistical Report (including SAS Output)
Select	Pilot Dose Duration-Response Study
Select	Pivotal Bioequivalence Study
Select	Other
Comments	
	Method Validation Report
Select	Pilot Dose Duration-Response Study
Select	Pivotal Bioequivalence Study
Select	Other
Comments	
	SAS Dataset (XPT) ***(For Pilot Dose Duration-Response Study and Pivotal BE Study)***
	Pilot Dose Duration-Response Study Data
Select	Table 24. Chroma Meter Raw Data
Select	Table 25. Baseline-Adjusted, Chroma Meter Raw Data
Select	Table 26. Baseline-Adjusted, Untreated Site-Corrected Chroma Meter Raw Data
Select	Table 27. Area Under Effect Curve Data, All Subjects at Each Dose Duration
	Pivotal Bioequivalence Study Data Submission Format
Select	Table 28. Chroma Meter Raw Data
Select	Table 29. Baseline-Adjusted, Chroma Meter Raw Data
Select	Table 30. Baseline-Adjusted, Untreated Site-Corrected, Chroma Meter Raw Data
Select	Table 31. Area Under Effect Curve Data, All Subjects at Each Dose Duration
Comments	

N/A **In-Vitro Binding study(ies)**

2.7 Clinical Summary

2.7

In Vitro Binding Bioequivalence Study Summary Tables and SAS Transport Formatted Tables for Dataset Submission

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM364105.pdf

Select E-Submission: PDF
Select MS Word

I. For Calcium Acetate Drug Products

Select	Table I.1.	Submission Summary
Select	Table I.2.	Summary of In vitro binding study
Select	Table I.3.	Pre-Study Analytical Method Validation
Select	Table I.4.	Summary of In Vitro Dissolution Studies, if applicable
Select	Table I.5.	Formulation Data
Select	Table I.6.	Reanalysis of Study Samples
Select	Table I.7.	Study Information
Select	Table I.8.	Product Information
	Table I.9.	Assay Validation
Select		1. Phosphate
Select		2. Calcium
Select	Table I.10.	SOP's Dealing with Analytical Repeats
Select	Table I.11.	Calcium Amount in the Supernatant after Binding
Select	Table I.12.	Phosphate Amount in the Supernatant after Binding

Comments

II. For a polymer drug that binds to either phosphate (e.g., Sevelamer) or bile acid (e.g., Colesevelam, Cholestyramine, or Colestipol)

Select	Table II.1.	Submission Summary
	Table II.2.	In-Vitro Equilibrium Binding Sutdies
Select		1. Summary of k_1 and k_2- without Acid Pre-Treatment (if applicable)
Select		2. Summary of k_1 and k_2- with Acid Pre-Treatment (if applicable)
Select	Table II.3.	Pre Study Analytical Method Validation
Select	Table II.4.	Summary of In Vitro Disintegration Studies
Select	Table II.5.	Formulation Data
Select	Table II.6.	Reanalysis of Study Samples
Select	Table II.7.	Study Information (separate table for each in-vitro binding BE study)
Select	Table II.8.	Product Information (separate table for each in-vitro binding BE study)
	Table II.9.	Study Design
Select		1. In-Vitro Kinetic Binding Study
Select		2. In-Vitro Equilibrium Binding Study
Select	Table II.10.	Assay Validation
Select	Table II.11.	SOP's Dealing with Analytical Repeats
	Table II.12.	In-Vitro Kinetic Binding Study Results
Select		1. T/R Ratios of Mean Phosphate/Bile Acid Binding
Select		2. With Acid Pre-Treatment (if applicable)
	Table II.13.	In-Vitro Equilibrium Binding Study Results
Select		1. Summary of Mean Binding Data (Without Acid-Pretreatment)
Select		1. Summary of Mean Binding Data (With Acid-Pre-Treatment) (if applicable)

