

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**021529Orig1s007**

*Trade Name:* NEXPLANON

*Generic or Proper Name:* etonogestrel implant

*Sponsor:* Organon USA Inc.

*Approval Date:* May 13, 2011

*Indication:* Nexplanon is a progestin indicated for use by women to prevent pregnancy.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 021529Orig1s007

### CONTENTS

#### Reviews / Information Included in this NDA Review.

<b>Approval Letter</b>	<b>X</b>
<b>Other Action Letters</b>	
<b>Labeling</b>	<b>X</b>
<b>REMS</b>	
<b>Summary Review</b>	<b>X</b>
<b>Officer/Employee List</b>	
<b>Office Director Memo</b>	
<b>Cross Discipline Team Leader Review</b>	
<b>Medical Review(s)</b>	<b>X</b>
<b>Chemistry Review(s)</b>	<b>X</b>
<b>Environmental Assessment</b>	
<b>Pharmacology Review(s)</b>	<b>X</b>
<b>Statistical Review(s)</b>	<b>X</b>
<b>Microbiology / Virology Review(s)</b>	<b>X</b>
<b>Clinical Pharmacology/Biopharmaceutics Review(s)</b>	<b>X</b>
<b>Other Reviews</b>	<b>X</b>
<b>Risk Assessment and Risk Mitigation Review(s)</b>	
<b>Proprietary Name Review(s)</b>	<b>X</b>
<b>Administrative/Correspondence Document(s)</b>	

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*APPLICATION NUMBER:*

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**APPROVAL LETTER**



NDA 021529/S-007

**SUPPLEMENT APPROVAL**

Organon USA Inc.  
Attention: Tonja Wynn Hampton, M.D.  
Director, Worldwide Regulatory Affairs  
56 Livingston Avenue  
Roseland, NJ 07068

Dear Dr. Hampton:

Please refer to your Supplemental New Drug Application (sNDA) dated July 29, 2009, received July 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NEXPLANON (etonogestrel implant) 68 mg.

We acknowledge receipt of your amendments dated September 18, 24, October 9, December 22, 2009, and January 13, 29, February 3, March 1, 29, 30, April 8, 28, May 7, June 7, July 6, 9, 27, August 2, 9 (2), 11 (2), 17, 18, 20 (2), 27, October 6, November 10, 30 (2), 2010, and January 18, 19, March 16, 17, April 5, 25, May 2, 3, 4, 9, and 10, 2011.

This supplemental new drug application provides for a new radiopaque version of the etonogestrel implant for the indication of “use by women to prevent pregnancy” and a new device for insertion of the implant.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and the patient package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the carton and container labels submitted on March 17, 2011, as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 021529/S-007.**” Approval of this submission by FDA is not required before the labeling is used.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

### **POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitment:

**1754-1:** A descriptive observational cohort study of insertion, localization, and removal related events associated with Nexplanon use. The proposed protocol should include details on the study design, methodology, and analysis plan. This study will need to include a minimum of 5,000 patients who received Nexplanon. Interim status reports to include numbers of subjects

enrolled and information on insertion and removal events will be submitted to this NDA at least annually.

The timetable you submitted on May 4, 2011, states that you will conduct this study according to the following schedule:

<b>Final Protocol Submission:</b>	July 2011
<b>Study Completion:</b>	October 2017
<b>Final Report Submission:</b>	March 2018

Submit the clinical protocol to your IND 042877 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate: (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must 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/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

## **LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program  
Office of Special Health Issues  
Food and Drug Administration  
10903 New Hampshire Ave  
Building 32, Mail Stop 5353  
Silver Spring, MD 20993

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We also request that you submit additional quarterly safety reports based on all postmarketing reports of implant insertion-, localization-, and removal-related events for Nexplanon. We request that you submit these reports for a period of at least 3 years following launch of Nexplanon in the US.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Scott Monroe, M.D.  
Director  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURES:  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SCOTT E MONROE  
05/13/2011

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**021529Orig1s007**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEXPLANON safely and effectively. See full prescribing information for NEXPLANON.

### NEXPLANON® (etonogestrel implant) Radiopaque Subdermal Use Only

Initial U.S. Approval: 2001

#### INDICATIONS AND USAGE

NEXPLANON is a progestin indicated for use by women to prevent pregnancy. (1)

#### DOSAGE AND ADMINISTRATION

Insert one NEXPLANON subdermally just under the skin at the inner side of the non-dominant upper arm. NEXPLANON must be removed no later than by the end of the third year. (2)

#### DOSAGE FORMS AND STRENGTHS

NEXPLANON consists of a single, radiopaque, rod-shaped implant, containing 68 mg etonogestrel, pre-loaded in the needle of a disposable applicator. (3)

#### CONTRAINDICATIONS

- Known or suspected pregnancy. (4)
- Current or past history of thrombosis or thromboembolic disorders. (4, 5.4)
- Liver tumors, benign or malignant, or active liver disease. (4, 5.7)
- Undiagnosed abnormal genital bleeding. (4, 5.2)
- Known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive cancer, now or in the past. (4, 5.6)
- Allergic reaction to any of the components of NEXPLANON. (4, 6)

#### WARNINGS AND PRECAUTIONS

- Insertion and removal complications: Pain, paresthesias, bleeding, hematoma, scarring or infection may occur. (5.1)

- Menstrual bleeding pattern: Counsel women regarding changes in bleeding frequency, intensity, or duration. (5.2)
- Ectopic pregnancies: Be alert to the possibility of an ectopic pregnancy in women using NEXPLANON who become pregnant or complain of lower abdominal pain. (5.3)
- Thrombotic and other vascular events: The NEXPLANON implant should be removed in the event of a thrombosis. (5.4)
- Liver disease: Remove the NEXPLANON implant if jaundice occurs. (5.7)
- Elevated blood pressure: The NEXPLANON implant should be removed if blood pressure rises significantly and becomes uncontrolled. (5.9)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women using NEXPLANON. (5.11)

#### ADVERSE REACTIONS

Most common ( $\geq 10\%$ ) adverse reactions reported in clinical trials were change in menstrual bleeding pattern, headache, vaginitis, weight increase, acne, breast pain, abdominal pain, and pharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Schering Corporation, a subsidiary of Merck & Co., Inc., at 1-800-526-4099 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes, such as CYP3A4, may decrease the effectiveness of progestin hormonal contraceptives or increase breakthrough bleeding. (7.1)

#### USE IN SPECIFIC POPULATIONS

- Pregnant women: NEXPLANON should be removed if maintaining a pregnancy. (8.1)
- Overweight women: NEXPLANON may become less effective in overweight women over time, especially in the presence of other factors that decrease etonogestrel concentrations, such as concomitant use of hepatic enzyme inducers. (8.8)

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

Revised: 05/2011

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Initiating Contraception with NEXPLANON
- 2.2 Insertion of NEXPLANON
- 2.3 Removal of NEXPLANON
- 2.4 Replacing NEXPLANON

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Complications of Insertion and Removal
- 5.2 Changes in Menstrual Bleeding Patterns
- 5.3 Ectopic Pregnancies
- 5.4 Thrombotic and Other Vascular Events
- 5.5 Ovarian Cysts
- 5.6 Carcinoma of the Breast and Reproductive Organs
- 5.7 Liver Disease
- 5.8 Weight Gain
- 5.9 Elevated Blood Pressure
- 5.10 Gallbladder Disease
- 5.11 Carbohydrate and Lipid Metabolic Effects
- 5.12 Depressed Mood
- 5.13 Return to Ovulation
- 5.14 Fluid Retention
- 5.15 Contact Lenses
- 5.16 Monitoring
- 5.17 Drug-Laboratory Test Interactions

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

### 7 DRUG INTERACTIONS

- 7.1 Changes in Contraceptive Effectiveness Associated with Coadministration of Other Products
- 7.2 Increase in Plasma Concentrations of Etonogestrel Associated with Coadministered Drugs
- 7.3 Changes in Plasma Concentrations of Coadministered Drugs

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment
- 8.8 Overweight Women

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

- 14.1 Pregnancy
- 14.2 Return to Ovulation
- 14.3 Implant Insertion and Removal Characteristics

### 16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Storage and Handling

### 17 PATIENT COUNSELING INFORMATION

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

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

NEXPLANON® is indicated for use by women to prevent pregnancy.

### 2 DOSAGE AND ADMINISTRATION

The efficacy of NEXPLANON does not depend on daily, weekly or monthly administration.

All healthcare providers should receive instruction and training prior to performing insertion and/or removal of NEXPLANON.

A single NEXPLANON implant is inserted subdermally in the upper arm. To reduce the risk of neural or vascular injury, the implant should be inserted at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. The implant should be inserted subdermally just under the skin to avoid the large blood vessels and nerves that lie deeper in the subcutaneous tissues in the sulcus between the triceps and biceps muscles. NEXPLANON must be inserted by the expiration date stated on the packaging. NEXPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method. The implant must be removed by the end of the third year and may be replaced by a new implant at the time of removal, if continued contraceptive protection is desired.

#### 2.1 Initiating Contraception with NEXPLANON

**IMPORTANT: Rule out pregnancy before inserting the implant.**

Timing of insertion depends on the woman's recent contraceptive history, as follows:

- No preceding hormonal contraceptive use in the past month

NEXPLANON should be inserted between Day 1 (first day of menstrual bleeding) and Day 5 of the menstrual cycle, even if the woman is still bleeding.

If inserted as recommended, back-up contraception is not necessary. If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

- Switching contraceptive method to NEXPLANON

Combination hormonal contraceptives:

NEXPLANON should preferably be inserted on the day after the last active tablet of the previous combined oral contraceptive or on the day of removal of the vaginal ring or transdermal patch. At the latest, NEXPLANON should be inserted on the day following the usual tablet-free, ring-free, patch-free or placebo tablet interval of the previous combined hormonal contraceptive.

If inserted as recommended, back-up contraception is not necessary. If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

Progestin-only contraceptives:

There are several types of progestin-only methods. NEXPLANON should be inserted as follows:

- **Injectable Contraceptives:** Insert NEXPLANON on the day the next injection is due.
- **Minipill:** A woman may switch to NEXPLANON on any day of the month. NEXPLANON should be inserted within 24 hours after taking the last tablet.
- **Contraceptive implant or intrauterine system (IUS):** Insert NEXPLANON on the same day the previous contraceptive implant or IUS is removed.

If inserted as recommended, back-up contraception is not necessary. If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

- Following abortion or miscarriage

- **First Trimester:** NEXPLANON should be inserted within 5 days following a first trimester abortion or miscarriage.
- **Second Trimester:** Insert NEXPLANON between 21 to 28 days following second trimester abortion or miscarriage.

If inserted as recommended, back-up contraception is not necessary. If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

- Postpartum
  - Not Breastfeeding: NEXPLANON should be inserted between 21 to 28 days postpartum. If inserted as recommended, back-up contraception is not necessary. If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.
  - Breastfeeding: NEXPLANON should be inserted after the fourth postpartum week [see *Use in Specific Populations (8.3)*]. The woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

## 2.2 Insertion of NEXPLANON

The basis for successful use and subsequent removal of NEXPLANON is a correct and carefully performed subdermal insertion of the single, rod-shaped implant in accordance with the instructions. Both the healthcare provider and the woman should be able to feel the implant under the skin after placement.

**All healthcare providers performing insertions and/or removals of NEXPLANON should receive instructions and training prior to inserting or removing the implant. Information concerning the insertion and removal of NEXPLANON will be sent upon request free of charge [1-877-467-5266].**

### Preparation

Prior to inserting NEXPLANON carefully read the instructions for insertion as well as the full prescribing information.

Before insertion of NEXPLANON, the healthcare provider should confirm that:

- The woman is not pregnant nor has any other contraindication for the use of NEXPLANON [see *Contraindications (4)*].
- The woman has had a medical history and physical examination, including a gynecologic examination, performed.
- The woman understands the benefits and risks of NEXPLANON.
- The woman has received a copy of the Patient Labeling included in packaging.
- The woman has reviewed and completed a consent form to be maintained with the woman's chart.
- The woman does not have allergies to the antiseptic and anesthetic to be used during insertion.

Insert NEXPLANON under aseptic conditions.

The following equipment is needed for the implant insertion:

- An examination table for the woman to lie on
- Sterile surgical drapes, sterile gloves, antiseptic solution, sterile marker (optional)
- Local anesthetic, needles, and syringe
- Sterile gauze, adhesive bandage, pressure bandage

### Insertion Procedure

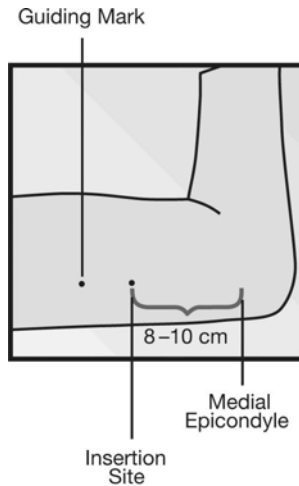
Step 1. Have the woman lie on her back on the examination table with her non-dominant arm flexed at the elbow and externally rotated so that her wrist is parallel to her ear or her hand is positioned next to her head (Figure 1).



Figure 1

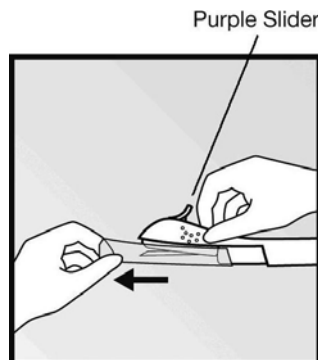
Step 2. Identify the insertion site, which is at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus (Figure 2). **The implant should be inserted subdermally just under the skin to avoid the large blood vessels and nerves that lie deeper in the subcutaneous tissue in the sulcus between the triceps and biceps muscles** [see *Warnings and Precautions (5.1)*].

Step 3. Make two marks with a sterile marker: first, mark the spot where the etonogestrel implant will be inserted, and second, mark a spot a few centimeters proximal to the first mark (Figure 2). This second mark will later serve as a direction guide during insertion.



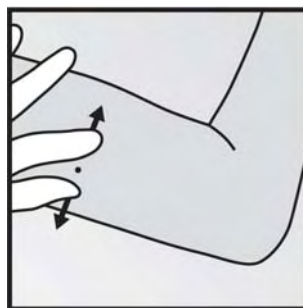
**Figure 2**

- Step 4. Clean the insertion site with an antiseptic solution.
- Step 5. Anesthetize the insertion area (for example, with anesthetic spray or by injecting 2 mL of 1% lidocaine just under the skin along the planned insertion tunnel).
- Step 6. Remove the sterile preloaded disposable NEXPLANON applicator carrying the implant from its blister. The applicator should not be used if sterility is in question.
- Step 7. Hold the applicator just above the needle at the textured surface area. Remove the transparent protection cap by sliding it horizontally in the direction of the arrow away from the needle (Figure 3). If the cap does not come off easily, the applicator should not be used. You can see the white colored implant by looking into the tip of the needle. **Do not touch the purple slider until you have fully inserted the needle subdermally, as it will retract the needle and prematurely release the implant from the applicator.**



**Figure 3**

- Step 8. With your free hand, stretch the skin around the insertion site with thumb and index finger (Figure 4).



**Figure 4**

- Step 9. Puncture the skin with the tip of the needle angled about 30° (Figure 5).

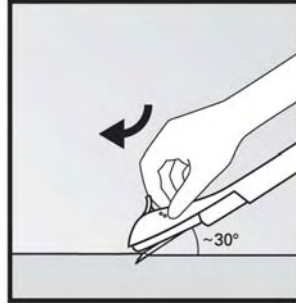


Figure 5

Step 10. Lower the applicator to a horizontal position. While lifting the skin with the tip of the needle (Figure 6), slide the needle to its full length. You may feel slight resistance but do not exert excessive force. **If the needle is not inserted to its full length, the implant will not be inserted properly.**

**You can best see movement of the needle if you are seated and are looking at the applicator from the side and NOT from above. In this position, you can clearly see the insertion site and the movement of the needle just under the skin.**

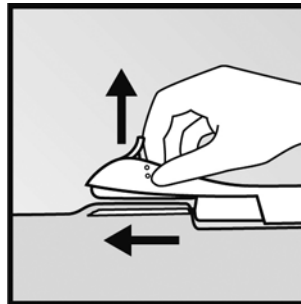


Figure 6

Step 11. Keep the applicator in the same position with the needle inserted to its full length. If needed, you may use your free hand to keep the applicator in the same position during the following procedure. Unlock the purple slider by pushing it slightly down. Move the slider fully back until it stops (Figure 7). The implant is now in its final subdermal position, and the needle is locked inside the body of the applicator. The applicator can now be removed. **If the applicator is not kept in the same position during this procedure or if the purple slider is not completely moved to the back, the implant will not be inserted properly.**

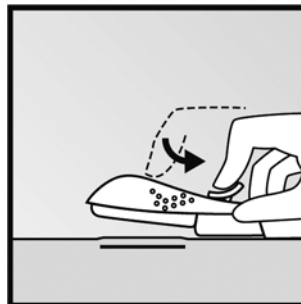
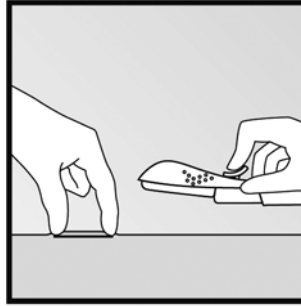


Figure 7

Step 12. **Always verify the presence of the implant in the woman's arm immediately after insertion by palpation.** By palpating both ends of the implant, you should be able to confirm the presence of the 4 cm rod (Figure 8).



**Figure 8**

If you cannot feel the implant or are in doubt of its presence,

- Check the applicator. The needle should be fully retracted and only the purple tip of the obturator should be visible.
- Use other methods to confirm the presence of the implant. Suitable methods are: two-dimensional X-ray, X-ray computerized tomography (CT scan), ultrasound scanning (USS) with a high-frequency linear array transducer (10 MHz or greater) or magnetic resonance imaging (MRI). If these methods fail, call 1-877-467-5266 for information on the procedure for measuring etonogestrel blood levels.

**Until the presence of the implant has been verified, the woman should be advised to use a non-hormonal contraceptive method, such as condoms.**

Step 13. Place a small adhesive bandage over the insertion site. Request that the woman palpate the implant.

Step 14. Apply a pressure bandage with sterile gauze to minimize bruising. The woman may remove the pressure bandage in 24 hours and the small bandage over the insertion site after 3 to 5 days.

Step 15. Complete the USER CARD and give it to the woman to keep. Also, complete the PATIENT CHART LABEL and affix it to the woman's medical record.

Step 16. The applicator is for single use only and should be disposed in accordance with the Center for Disease Control and Prevention guidelines for handling of hazardous waste.

### **2.3 Removal of NEXPLANON**

#### **Preparation**

Before initiating the removal procedure, the healthcare provider should carefully read the instructions for removal and consult the USER CARD and/or the PATIENT CHART LABEL for the location of the implant. The exact location of the implant in the arm should be verified by palpation. If the implant is not palpable, two-dimensional X-ray can be performed to verify its presence.

A non-palpable implant should always be first located prior to removal. Suitable methods for localization include: two-dimensional X-ray, X-ray computer tomography (CT), ultrasound scanning (USS) with a high-frequency linear array transducer (10 MHz or greater) or magnetic resonance imaging (MRI). If these imaging methods fail to locate the implant, etonogestrel blood level determination can be used for verification of the presence of the implant. For details on etonogestrel blood level determination, call 1-877-467-5266 for further instructions.

After localization of a non-palpable implant, consider conducting removal with ultrasound guidance.

There have been occasional reports of migration of the implant; usually this involves minor movement relative to the original position. This may complicate localization of the implant by palpation, CT, USS and/or MRI, and removal may require a larger incision and more time.

**Exploratory surgery without knowledge of the exact location of the implant is strongly discouraged.** Removal of deeply inserted implants should be conducted with caution in order to prevent injury to deeper neural or vascular structures in the arm and be performed by healthcare providers familiar with the anatomy of the arm.

Before removal of the implant, the healthcare provider should confirm that:

- The woman does not have allergies to the antiseptic or anesthetic to be used.

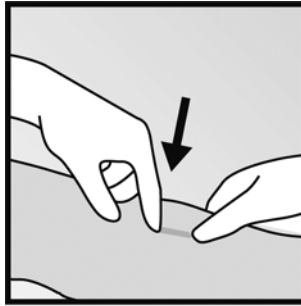
Remove the implant under aseptic conditions.

The following equipment is needed for removal of the implant:

- An examination table for the woman to lie on
- Sterile surgical drapes, sterile gloves, antiseptic solution, sterile marker (optional)
- Local anesthetic, needles, and syringe
- Sterile scalpel, forceps (straight and curved mosquito)
- Skin closure, sterile gauze, adhesive bandage and pressure bandages

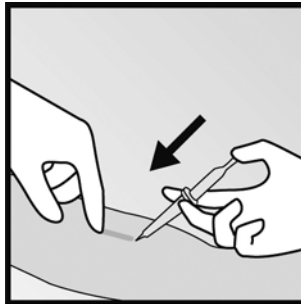
### **Removal Procedure**

Step 1. Clean the site where the incision will be made and apply an antiseptic. Locate the implant by palpation and mark the distal end (end closest to the elbow), for example, with a sterile marker (Figure 9).