Comments

III. For Lanthanum Drug Products

Select	Table III.1.	Submission Summary
	Table III.2.	Summary of Mean Binding Data
Select		pH 1.2
Select		pH 3
Select		pH 5
Select	Table III.3.	Summary of Dissolution Bioequivalence Data
Select	Table III.4.	Pre-Study Analytical Method Validation (for In-Vitro Binding Study Sample Analysis
Select	Table III.5.	Pre-Study Analytical Method Validation (for In-Vitro Dissolution Bioequivalence Study Sample Analysis)
Select	Table III.6.	Summary of In-Vitro Dissolution Studies (for both In-Vitro Dissolution Bioequivalence Studies and Regulatory Dissolution Studies)
Select	Table III.7.	Formulation Data
Select	Table III.8.	Reanalysis of Study Samples
Select	Table III.9.	Study Information
Select	Table III.10.	Product Information
	Table III.11.	Study Design
Select		1. In-Vitro Kinetic Binding Study
Select		2. In-Vitro Equilibrium Binding Study
Select	Table III.12.	Assay Validation
Select	Table III.13.	SOP's Dealing with Analytical Repeats
	Table III.14.	In-Vitro Kinetic Binding Study Results
Select		1. pH 1.2 T/R Ratios of Mean Phosphate Binding
Select		2. pH 3.0 T/R Ratios of Mean Phosphate Binding
Select		3. pH 5.0 T/R Ratios of Mean Phosphate Binding
Select	Table III.15.	In-Vitro Equilibrium Binding Study Results – Summary of Mean Binding Data
Select	Table 16.	Composition of Meal Used in Fed Bioequivalence Study

Comments

5.3.1.2 and 5.3.1.4

Select	Study(ies) meets BE criteria (90% CI of 80-120, k2)
Comments	

Select	**BE Study(ies) per the Recommendations in the Individual Product BE Guidance**
Comments	
	Clinical Report
Select	Equilibrium Binding
Select	Kinetic Binding
Select	Other
Comments	
	Individual and Mean Data
Select	Equilibrium Binding
Select	Kinetic Binding
Select	Other
Comments	
	Graphs, Linear, & Ln
Select	Equilibrium Binding
Select	Kinetic Binding
Select	Other
Comments	
	SAS Datasets
Select	Equilibrium Binding
Select	Kinetic Binding
Select	Other
Comments	
	SAS Datasets (XPT) (*For all but binding studies of Calcium Acetate Drug Products)*
Select	Equilibrium Binding (separate dataset for each binding condition per product-specific guidance)
Select	Kinetic Binding (separate dataset for **each** binding condition per product-specific guidance (e.g., different
Select	concentrations of adsorbate, different pH, with/without acid treatment))
	Other
Comments	
	Statistical Report (including SAS Output)
Select	Equilibrium Binding
Select	Kinetic Binding
Select	Other
Comments	
	Method Validation Report
Select	Equilibrium Binding
Select	Kinetic Binding
Select	Other
Comments	

N/A **Nasal Products**

2.7 Clinical Summary

2.7

Bioequivalence Summary Tables for Aqueous Nasal Spray Products
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf

Select E-Submission: PDF
Select MS Word

Select	Table 1.	Formulation Table
Select	Table 2.	Batch Information
Select	Table 3.	Device Comparability
Select	Table 4.	Actuation Methods
	Table 5.	**Single Actuation Content through Container Life Test**
Select	Table 5.1.	Study Information
Select	Table 5.2.	Analytical Method Validation for HPLC
	Table 5.3.	Calibration of Manual and/or Automated Spray Pump Actuator (For Single Actuation Content and Priming/Repriming studies)
Select	Table 5.3.1.	Precision
Select	Table 5.3.2.	Ruggedness (By Date)
Select	Table 5.3.3.	Ruggedness (By Analyst)
Select	Table 5.3.4.	Ruggedness (Unit to Unit if more than one unit is used)
Select	Table 5.4.	Results Summary
	Table 6.	**Priming and Re-priming Test**
Select	Table 6.1.	Study Information
Select	Table 6.2.	Analytical Method Validation for HPLC (if different from Table 5.2)
Select	Table 6.3.	Results Summary – Priming and Re-priming
	Table 7.	**Droplet Size Distribution by Laser Diffraction Test**
Select	Table 7.1.	Study Information
	Table 7.2.	Validation Summary Tables for Droplet Size Distribution by Laser Diffraction
Select	Table 7.2.1.	Precision
Select	Table 7.2.2.	Intermediate Precision (By Date)
Select	Table 7.2.3.	Intermediate Precision (By Analyst)
Select	Table 7.3.	Results Summary – Droplet Size Distribution by Laser Diffraction
	Table 8.	**Drug in Small Particles/Droplets by Cascade Impactor (CI) Test**
Select	Table 8.1.	Study Information
Select	Table 8.2.	Validation Summary Table for Particle Size Distribution by Cascade Impactor – Analytical Method Validation for HPLC
	Table 8.3.	Validation Tables for Cascade Impaction
Select	Table 8.3.1.	Precision
Select	Table 8.3.2.	Intermediate Precision (By Date)
Select	Table 8.3.3.	Intermediate Precision (By Analyst)
Select	Table 8.4.	Results Summary – Drug in Small Particles/Cascade Impactor (CI)
	Table 9.	**Spray Pattern Test**
Select	Table 9.1.	Study Information
	Table 9.2.	Validation Summary Tables for Spray Pattern
Select	Table 9.2.1.	Precision
Select	Table 9.2.2.	Intermediate Precision (By Date)
Select	Table 9.2.3.	Intermediate Precision (By Analyst)

	Select	Table 9.3.	Results Summary – Spray Pattern
		Table 10.	**Plume Geometry Test**
	Select	Table 10.1	Study Information
		Table 10.2.	Validation Summary Tables for Plume Geometry
	Select	Table 10.2.1.	Precision
	Select	Table 10.2.2.	Intermediate Precision (By Date)
	Select	Table 10.2.3.	Intermediate Precision (By Analyst)
	Select	Table 10.2.4.	Robustness for varies parameters (the selection of parameters is optional)
	Select	Table 10.3.	Results – Plume Geometry
	Comments		

2.7

Clinical Endpoint Summary Tables
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM400548.pdf

Select E-Submission: PDF
Select MS Word

Select	Table 1.	Submission Summary
Select	Table 2.	Summary of Clinical Endpoint Bioequivalence Studies
	Table 3.	Summary of Skin Irritation/sensitization/adhesion study(ies)
Select		#1 Skin irritation/sensitization/adhesion study(ies)
Select		#2 Adhesion data from PK study
Select		#3 Adhesion Study
Select	Table 4.	Study Center Information
Select	Table 5.	Study Inclusion/Exclusion Criteria
Select	Table 6.	Prohibited Concomitant Medication List
Select	Table 7.	Product Information
Select	Table 8.	Study Schedule (for example)
Select	Table 9.	Study Populations (General)
Select	Table 10.	Subject Populations (specific for Nasal Spray Products)
Select	Table 11.	Subject Populations (specific for Skin irritation/sensitization/adhesion studies)
Select	Table 12.	Summary of Protocol Deviations
Select	Table 13.	Summary of Patient Discontinuation/Early Termination from the study
Select	Table 14.	Demographic Characteristics at Baseline for the Safety Population, (M)ITT Population, and Per Protocol (PP) Population
Select	Table 15.	Primary Endpoint Analysis result for a clinical endpoint bioequivalence study
	Table 16.	Non-inferiority Analysis result for a skin irritation/sensitization/adhesion study
Select		A. Irritation and adhesion scores
Select		B. Sensitization analysis
	Table 17.	Frequency Tables (specific for skin irritation/sensitization/adhesion studies)
Select		A. Irritation Scores(combined irritation and other effect scores) for Per Protocol population
Select		B. Adhesion scores for Per Protocol Population
Select		C. Irritation scores (combined irritation and other effect scores) for Per Protocol Population during Challenge Period/Re-challenge Period
Select	Table 18.	Patch removal or move date due to significant skin irritation (specific for skin irritation/sensitization/adhesion studies)
Select	Table 19.	Proportion of subjects with adhesion score of 2 or more and 3 or more per treatment (specific for skin irritation/sensitization/adhesion studies)
Select	Table 20.	Summary of Adverse Events
Select	Table 21.	Formulation
Select		a. For a waiver of bioequivalence study requirements or for a test product that requires qualitative and quantitative sameness to the RLD
Select	Table 22	OGD Excipient/Impurity Toxicology Data Table