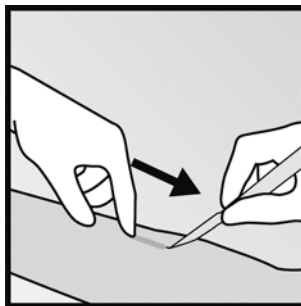
**Figure 9**

Step 2. Anesthetize the arm, for example, with 0.5 to 1 mL 1% lidocaine at the marked site where the incision will be made (Figure 10). Be sure to inject the local anesthetic under the implant to keep it close to the skin surface.



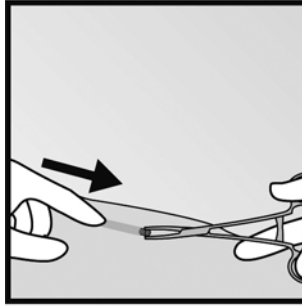
**Figure 10**

Step 3. Push down the proximal end of the implant (Figure 11) to stabilize it; a bulge may appear indicating the distal end of the implant. Starting at the distal tip of the implant, make a longitudinal incision of 2 mm towards the elbow.



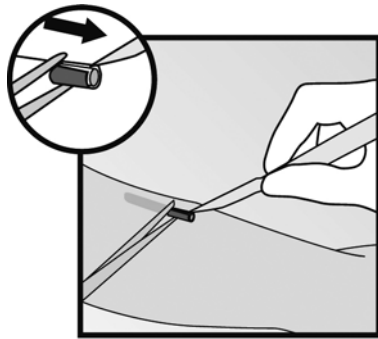
**Figure 11**

Step 4. Gently push the implant towards the incision until the tip is visible. Grasp the implant with forceps (preferably curved mosquito forceps) and gently remove the implant (Figure 12).

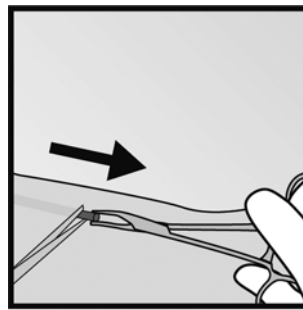


**Figure 12**

Step 5. If the implant is encapsulated, make an incision into the tissue sheath and then remove the implant with the forceps (Figures 13 and 14).

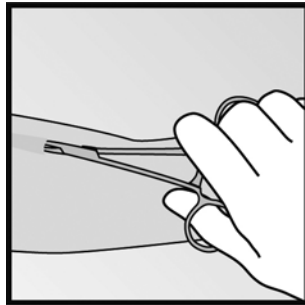


**Figure 13**

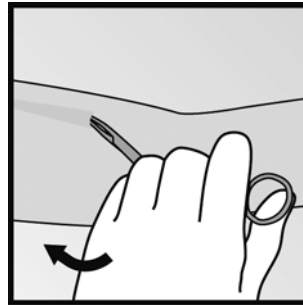


**Figure 14**

Step 6. If the tip of the implant does not become visible in the incision, gently insert a forceps into the incision (Figure 15). Flip the forceps over into your other hand (Figure 16).

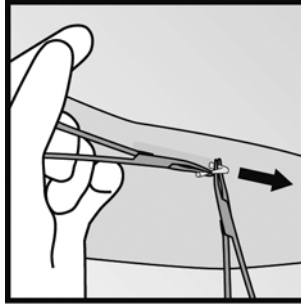


**Figure 15**



**Figure 16**

Step 7. With a second pair of forceps carefully dissect the tissue around the implant and grasp the implant (Figure 17). The implant can then be removed.



**Figure 17**

Step 8. Confirm that the entire implant, which is 4 cm long, has been removed by measuring its length. If a partial implant (less than 4 cm) is removed, the remaining piece should be removed by following the instructions in section 2.3. [See *Dosage and Administration (2.3)*.] If the woman would like to continue using NEXPLANON, a new implant may be inserted immediately after the old implant is removed using the same incision [see *Dosage and Administration (2.4)*].

Step 9. After removing the implant, close the incision with a steri-strip and apply an adhesive bandage.

Step 10. Apply a pressure bandage with sterile gauze to minimize bruising. The woman may remove the pressure bandage in 24 hours and the small bandage in 3 to 5 days.

#### **2.4 Replacing NEXPLANON**

Immediate replacement can be done after removal of the previous implant and is similar to the insertion procedure described in section 2.2 Insertion of NEXPLANON.

The new implant may be inserted in the same arm, and through the same incision from which the previous implant was removed. If the same incision is being used to insert a new implant, anesthetize the insertion site [for example, 2 mL lidocaine (1%)] applying it just under the skin along the 'insertion canal.'

Follow the subsequent steps in the insertion instructions [see *Dosage and Administration (2.2)*].

### **3 DOSAGE FORMS AND STRENGTHS**

Single, white/off-white, soft, radiopaque, flexible, ethylene vinylacetate (EVA) implant, 4 cm in length and 2 mm in diameter containing 68 mg etonogestrel and 15 mg of barium sulfate.

### **4 CONTRAINDICATIONS**

NEXPLANON should not be used in women who have

- Known or suspected pregnancy
- Current or past history of thrombosis or thromboembolic disorders
- Liver tumors, benign or malignant, or active liver disease
- Undiagnosed abnormal genital bleeding
- Known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive cancer, now or in the past
- Allergic reaction to any of the components of NEXPLANON [see *Adverse Reactions (6)*]

### **5 WARNINGS AND PRECAUTIONS**

**The following information is based on experience with either the non-radiopaque etonogestrel implant (IMPLANON), other progestin-only contraceptives, or experience with combination (estrogen plus progestin) oral contraceptives.**

#### **5.1 Complications of Insertion and Removal**

NEXPLANON should be inserted subdermally so that it will be palpable after insertion, and this should be confirmed by palpation immediately after insertion. Failure to insert NEXPLANON properly may go unnoticed unless it is palpated immediately after insertion. Undetected failure to insert the implant may lead to an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paresthesias, bleeding, hematoma, scarring or infection, may occur.

If NEXPLANON is inserted too deeply (intramuscular or in the fascia), neural or vascular injury may occur. To reduce the risk of neural or vascular injury, NEXPLANON should be inserted at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. NEXPLANON should be inserted subdermally just under the skin to avoid the large blood vessels and nerves that lie deeper in the subcutaneous tissues in the sulcus between the triceps and biceps muscles. Deep insertions of the non-radiopaque etonogestrel implant (IMPLANON) have been associated with paraesthesia (due to neural injury) and migration of the implant (due to intramuscular or fascial insertion), and in a very few cases with intravascular insertion. If infection develops at the insertion site, start suitable treatment. If the infection persists, the implant should be removed. Incomplete insertions or infections may lead to expulsion.

Implant removal may be difficult or impossible if the implant is not inserted correctly, is inserted too deeply, not palpable, encased in fibrous tissue, or has migrated. Deep insertions may lead to difficult localization of the implant and may also result in the need for a surgical procedure in an operating room in order to remove the implant. Exploratory surgery without knowledge of the exact location of the implant is strongly discouraged. Removal of deeply inserted implants should be conducted with caution in order

to prevent injury to deeper neural or vascular structures in the arm and be performed by healthcare providers familiar with the anatomy of the arm. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.

## 5.2 Changes in Menstrual Bleeding Patterns

After starting NEXPLANON, women are likely to have a change from their normal menstrual bleeding pattern. These may include changes in bleeding frequency (absent, less, more frequent or continuous), intensity (reduced or increased) or duration. In clinical trials of the non-radiopaque etonogestrel implant (IMPLANON), bleeding patterns ranged from amenorrhea (1 in 5 women) to frequent and/or prolonged bleeding (1 in 5 women). The bleeding pattern experienced during the first three months of NEXPLANON use is broadly predictive of the future bleeding pattern for many women. Women should be counseled regarding the bleeding pattern changes they may experience so that they know what to expect. Abnormal bleeding should be evaluated as needed to exclude pathologic conditions or pregnancy.

In clinical studies of the non-radiopaque etonogestrel implant, reports of changes in bleeding pattern were the most common reason for stopping treatment (11.1%). Irregular bleeding (10.8%) was the single most common reason women stopped treatment, while amenorrhea (0.3%) was cited less frequently. In these studies, women had an average of 17.7 days of bleeding or spotting every 90 days (based on 3,315 intervals of 90 days recorded by 780 patients). The percentages of patients having 0, 1-7, 8-21, or >21 days of spotting or bleeding over a 90-day interval while using the non-radiopaque etonogestrel implant are shown in Table 1.

**Table 1: Percentages of Patients with 0, 1-7, 8-21, or >21 Days of Spotting or Bleeding over a 90-Day Interval while using the Non-Radiopaque Etonogestrel Implant (IMPLANON)**

Total Days of Spotting or Bleeding	Percentage of Patients		
	Treatment Days 91-180 (N = 745)	Treatment Days 271-360 (N = 657)	Treatment Days 631-720 (N = 547)
0 Days	19%	24%	17%
1-7 Days	15%	13%	12%
8-21 Days	30%	30%	37%
>21 Days	35%	33%	35%

Bleeding patterns observed with use of the non-radiopaque etonogestrel implant for up to 2 years, and the proportion of 90-day intervals with these bleeding patterns, are summarized in Table 2.

**Table 2: Bleeding Patterns Using the Non-Radiopaque Etonogestrel Implant (IMPLANON) during the First 2 Years of Use<sup>A</sup>**

BLEEDING PATTERNS	DEFINITIONS	% <sup>B</sup>
Infrequent	Less than three bleeding and/or spotting episodes in 90 days (excluding amenorrhea)	33.6
Amenorrhea	No bleeding and/or spotting in 90 days	22.2
Prolonged	Any bleeding and/or spotting episode lasting more than 14 days in 90 days	17.7
Frequent	More than 5 bleeding and/or spotting episodes in 90 days	6.7

<sup>A</sup> Based on 3,315 recording periods of 90 days duration in 780 women, excluding the first 90 days after implant insertion

<sup>B</sup> % = Percentage of 90-day intervals with this pattern

In case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy.

## 5.3 Ectopic Pregnancies

As with all progestin-only contraceptive products, be alert to the possibility of an ectopic pregnancy among women using NEXPLANON who become pregnant or complain of lower abdominal pain. Although ectopic pregnancies are uncommon among women using NEXPLANON, a pregnancy that occurs in a woman using NEXPLANON may be more likely to be ectopic than a pregnancy occurring in a woman using no contraception.

## 5.4 Thrombotic and Other Vascular Events

The use of combination hormonal contraceptives (progestin plus estrogen) increases the risk of vascular events, including arterial events (strokes and myocardial infarctions) or deep venous thrombotic events (venous thromboembolism, deep venous thrombosis, retinal vein thrombosis, and pulmonary embolism). NEXPLANON is a progestin-only contraceptive. It is unknown whether this increased risk is applicable to etonogestrel alone. It is recommended, however, that women with risk factors known to increase the risk of venous and arterial thromboembolism be carefully assessed.

There have been postmarketing reports of serious arterial and venous thromboembolic events, including cases of pulmonary emboli (some fatal), deep vein thrombosis, myocardial infarction, and strokes, in women using the non-radiopaque etonogestrel implant. NEXPLANON should be removed in the event of a thrombosis.

Due to the risk of thromboembolism associated with pregnancy and immediately following delivery, NEXPLANON should not be used prior to 21 days postpartum. Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence.

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

Consider removal of the NEXPLANON implant in case of long-term immobilization due to surgery or illness.

#### **5.5 Ovarian Cysts**

If follicular development occurs, atresia of the follicle is sometimes delayed, and the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally, these enlarged follicles disappear spontaneously. On rare occasion, surgery may be required.

#### **5.6 Carcinoma of the Breast and Reproductive Organs**

Women who currently have or have had breast cancer should not use hormonal contraception because breast cancer may be hormonally sensitive [see *Contraindications (4)*]. Some studies suggest that the use of combination hormonal contraceptives might increase the incidence of breast cancer; however, other studies have not confirmed such findings.

Some studies suggest that the use of combination hormonal contraceptives is associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings are due to differences in sexual behavior and other factors.

Women with a family history of breast cancer or who develop breast nodules should be carefully monitored.

#### **5.7 Liver Disease**

Disturbances of liver function may necessitate the discontinuation of hormonal contraceptive use until markers of liver function return to normal. Remove NEXPLANON if jaundice develops.

Hepatic adenomas are associated with combination hormonal contraceptives use. An estimate of the attributable risk is 3.3 cases per 100,000 for combination hormonal contraceptives users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON.

The progestin in NEXPLANON may be poorly metabolized in women with liver impairment. Use of NEXPLANON in women with active liver disease or liver cancer is contraindicated [see *Contraindications (4)*].

#### **5.8 Weight Gain**

In clinical studies, mean weight gain in U.S. non-radiopaque etonogestrel implant (IMPLANON) users was 2.8 pounds after one year and 3.7 pounds after two years. How much of the weight gain was related to the non-radiopaque etonogestrel implant is unknown. In studies, 2.3% of the users reported weight gain as the reason for having the non-radiopaque etonogestrel implant removed.

#### **5.9 Elevated Blood Pressure**

Women with a history of hypertension-related diseases or renal disease should be discouraged from using hormonal contraception. For women with well-controlled hypertension, use of NEXPLANON can be considered. Women with hypertension using NEXPLANON should be closely monitored. If sustained hypertension develops during the use of NEXPLANON, or if a significant increase in blood pressure does not respond adequately to antihypertensive therapy, NEXPLANON should be removed.

#### **5.10 Gallbladder Disease**

Studies suggest a small increased relative risk of developing gallbladder disease among combination hormonal contraceptive users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON.

#### **5.11 Carbohydrate and Lipid Metabolic Effects**

Use of NEXPLANON may induce mild insulin resistance and small changes in glucose concentrations of unknown clinical significance. Carefully monitor prediabetic and diabetic women using NEXPLANON.

Women who are being treated for hyperlipidemia should be followed closely if they elect to use NEXPLANON. Some progestins may elevate LDL levels and may render the control of hyperlipidemia more difficult.

#### **5.12 Depressed Mood**

Women with a history of depressed mood should be carefully observed. Consideration should be given to removing NEXPLANON in patients who become significantly depressed.

#### **5.13 Return to Ovulation**

In clinical trials with the non-radiopaque etonogestrel implant (IMPLANON), the etonogestrel levels in blood decreased below sensitivity of the assay by one week after removal of the implant. In addition, pregnancies were observed to occur as early as 7 to 14 days after removal. Therefore, a woman should re-start contraception immediately after removal of the implant if continued contraceptive protection is desired.

#### **5.14 Fluid Retention**

Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. It is unknown if NEXPLANON causes fluid retention.

### 5.15 Contact Lenses

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

### 5.16 Monitoring

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

### 5.17 Drug-Laboratory Test Interactions

Sex hormone-binding globulin concentrations may be decreased for the first six months after NEXPLANON insertion followed by gradual recovery. Thyroxine concentrations may initially be slightly decreased followed by gradual recovery to baseline.

## 6 ADVERSE REACTIONS

The following adverse reactions reported with the use of hormonal contraception are discussed elsewhere in the labeling:

- Changes in Menstrual Bleeding Patterns [see *Warnings and Precautions* (5.2)]
- Ectopic Pregnancies [see *Warnings and Precautions* (5.3)]
- Thrombotic and Other Vascular Events [see *Warnings and Precautions* (5.4)]
- Liver Disease [see *Warnings and Precautions* (5.7)]

### 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.

In clinical trials involving 942 women who were evaluated for safety, change in menstrual bleeding patterns (irregular menses) was the most common adverse reaction causing discontinuation of use of the non-radiopaque etonogestrel implant (IMPLANON) (11.1% of women).

Adverse reactions that resulted in a rate of discontinuation of  $\geq 1\%$  are shown in Table 3.

**Table 3: Adverse Reactions Leading to Discontinuation of Treatment in 1% or More of Subjects in Clinical Trials of the Non-Radiopaque Etonogestrel Implant (IMPLANON)**

Adverse Reactions	All Studies N = 942
Bleeding Irregularities*	11.1%
Emotional Lability†	2.3%
Weight Increase	2.3%
Headache	1.6%
Acne	1.3%
Depression‡	1.0%

\* Includes "frequent", "heavy", "prolonged", "spotting", and other patterns of bleeding irregularity.

† Among US subjects (N=330), 6.1% experienced emotional lability that led to discontinuation.

‡ Among US subjects (N=330), 2.4% experienced depression that led to discontinuation.

Other adverse reactions that were reported by at least 5% of subjects in the non-radiopaque etonogestrel implant clinical trials are listed in Table 4.

**Table 4: Common Adverse Reactions Reported by ≥5% of Subjects in Clinical Trials with the Non-Radiopaque Etonogestrel Implant (IMPLANON)**

Adverse Reactions	All Studies N = 942
Headache	24.9%
Vaginitis	14.5%
Weight increase	13.7%
Acne	13.5%
Breast pain	12.8%
Abdominal pain	10.9%
Pharyngitis	10.5%
Leukorrhea	9.6%
Influenza-like symptoms	7.6%
Dizziness	7.2%
Dysmenorrhea	7.2%
Back pain	6.8%
Emotional lability	6.5%
Nausea	6.4%
Pain	5.6%
Nervousness	5.6%
Depression	5.5%
Hypersensitivity	5.4%
Insertion site pain	5.2%

In a clinical trial of NEXPLANON, in which investigators were asked to examine the implant site after insertion, implant site reactions were reported in 8.6% of women. Erythema was the most frequent implant site complication, reported during and/or shortly after insertion, occurring in 3.3% of subjects. Additionally, hematoma (3.0%), bruising (2.0%), pain (1.0%), and swelling (0.7%) were reported.

## 6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of the non-radiopaque etonogestrel implant (IMPLANON). Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Gastrointestinal disorders:* constipation, diarrhea, flatulence, vomiting.

*General disorders and administration site conditions:* edema, fatigue, implant site reaction, pyrexia.

*Infections and infestations:* rhinitis, urinary tract infection.

*Investigations:* clinically relevant rise in blood pressure, weight decreased.

*Metabolism and nutrition disorders:* increased appetite.

*Musculoskeletal and connective tissue disorders:* arthralgia, musculoskeletal pain, myalgia.

*Nervous system disorders:* convulsions, migraine, somnolence.

*Pregnancy, puerperium and perinatal conditions:* ectopic pregnancy.

*Psychiatric disorders:* anxiety, insomnia, libido decreased.

*Renal and urinary disorders:* dysuria.

*Reproductive system and breast disorders:* breast discharge, breast enlargement, ovarian cyst, pruritus genital, vulvovaginal discomfort.

*Skin and subcutaneous tissue disorders:* (aggravation of) angioedema and/or aggravation of hereditary angioedema, alopecia, chloasma, hypertrichosis, pruritus, rash, seborrhea, urticaria.

*Vascular disorders:* hot flush.

Complications related to insertion or removal of the non-radiopaque etonogestrel implant reported include: bruising, slight local irritation, pain or itching, fibrosis at the implant site, paresthesia or paresthesia-like events, scarring and abscess.

## 7 DRUG INTERACTIONS

### 7.1 Changes in Contraceptive Effectiveness Associated with Coadministration of Other Products

Drugs or herbal products that induce enzymes, including CYP3A4, that metabolize progestins may decrease the plasma concentrations of progestins, and may decrease the effectiveness of NEXPLANON. In women on long-term treatment with hepatic enzyme inducing drugs, it is recommended to remove the implant and to advise a contraceptive method that is unaffected by the interacting drug.

Some of these drugs or herbal products that induce enzymes, including CYP3A4, include:

- barbiturates
- bosentan
- carbamazepine
- fe bamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

#### **HIV Antiretrovirals**

Significant changes (increase or decrease) in the plasma levels of progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors. Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

#### **7.2 Increase in Plasma Concentrations of Etonogestrel Associated with Coadministered Drugs**

CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma concentrations of etonogestrel.

#### **7.3 Changes in Plasma Concentrations of Coadministered Drugs**

Hormonal contraceptives may affect the metabolism of other drugs. Consequently, plasma concentrations may either increase (for example, cyclosporin) or decrease (for example, lamotrigine). Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

### **8 USE IN SPECIFIC POPULATIONS**

#### **8.1 Pregnancy**

NEXPLANON is not indicated for use during pregnancy [see *Contraindications (4)*].

Teratology studies have been performed in rats and rabbits using oral administration up to 390 and 790 times the human etonogestrel dose (based upon body surface), respectively, and revealed no evidence of fetal harm due to etonogestrel exposure.

Studies have revealed no increased risk of birth defects in women who have used combination oral contraceptives before pregnancy or during early pregnancy. There is no evidence that the risk associated with etonogestrel is different from that of combination oral contraceptives.

NEXPLANON should be removed if maintaining a pregnancy.