Comments

5.3.1.2 and 5.3.1.4 BE In-Vitro

NASALLY ADMINISTERED DRUG PRODUCT (in-vitro)

(1) Lack of SAS data in CORRECT format is considered INADEQUATE for filing (See SAS Data Tables for Aqueous Nasal Spray Product In Vitro Bioequivalence Study Data Submission, page 22 to 28 of the document referred in the previous slide); (2) Failure of in vivo BE study with PK endpoint to meet acceptable CI limits is also considered INADEQUATE for filing; (3) In vitro BE test outcomes for nasal products are NOT considered at filing stage (i.e., review issues)

Recommended In-Vitro Studies

Select	Single Actuation Content through Container Life
Select	Droplet Size Distribution by Laser Diffraction
Select	Drug in Small Particles/Droplets, or by Particle/Droplet Size Distribution by Cascade Impactor
Select	Spray Pattern
Select	Plume Geometry
Select	Priming and Repriming

Comments

Sufficient Number of Test and Reference Lots (3)

Select	Single Actuation Content through Container Life
Select	Droplet Size Distribution by Laser Diffraction
Select	Drug in Small Particles/Droplets, or by Particle/Droplet Size Distribution by Cascade Impactor
Select	Spray Pattern
Select	Plume Geometry
Select	Priming and Repriming

Comments

Select **For suspensions, 3 distinct API lots and pump container closure lots**

Comments

Study Report

Select	Single Actuation Content through Container Life
Select	Droplet Size Distribution by Laser Diffraction
Select	Drug in Small Particles/Droplets, or by Particle/Droplet Size Distribution by Cascade Impactor
Select	Spray Pattern
Select	Plume Geometry
Select	Priming and Repriming

Comments

Select **Statistical Report (Including SAS Output)**

Comments

SAS OUTPUT (XPT)

Select	Single Actuation Content Through Container Life
Select	Priming and Repriming
Select	Droplet Size Distribution by Laser Diffraction
Select	Plume Geometry
Select	Spray Pattern
Select	Drug in Small Particles/Droplets by Cascade Impactor

Comments

5.3.1.2 and 5.3.1.4 BE In-Vivo

Select	**BE Study(ies) per the Recommendations in the Individual Product BE Guidance**
Comments	
	BE Study Protocol
Select	Fasting
Select	Other
Comments	
	Clinical Report
Select	Fasting
Select	Other
Comments	
	Individual and Mean Data
Select	Fasting
Select	Other
Comments	
	Graphs, Linear, & Ln
Select	Fasting
Select	Other
Comments	
	SAS Datasets (XPT)
Select	Fasting
Select	Other
Comments	
	Statistical Report (including SAS Output)
Select	Fasting
Select	Other
Comments	
	Method Validation Report
Select	Fasting
Select	Other
Comments	
	Study Bioanalytical or Analytical Report
Select	Fasting
Select	Other
Comments	
	Chromatograms, 20%
Select	Fasting
Select	Other
Comments	
	Raw Numerical Data
Select	Fasting
Select	Other
Comments	