#### **8.3 Nursing Mothers**

Based on limited clinical data, NEXPLANON may be used during breastfeeding after the fourth postpartum week. Use of NEXPLANON before the fourth postpartum week has not been studied. Small amounts of etonogestrel are excreted in breast milk. During the first months after insertion of NEXPLANON, when maternal blood levels of etonogestrel are highest, about 100 ng of etonogestrel may be ingested by the child per day based on an average daily milk ingestion of 658 mL. Based on daily milk ingestion of 150 mL/kg, the mean daily infant etonogestrel dose one month after insertion of the non-radiopaque etonogestrel implant (IMPLANON) is about 2.2% of the weight-adjusted maternal daily dose, or about 0.2% of the estimated absolute maternal daily dose. The health of breast-fed infants whose mothers began using the non-radiopaque etonogestrel implant during the fourth to eighth week postpartum (n=38) was evaluated in a comparative study with infants of mothers using a non-hormonal IUD (n=33). They were breast-fed for a mean duration of 14 months and followed up to 36 months of age. No significant effects and no differences between the groups were observed on the physical and psychomotor development of these infants. No differences between groups in the production or quality of breast milk were detected.

Healthcare providers should discuss both hormonal and non-hormonal contraceptive options, as steroids may not be the initial choice for these patients.

#### **8.4 Pediatric Use**

Safety and efficacy of NEXPLANON have been established in women of reproductive age. Safety and efficacy of NEXPLANON are expected to be the same for postpubertal adolescents. However, no clinical studies have been conducted in women less than 18 years of age. Use of this product before menarche is not indicated.

#### **8.5 Geriatric Use**

This product has not been studied in women over 65 years of age and is not indicated in this population.

#### **8.6 Hepatic Impairment**

No studies were conducted to evaluate the effect of hepatic disease on the disposition of NEXPLANON. The use of NEXPLANON in women with active liver disease is contraindicated [see *Contraindications (4)*].

### 8.7 Renal Impairment

No studies were conducted to evaluate the effect of renal disease on the disposition of NEXPLANON.

### 8.8 Overweight Women

The effectiveness of the etonogestrel implant in women who weighed more than 130% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

### 10 OVERDOSAGE

Overdosage may result if more than one implant is inserted. In case of suspected overdose, the implant should be removed.

### 11 DESCRIPTION

NEXPLANON is a radiopaque, progestin-only, soft, flexible implant preloaded in a sterile, disposable applicator for subdermal use. The implant is white/off-white, non-biodegradable and 4 cm in length with a diameter of 2 mm (see Figure 18). Each implant consists of an ethylene vinylacetate (EVA) copolymer core, containing 68 mg of the synthetic progestin etonogestrel and barium sulfate (radiopaque ingredient), surrounded by an EVA copolymer skin. Once inserted subdermally, the release rate is 60-70 mcg/day in week 5-6 and decreases to approximately 35-45 mcg/day at the end of the first year, to approximately 30-40 mcg/day at the end of the second year, and then to approximately 25-30 mcg/day at the end of the third year. NEXPLANON is a progestin-only contraceptive and does not contain estrogen. NEXPLANON does not contain latex.

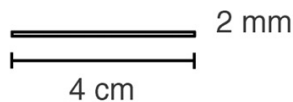


Figure 18 (Not to scale)

Etonogestrel [13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one], structurally derived from 19-nortestosterone, is the synthetic biologically active metabolite of the synthetic progestin desogestrel. It has a molecular weight of 324.46 and the following structural formula (Figure 19).

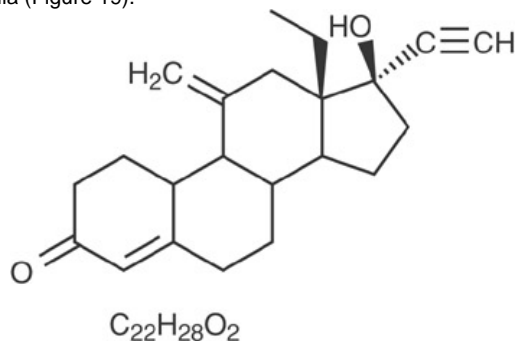


Figure 19

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

The contraceptive effect of NEXPLANON is achieved by suppression of ovulation, increased viscosity of the cervical mucus, and alterations in the endometrium.

#### 12.2 Pharmacodynamics

Exposure-response relationships of NEXPLANON are unknown.

#### 12.3 Pharmacokinetics

##### Absorption

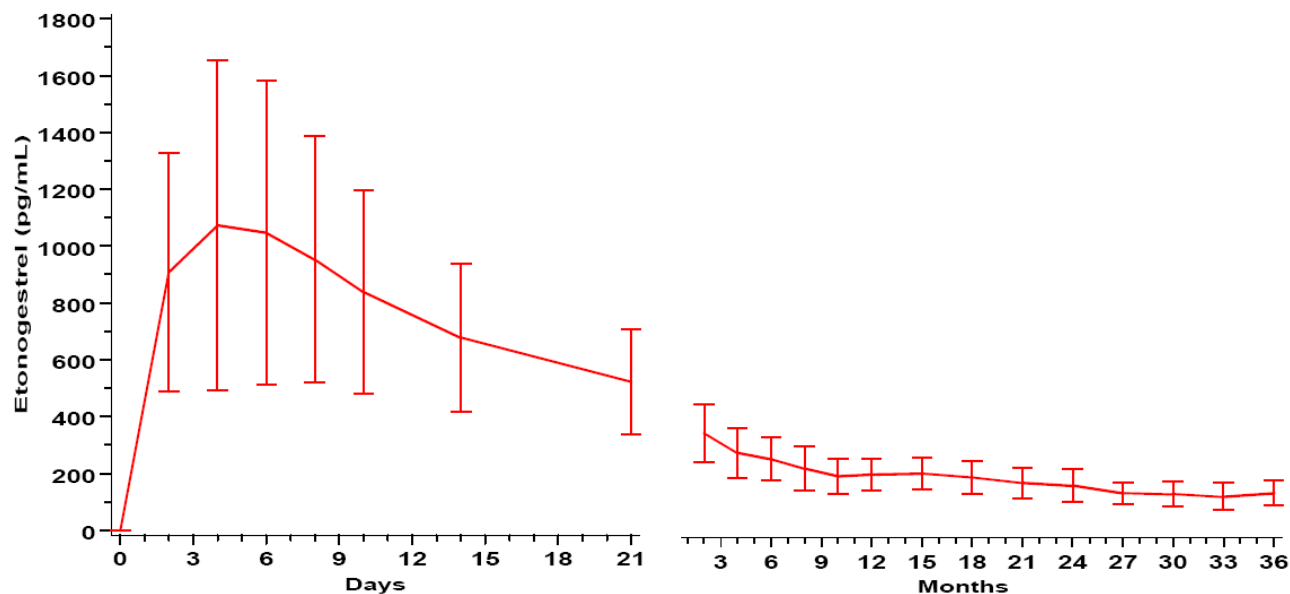
After subdermal insertion of the etonogestrel implant, etonogestrel is released into the circulation and is approximately 100% bioavailable.

In a three year clinical trial, NEXPLANON and the non-radiopaque etonogestrel implant (IMPLANON) yielded comparable systemic exposure to etonogestrel. For NEXPLANON, the mean ( $\pm$  SD) maximum serum etonogestrel concentrations were 1200 ( $\pm$  604) pg/mL and were reached within the first two weeks after insertion (n=50). The mean ( $\pm$  SD) serum etonogestrel concentration decreased gradually over time, declining to 202 ( $\pm$  55) pg/mL at 12 months (n=41), 164 ( $\pm$  58) pg/mL at 24 months (n=37), and 138 ( $\pm$  43) pg/mL at 36 months (n=32). For the non-radiopaque etonogestrel implant (IMPLANON), the mean ( $\pm$  SD) maximum serum

etonogestrel concentrations were 1145 ( $\pm$  577) pg/mL and were reached within the first two weeks after insertion (n=53). The mean ( $\pm$  SD) serum etonogestrel concentration decreased gradually over time, declining to 223 ( $\pm$  73) pg/mL at 12 months (n=40), 172 ( $\pm$  77) pg/mL at 24 months (n=32), and 153 ( $\pm$  52) pg/mL at 36 months (n=30).

The pharmacokinetic profile of NEXPLANON is shown in Figure 20.

**Figure 20: Mean ( $\pm$  SD) serum concentration-time profile of etonogestrel after insertion of NEXPLANON during 3 years of use**



#### Distribution

The apparent volume of distribution averages about 201 L. Etonogestrel is approximately 32% bound to sex hormone binding globulin (SHBG) and 66% bound to abumin in blood.

#### Metabolism

*In vitro* data shows that etonogestrel is metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme. The biological activity of etonogestrel metabolites is unknown.

#### Excretion

The elimination half-life of etonogestrel is approximately 25 hours. Excretion of etonogestrel and its metabolites, either as free steroid or as conjugates, is mainly in urine and to a lesser extent in feces. After removal of the implant, etonogestrel concentrations decreased below sensitivity of the assay by one week.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 mcg etonogestrel per day (equal to approximately 1.8-3.6 times the systemic steady state exposure in women using NEXPLANON), no drug-related carcinogenic potential was observed. 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. Fertility returned after withdrawal from treatment.

### 14 CLINICAL STUDIES

#### 14.1 Pregnancy

In clinical trials of up to 3 years duration that involved 923 subjects, 18-40 years of age at entry, and 1,756 women-years of use with the non-radiopaque etonogestrel implant (IMPLANON), the total exposures expressed as 28-day cycle equivalents by study year were:

- Year 1: 10,866 cycles
- Year 2: 8,581 cycles
- Year 3: 3,442 cycles

The clinical trials excluded women who:

- Weighed more than 130% of their ideal body weight
- Were chronically taking medications that induce liver enzymes

In the subgroup of women, 18-35 years of age at entry, 6 pregnancies during 20,648 cycles of use were reported. Two pregnancies occurred in each of Years 1, 2, and 3. Each conception was likely to have occurred shortly before or within 2 weeks after removal of the non-radiopaque etonogestrel implant. With these 6 pregnancies, the cumulative Pearl Index was 0.38 pregnancies per 100 women-years of use.

#### 14.2 Return to Ovulation

In clinical trials with the non-radiopaque etonogestrel implant (IMPLANON), the etonogestrel levels in blood decreased below sensitivity of the assay by one week after removal of the implant. In addition, pregnancies were observed to occur as early as 7 to 14 days after removal. Therefore, a woman should re-start contraception immediately after removal of the implant if continued contraceptive protection is desired.

#### 14.3 Implant Insertion and Removal Characteristics

Out of 301 insertions of the NEXPLANON implant in a clinical trial, the mean insertion time (from the removal of the protection cap of the applicator until retraction of the needle from the arm) was  $27.9 \pm 29.3$  seconds. After insertion, 300 out of 301 (99.7%) NEXPLANON implants were palpable. The single, non-palpable implant was not inserted according to the instructions.

For 112 out of 114 (98.2%) subjects in 2 clinical trials for whom insertion and removal data were available, NEXPLANON implants were clearly visible with use of two-dimensional x-ray after insertion. The two implants that were not clearly visible after insertion were clearly visible with two-dimensional x-ray before removal.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 16.1 How Supplied

One NEXPLANON package consists of a single implant containing 68 mg etonogestrel that is 4 cm in length and 2 mm in diameter, which is pre-loaded in the needle of a disposable applicator. The sterile applicator containing the implant is packed in a blister pack.

NDC 0052-0274-01

#### 16.2 Storage and Handling

Store NEXPLANON (etonogestrel implant) Radiopaque at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Avoid storing NEXPLANON at temperatures above 30°C (86°F).

### 17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

#### Information for Patients


- Counsel women about the insertion and removal procedure of the NEXPLANON implant. Provide the woman with a copy of the Patient Labeling and ensure that she understands the information in the Patient Labeling before insertion and removal. A USER CARD and consent form are included in the packaging. Have the woman complete a consent form and retain it in your records. The USER CARD should be filled out and given to the woman after insertion of the NEXPLANON implant so that she will have a record of the location of the implant in the upper arm and when it should be removed.
- Counsel women that NEXPLANON does not protect against HIV infection (AIDS) or other sexually transmitted diseases.
- Counsel women that the use of NEXPLANON may be associated with changes in their normal menstrual bleeding patterns so that they know what to expect.

#### FDA-Approved Patient Labeling


See the full patient product information for NEXPLANON.

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Manufactured by: N.V. Organon, Oss,  
The Netherlands, a subsidiary of

 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

Distributed by: Schering Corporation, a subsidiary of

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37308

## FDA-Approved Patient Labeling

### **NEXPLANON® (etonogestrel implant) Radiopaque Subdermal Use Only**

**NEXPLANON® does not protect against HIV infection (the virus that causes AIDS) or other sexually transmitted diseases.** Read this Patient Information leaflet carefully before you decide if NEXPLANON is right for you. This information does not take the place of talking with your healthcare provider. If you have any questions about NEXPLANON, ask your healthcare provider.

#### **What is NEXPLANON?**

NEXPLANON is a hormone-releasing birth control implant for use by women to prevent pregnancy for up to 3 years. The implant is a flexible plastic rod about the size of a matchstick that contains a progestin hormone called etonogestrel. It also contains a small amount of barium sulfate so that the implant can be seen by X-ray. Your healthcare provider will insert the implant just under the skin of the inner side of your upper arm. You can use a single NEXPLANON implant for up to 3 years. NEXPLANON does not contain estrogen.



#### **What if I need birth control for more than 3 years?**

The NEXPLANON implant must be removed after 3 years. Your healthcare provider can insert a new implant under your skin after taking out the old one if you choose to continue using NEXPLANON for birth control.

#### **What if I change my mind about birth control and want to stop using NEXPLANON before 3 years?**

Your healthcare provider can remove the implant at any time. You may become pregnant as early as the first week after removal of the implant. If you do not want to get pregnant after your healthcare provider removes the NEXPLANON implant, you should start another birth control method right away.

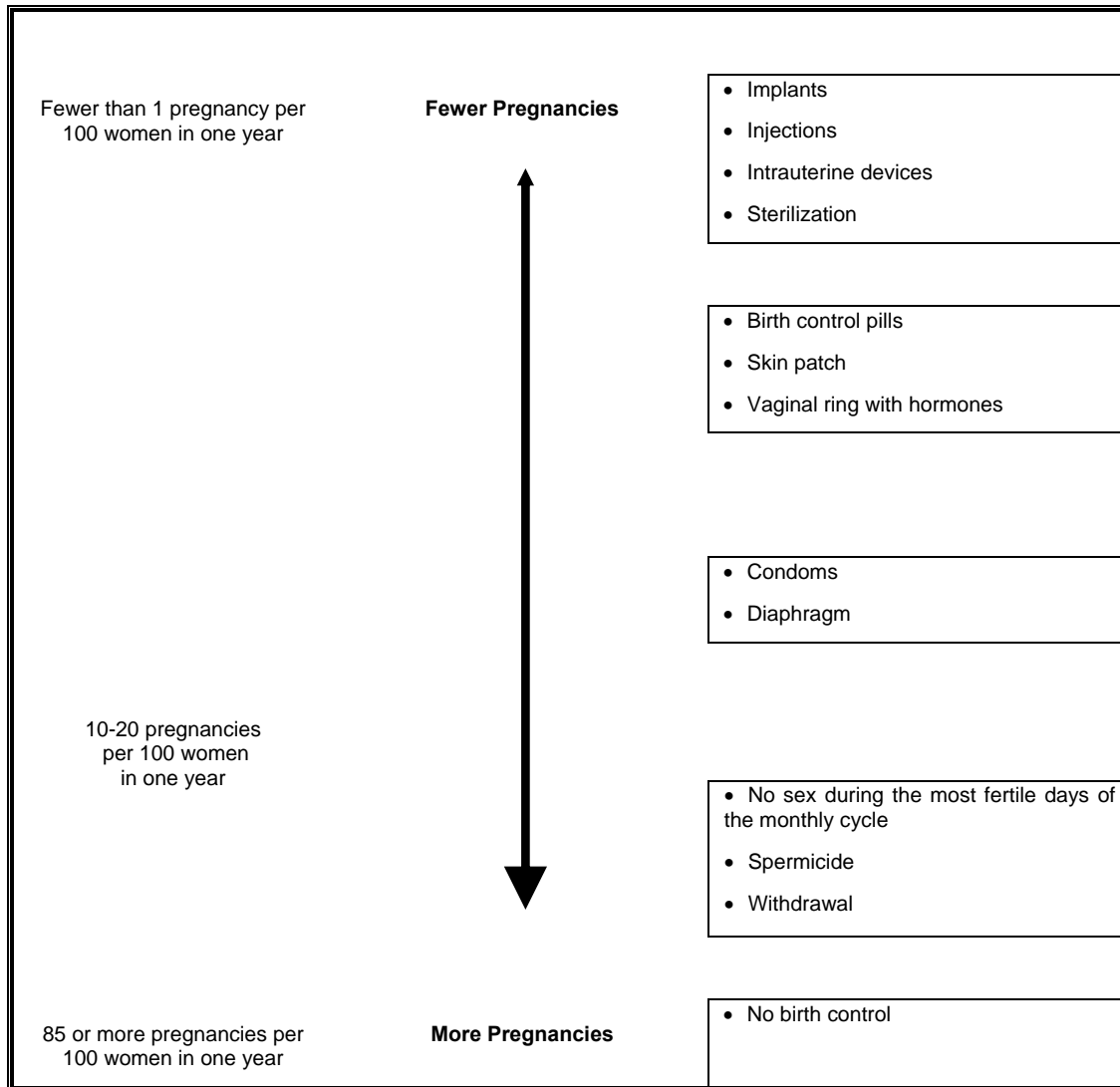
#### **How does NEXPLANON work?**

NEXPLANON prevents pregnancy in several ways. The most important way is by stopping the release of an egg from your ovary. NEXPLANON also thickens the mucus in your cervix and this change may keep sperm from reaching the egg. NEXPLANON also changes the lining of your uterus.

#### **How well does NEXPLANON work?**

When the NEXPLANON implant is placed correctly, your chance of getting pregnant is very low (less than 1 pregnancy per 100 women who use NEXPLANON for 1 year). It is not known if NEXPLANON is as effective in very overweight women because studies did not include many overweight women.

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 NEXPLANON?**

Do not use NEXPLANON if you:

- Are pregnant or think you may be pregnant
- Have, or have had blood clots, such as blood clots in your legs (deep venous thrombosis), lungs (pulmonary embolism), eyes (total or partial blindness), heart (heart attack), or brain (stroke)
- Have liver disease or a liver tumor
- Have unexplained vaginal bleeding
- Have breast cancer or any other cancer that is sensitive to progestin (a female hormone), now or in the past
- Are allergic to anything in NEXPLANON

Tell your healthcare provider if you have or have had any of the conditions listed above. Your healthcare provider can suggest a different method of birth control.

In addition, talk to your healthcare provider about using NEXPLANON if you:

- Have diabetes
- Have high cholesterol or triglycerides
- Have headaches
- Have gal bladder or kidney problems
- Have a history of depressed mood
- Have high blood pressure
- Have an allergy to numbing medicines (anesthetics) or medicines used to clean your skin (antiseptics). These medicines will be used when the implant is placed into or removed from your arm.

### **Interaction with Other Medicines**

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Certain medicines may make NEXPLANON less effective, including:

- barbiturates
- bosentan
- carbamazepine
- febamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate
- HIV medicines

Ask your healthcare provider if you are not sure if your medicine is one listed above.

If there are medicines that you have been taking for a long time, that make NEXPLANON less effective, tell your healthcare provider. Your healthcare provider may remove the NEXPLANON implant and recommend a birth control method that can be used effectively with these medicines.

When you are using NEXPLANON, tell all of your healthcare providers that you have NEXPLANON in place in your arm.

### **How is the NEXPLANON implant placed and removed?**

Your healthcare provider will place and remove the NEXPLANON implant in a minor surgical procedure in his or her office. The implant is placed just under the skin on the inner side of your upper arm.

The timing of insertion is important. Your healthcare provider may:

- Perform a pregnancy test before inserting NEXPLANON
- Schedule the insertion at a specific time of your menstrual cycle (for example, within the first days of your regular menstrual bleeding)

**Immediately after the NEXPLANON implant has been placed, you and your healthcare provider should check that the implant is in your arm by feeling for it.**

**If you and your healthcare provider cannot feel the NEXPLANON implant, use a non-hormonal birth control method (such as condoms) until your healthcare provider confirms that the implant is in place.** You may need special tests to check that the implant is in place or to help find the implant when it is time to take it out.

Your healthcare provider will cover the site where NEXPLANON was placed with 2 bandages. Leave the top bandage on for 24 hours. Keep the smaller bandage clean, dry, and in place for 3 to 5 days.

You will be asked to review and sign a consent form prior to inserting the NEXPLANON implant. You will also get a USER CARD to keep at home with your health records. Your healthcare provider will fill out the USER CARD with the date the implant was inserted and the date the implant is to be removed. Keep track of the date the implant is to be removed. Schedule an appointment with your healthcare provider to remove the implant on or before the removal date.

Be sure to have checkups as advised by your healthcare provider.