5.3.1.2 and 5.3.1.4 DCR/Stat In-Vitro

Select	**All Studies (#Study Number)**
Comments	
Select	**Study Report**
Comments	
Select	**Protocol** (original and amendments)
Comments	
Select	**Placebo Formulation**
Comments	
Select	**Date of Data Unblinded**
Comments	
Select	**Date of Data Locked**
Comments	
Select	**Clinical Site(s) and Study Investigator(s) list** (if no U.S. sites used, ask for justification whether the sponsor's study population is representative of the disease state in the U.S. population)
Select	**Study Investigator(s) CVs**
Comments	
Select	**Statistical Analysis Plan**
Comments	
	IRB Approval
Select	**Approval letters for protocol**
Select	**Approved consent/assent forms** (IRB letter/memo with stamped date of approval and/or IRB letterhead with date showing approval)
Comments	
Select	**Consent Forms**
Comments	
Select	**All Case Report Forms** (at minimum, should have for all patients who were dropped from the analysis population, demonstrated protocol deviations, demonstrated protocol violations, experienced serious adverse events, and a random sample of 10% of all enrolled patients)
Comments	
Select	**Data definition file** (describes the variables in each data set)
Comments	
	Primary Endpoint
Select	Defined (within BE limits)
Select	Superiority over placebo
Comments	
	Secondary Endpoint
Select	Defined (within BE limits)
Select	Superiority over placebo
Comments	
Select	**Provides all SAS programs and list of all programs** (Used to generate the analysis datasets and efficacy results)
Comments	
	SAS Dataset (XPT)
Select	Randomization Schedule
Select	Demographic Data
Select	Reasons for discontinuation from the study if discontinued
Select	Adverse Events
Select	Concomitant Medications
Select	Individual subject's scores/data per visit
Select	Protocol Deviations
Select	Raw Data (NO-LOCF)

Select	LOCF Data
Select	Identification of the mITT population
Select	Reasons for Exclusion
Select	Identification of the PP population
Select	Reasons for Exclusion
Select	Summary Data (usually it is the ADSL.xpt dataset with efficacy measures or the combined dataset of ADSL.xpt and efficacy dataset)
Comments	

N/A **BCS**

2.7 Clinical Summary

2.7	**BCS-Based Study Summary and Formulation Tables** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM396512.pdf **Select E-Submission: PDF** **Select MS Word** **Select** Table 1. Method Validation for Solubility Testing **Select** Table 2. Solubility Data for (Drug Name) in Different Buffered Media at (pH range) **Select** Table 3. Pivotal Permeability Study Information **Select** Table 4. Materials and Methods for Validation of Permeability Study **Select** Table 5. Permeability Validation Protocol for Each Model Compound **Select** Table 6. Standard Operating Procedures **Select** Table 7. Permeability Study Validation Summary Data: Permeability Coefficients, %Recovery for Model Compounds **Select** Table 8. Analytical Method Validation (For Pivotal Permeability Study) **Select** Table 9. Pivotal Permeability Study Design **Select** Table 10. Pivotal Permeability Study: Apical-to-Basolateral (A-to-B) Permeability of Test Compound and Internal Standards **Select** Table 11. Pivotal Permeability Study: Basolateral-to-Apical (B-to-A) Permeability of Test Compound and Internal Standards **Select** Table 12. Pivotal Permeability Study: Ratio of B-to-A Papp vs. A-to-B Papp **Select** Table 13. Gastrointestinal Tract Instability **Select** Table 14. Dissolution Method Information **Select** Table 15. Information of Analytical Method Used to Analyze Dissolution Samples **Select** Table 16. Dissolution Data **Select** ▪ Comparative In Vitro Dissolution Data (12-unit individual data test vs. RLD) **Select** Table 17. Formulation Data Comments

BCS Data

Select	**In-Vitro Solubility Testing** A drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of multiple media with pH ranging from 1 to 6.8.
Select	▪ Solubility Testing in multiple pH ranging from 1 to 6.8
Select	▪ Information on chemical structure, molecular weight, nature of drug substance and dissociation constant (pKa) (multiple locations, i.e., 2.3, 3.2.S)
Select	▪ Test results summarized in tabular format
Comments	
Select	**In-Vitro Permeability Testing** A drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 85% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.
Select	▪ Drug substance is 85% or more permeable (performed study or per RLD labeling)
Comments	
Select	**In-Vitro Dissolution Testing** A drug substance is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 500 mL or less in each of the following media: 0.1 N HCl or pH 1.2 buffer, pH 4.5 buffer, and pH 6.8 buffer.
Select	▪ 85% dissolved within 30 minutes in all three media
Select	▪ Mean percent dissolved, range of dissolution and coefficient of variation in tabular format
Select	▪ Half-tablet dissolution for all strengths per drug product specific guidance including OGD/USP media
Comments	

Karl
Hill

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