### **What are the most common side effects I can expect while using NEXPLANON?**

#### **• Changes in Menstrual Bleeding Patterns (menstrual periods)**

The most common side effect of NEXPLANON is a change in your normal menstrual bleeding pattern. In studies, one out of ten women stopped using the implant because of an unfavorable change in their bleeding pattern. You may experience longer or shorter bleeding during your periods or have no bleeding at all. The time between periods may vary, and in between periods you may also have spotting.

Tell your healthcare provider right away if:

- You think you may be pregnant
- Your menstrual bleeding is heavy and prolonged

Besides changes in menstrual bleeding patterns, other frequent side effects that caused women to stop using the implant include:

- Mood swings
- Weight gain
- Headache
- Acne
- Depressed mood

Other common side effects include:

- Headache
- Vaginitis (inflammation of the vagina)
- Weight gain
- Acne
- Breast pain
- Viral infections such as sore throats or flu-like symptoms
- Stomach pain
- Painful periods
- Mood swings, nervousness, or depressed mood
- Back pain
- Nausea
- Dizziness
- Pain
- Pain at the site of insertion

This is not a complete list of possible side effects. For more information, ask your healthcare provider for advice about any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

### **What are the possible risks of using NEXPLANON?**

#### **• Problems with Insertion and Removal**

The implant may not be placed in your arm at all due to a failed insertion. If this happens, you may become pregnant. Immediately after insertion, and with help from your healthcare provider, you should be able to feel the implant under your skin. If you can't feel the implant, tell your healthcare provider.

Removal of the implant may be very difficult or impossible because the implant is not where it should be. Special procedures, including surgery in the hospital, may be needed to remove the implant. If the implant is not removed, then the effects of NEXPLANON will continue for a longer period of time.

Other problems related to insertion and removal are:

- Pain, irritation, swelling, or bruising at the insertion site
- Scarring, including a thick scar called a keloid around the insertion site
- Infection
- Scar tissue may form around the implant making it difficult to remove
- The implant may come out by itself. You may become pregnant if the implant comes out by itself. Use a back up birth control method and call your healthcare provider right away if the implant comes out.
- The need for surgery in the hospital to remove the implant
- Injury to nerves or blood vessels in your arm
- The implant breaks making removal difficult

#### **• Ectopic Pregnancy**

If you become pregnant while using NEXPLANON, you have a slightly higher chance that the pregnancy will be ectopic (occurring outside the womb) than do women who do not use birth control. Unusual vaginal bleeding or lower stomach (abdominal) pain may be a sign of ectopic pregnancy. Ectopic pregnancy is a medical emergency that often requires surgery. Ectopic pregnancies can cause serious internal bleeding, infertility, and even death. Call your healthcare provider right away if you think you are pregnant or have unexplained lower stomach (abdominal) pain.

#### **• Ovarian Cysts**

Cysts may develop on the ovaries and usually go away without treatment but sometimes surgery is needed to remove them.

#### **• Breast Cancer**

It is not known whether NEXPLANON use changes a woman's risk for breast cancer. If you have breast cancer now, or have had it in the past, do not use NEXPLANON because some breast cancers are sensitive to hormones.

#### **• Serious Blood Clots**

NEXPLANON may increase your chance of serious blood clots, especially if you have other risk factors such as smoking. It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke.

Some examples of serious blood clots are blood clots in the:

- Legs (deep vein thrombosis)
- Lungs (pulmonary embolism)
- Brain (stroke)
- Heart (heart attack)
- Eyes (total or partial blindness)

The risk of serious blood clots is increased in women who smoke. If you smoke and want to use NEXPLANON, you should quit. Your healthcare provider may be able to help.

Tell your healthcare provider at least 4 weeks before if you are going to have surgery or will need to be on bed rest. You have an increased chance of getting blood clots during surgery or bed rest.

- **Other Risks**

A few women who use birth control that contains hormones may get:

- High blood pressure
- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

**When should I call my healthcare provider?**

**Call your healthcare provider right away if you have:**

- Pain in your lower leg that does not go away
- Severe chest pain or heaviness in the chest
- Sudden shortness of breath, sharp chest pain, or coughing blood
- Sudden severe headache unlike your usual headaches
- Weakness or numbness in your arm, leg, or trouble speaking
- Sudden partial or complete blindness
- Yellowing of your skin or whites of your eyes, especially with fever, tiredness, loss of appetite, dark colored urine, or light colored bowel movements
- Severe pain, swelling, or tenderness in the lower stomach (abdomen)
- Lump in your breast
- Problems sleeping, lack of energy, tiredness, or you feel very sad
- Heavy menstrual bleeding

**What if I become pregnant while using NEXPLANON?**

You should see your healthcare provider right away if you think that you may be pregnant. It is important to remove the implant and make sure that the pregnancy is not ectopic (occurring outside the womb). Based on experience with other hormonal contraceptives, NEXPLANON is not likely to cause birth defects.

**Can I use NEXPLANON when I am breastfeeding?**


If you are breastfeeding your child, you may use NEXPLANON if 4 weeks have passed since you had your baby. A small amount of the hormone contained in NEXPLANON passes into your breast milk. The health of breast-fed children whose mothers were using the implant has been studied up to 3 years of age in a small number of children. No effects on the growth and development of the children were seen. If you are breastfeeding and want to use NEXPLANON, talk with your healthcare provider for more information.

**Additional Information**


This Patient Information leaflet contains important information about NEXPLANON. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider for information about NEXPLANON that is written for healthcare professionals. You may also call 1-877-467-5266 or visit [www.NEXPLANON-USA.com](http://www.NEXPLANON-USA.com).

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Manufactured by: N.V. Organon, Oss,  
The Netherlands, a subsidiary of

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021529Orig1s007**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	May 13, 2011
<b>From</b>	Scott Monroe, MD
<b>Subject</b>	Division Director Summary Review
<b>NDA</b>	NDA 021529/S007
<b>Applicant Name</b>	Organon USA Inc.
<b>Date of Submission</b>	July 30, 2009
<b>PDUFA Goal Date</b>	August 30, 2010 (with 3 month extension)
<b>Proprietary Name</b>	NEXPLANON®
<b>Established (USAN) Name</b>	Etonogestrel implant (radiopaque)
<b>Dosage Forms/Strengths</b>	Subdermal implant/68 mg etonogestrel
<b>Proposed Indication</b>	For use by women to prevent pregnancy
<b>Proposed Regimen</b>	Insert one implant subdermally at the inner side of the upper arm. The implant must be removed after 3 years.
<b>Action</b>	<i>Approve (see Section 13.1)</i>

<b>Material Reviewed/Consulted</b>	<b>Names of Discipline Reviewers</b>
<b>OND Action Package, including:</b>	
<b>Medical Officer Review</b>	Theresa van der Vlugt MD (Clinical Reviewer)
<b>Statistical Review</b>	Sonia Castillo PhD/Mahboob Sobhan PhD
<b>Pharmacology Toxicology Review</b>	Krishan Raheja DVM, PhD/Alexander Jordan PhD
<b>CMC Review</b>	Joel Hathaway PhD/Hasmukh Patel PhD
<b>Microbiology Review</b>	Steven Fong PhD
<b>Clinical Pharmacology Review</b>	Hyunjin Kim PharmD/Myong-Jin Kim PharmD
<b>DDMAC</b>	Janice Maniwang PharmD/Carrie Newcomer PharmD
<b>DSI</b>	Michael Skelly PhD/Martin Yau PhD
<b>CDTL Review</b>	Theresa van der Vlugt MD (also Clinical Team Leader)
<b>OSE/DMEPA</b>	Carlos Mena-Grillasca RPh/Carol Holquist RPh
<b>OSE/DRISK</b>	Barbara Fuller RN, MSN/Mary Willy PhD
<b>OSE/DPV-II</b>	Mark Miller PharmD/Robert Boucher MD
<b>CDRH</b>	Alan Stevens/Ronald Kaye/Nikhil Thakur

OND=Office of New Drugs

CMC=Chemistry, Manufacturing and Controls

DDMAC=Division of Drug Marketing, Advertising, and Communication

DSI=Division of Scientific Investigations

CDTL=Cross Discipline Team Leader

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Errors Prevention and Analysis

DRISK=Division of Risk Management

DPV-2=Division of Pharmacovigilance

CDRH=Center for Devices and Radiologic Health

## DIVISION DIRECTOR SUMMARY REVIEW

### 1. INTRODUCTION

The objective of this efficacy supplement (NDA 021529/S007) is to obtain marketing approval for (1) a radiopaque version of the currently approved and marketed etonogestrel implant (Implanon) and (2) a new device (applicator) to facilitate subdermal insertion of the radiopaque implant. The new radiopaque etonogestrel implant (also referred to as Nexplanon) is identical to Implanon with the exception that 15 mg of barium sulfate has been added to the core matrix of the implant rod, [REDACTED] (b) (4). Implanon was approved for marketing in the US in July 2006. Implanon consists of a non-biodegradable, single-rod implant, pre-filled in the stainless steel needle of a ready-for-use disposable applicator. The implant has a length of 4 cm and a diameter of 2 mm and contains 68 mg of the progestin etonogestrel. After subdermal insertion of the implant in the upper arm, there is a continuous, slowly decreasing release of etonogestrel that provides contraception for up to 3 years. The implant must be removed no later than 3 years after insertion and can be replaced by another implant if the woman wants to continue to use the product for contraception.

Implanon is a highly effective progestin-only contraceptive. In the clinical trials that supported approval of Implanon, the Pearl Index (an estimate of contraceptive efficacy) was 0.38 pregnancies per 100 women years of use. The manufacturer of Implanon currently provides the product only to healthcare providers who complete Company sponsored training for insertion and removal of the implant. If the implant is not properly inserted (e.g., inserted too deep in the tissue of the arm), it may be difficult to locate and remove. Addition of barium sulfate to the implant will allow localization of the implant by conventional 2 dimensional x-ray when the healthcare provider cannot locate the rod by palpation at the time of removal. The new applicator for subdermal insertion of the radiopaque implant rod is intended to provide several advantages over the currently approved insertion device as described in Section 2.1.2 of this Review. Among these advantages are (1) reduced likelihood that the implant rod will fall out of the device before insertion, (2) easier retraction of the inserter needle after subdermal placement of the implant rod, (3) one-hand operation of the device, and (4) the possibility of fewer deep insertions.

NDA 021925/S007 included data from 2 clinical trials as well as chemistry, manufacturing and controls (CMC) and clinical pharmacology data. Information specific to the development and non-clinical testing of the new inserter device also was submitted.

The only significant review issue that could have precluded approval of Nexplanon was the Applicant's failure to fulfill all of the criteria needed to demonstrate bioequivalence between the radiopaque implant (Nexplanon) and the currently approved and marketed non-radiopaque implant (Implanon). Although Nexplanon fully met the criteria for bioequivalence to Implanon for the pharmacokinetic (PK) criterion of AUC (area under the time-concentration curve) for all time intervals that were compared, Nexplanon did not meet the criterion for bioequivalence for the PK criterion of C<sub>max</sub> (maximal plasma concentration). Based on the PK analysis by the FDA's clinical pharmacologist, the upper limit for the 90% confidence interval (CI) for the ratio of (C<sub>max</sub> Nexplanon/C<sub>max</sub> Implanon) for plasma etonogestrel concentrations was 1.264. This value was minimally above 1.25, the generally accepted upper limit of the criterion for bioequivalence. This minimal increase in C<sub>max</sub> plasma concentrations (an increase of only 0.014 above the criterion for bioequivalence) was determined by both the clinical pharmacology

and clinical reviewers to not pose a safety concern. Among the factors considered in this determination was that women who use Nexplanon will be exposed to this minimal increase in C<sub>max</sub> etonogestrel concentrations only once every 3 years following insertion of the implant (see Section 5.2 for a more detailed discussion).

Late in the review cycle, it was determined that Nexplanon should not be approved in the absence of an inspection by the Office of Compliance of the Applicant's finished dosage manufacturing site and review of the Applicant's quality control processes to ensure that the new insertion device would function properly. Because of the time required to arrange and conduct a non-US inspection, the PDUFA goal date was not met. In February 2011, the Office of Compliance issued an overall "Acceptable" recommendation for the Applicant's manufacturing and testing facilities.

Based on their reviews of the information submitted by the Applicant and the overall recommendation of "Acceptable" by the Office of Compliance, all discipline reviewers, including the primary Clinical Reviewer/Cross Discipline Team Leader (Dr. van der Vlugt), the primary Clinical Pharmacology Reviewer (Dr. Kim), and the primary CMC Reviewer (Dr. Hathaway) have recommended that Nexplanon be approved for the indication of "for use by women to prevent pregnancy." I concur with the recommendations of the discipline reviewers that Nexplanon be approved.

## **2. BACKGROUND**

### **2.1 Description of the Product**

#### **2.1.1 Radiopaque Implant**

Nexplanon is a radiopaque, progestin-only, soft, flexible implant for subdermal use that is preloaded in a sterile, disposable applicator. The implant is white/off-white, non-biodegradable, and 4 cm in length with a diameter of 2 mm. Each implant consists of an ethylene vinylacetate (EVA) copolymer core, containing 68 mg of the synthetic progestin etonogestrel and 15 mg barium sulfate (radiopaque ingredient), surrounded by an EVA copolymer skin. Once inserted subdermally, the release rate of etonogestrel is 60-70 mcg/day in weeks 5-6 and decreases to approximately 35-45 mcg/day at the end of the first year, to approximately 30-40 mcg/day at the end of the second year, and then to approximately 25-30 mcg/day at the end of the third year. The implant must be removed no later than 3 years after insertion and can be replaced by another implant if the woman wants to continue to use Nexplanon for prevention of pregnancy.

Etonogestrel is structurally derived from 19-nortestosterone and is the synthetic biologically active metabolite of the synthetic progestin desogestrel. Etonogestrel is also the progestin in NuvaRing, a vaginal contraceptive ring that was approved for marketing in the US in 2001 and which contains both etonogestrel and ethinyl estradiol.

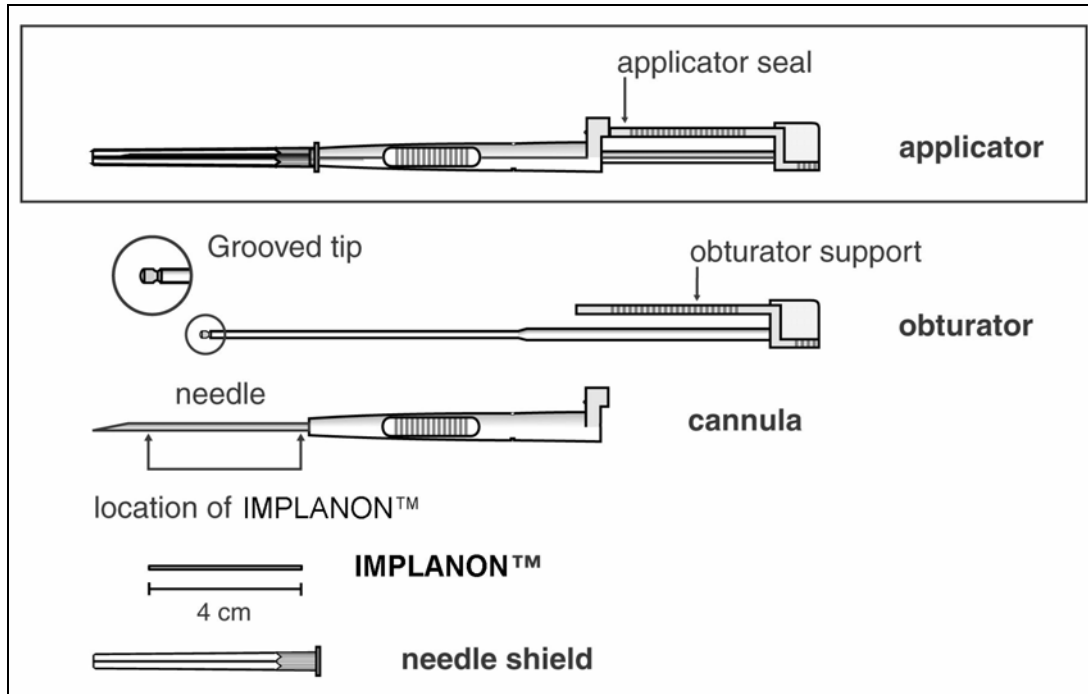
The composition of Nexplanon is identical to Implanon (which was approved for marketing in the US in 2006) with the exception that 15 mg of barium sulfate was added to the core matrix of the Nexplanon implant rod, (b) (4).

The likely primary mechanisms of action of Nexplanon for prevention of pregnancy include inhibition of ovulation, increased viscosity of the cervical mucus, and alterations in the endometrium.

### 2.1.2 Implant Insertion Device

The currently approved device for insertion of Implanon is shown in Figure 1. Proper placement of the implant requires that the healthcare provider closely follow the directions for use that are provided in approved labeling for Implanon.

**Figure 1 Schematic Drawing of the Approved Implanon Applicator**

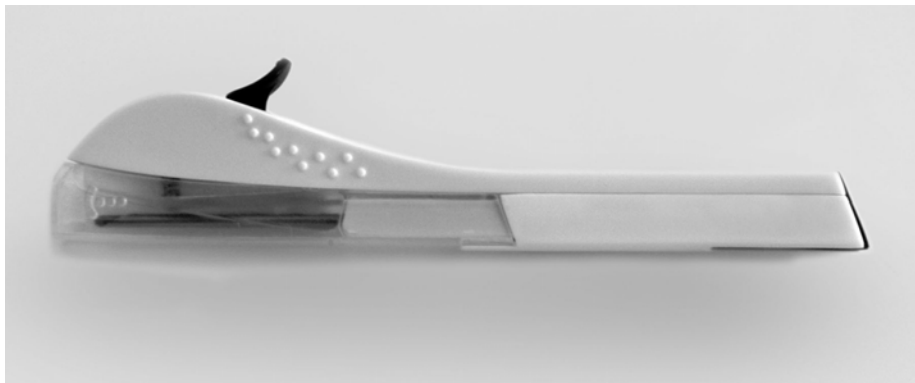


#### Division Director's Comments

- *Limitations of the Implanon applicator design include:*
  1. *The need to use both hands to operate the applicator.*
  2. *A tendency for the implant to fall out of the applicator before subdermal insertion if the applicator is inadvertently angled downward.*
  3. *A tendency for the implant to be improperly inserted if appropriate counter pressure is not exerted on the obturator during withdrawal of the applicator following subdermal placement of the implant.*

The redesigned (new) applicator for insertion of Nexplanon is shown in Figure 2. The new applicator was designed to address many of the limitations of the currently approved device. Among the improvements are: (1) one hand operation, (2) a locking mechanism to prevent the implant from falling out of the device, (3) less likelihood of the implant not being completely inserted in the proper subdermal location, and (4) the possibility that there will be fewer inadvertent “deep” insertions of the implant.

**Figure 2 Redesigned (New) Applicator for Insertion of Nexplanon**



Components of the new insertion applicator that improve its functionality are illustrated in Figure 3.

APPEARS THIS WAY  
ON ORIGINAL

**Figure 3 Components of the New Insertion Applicator**



- View 1: The needle protection cap (Item 1) assures that the implant remains inside the needle. In case of absence of an implant in the needle due to improper loading during the manufacturing process, the needle protection cap can not be easily removed as the retaining lever (Item 3 in View 2) will impede removal of the protection cap.
- View 2: After removal of the protection cap (Item 2) a retaining lever (Item 3) holds the implant in the needle.
- View 3: After subdermal insertion of the needle, the retaining lever (Item 4) is pushed upward, thereby “unlocking” the implant.
- View 4: While keeping the applicator in the same position after the needle has been inserted superficially into the subdermal connective tissue, the slider on top of the applicator (Item 5) can be unlocked by pushing it down and backwards. By sliding the slider backwards until it is arrested in the back of the slider groove, the needle is retracted into the applicator housing and the implant (Item 6), held in place by the obturator, is retained in the desired location just under the skin.
- View 5: After complete retraction of the slider, the needle (Item 8) is completely retracted into the housing and locked.

## **2.2 Regulatory History**

Implanon has been marketed outside of the US since 1998 and was approved for marketing in the US in July 2006. In August 2007, the Applicant had a teleconference with the Agency to discuss

their plans to develop a radiopaque version of the Implanon implant and a new insertion applicator. A number of options were discussed by which the Applicant could demonstrate bioequivalence between the to-be-developed radiopaque implant and Implanon. In the absence of having an acceptable *in vivo/in vitro* correlation (IVIVC) process, the Applicant was advised to provide data from a 3-year bioequivalence study (Study 34528). In regard to the new insertion applicator, the Applicant proposed to provide data from 300 insertions and x-ray localization data from 50 insertions (Study 34530). The Division of Reproductive and Urologic Products (DRUP) found the proposal to be acceptable.

#### **Division Director's Comments**

- *The original submission for this NDA supplement included the requested clinical and clinical pharmacology information.*
- *As the review progressed, it was recognized that the Applicant had additional clinical efficacy and safety data from on-going Study 34530. These additional data were requested and reviewed by the primary Clinical Reviewer.*

The radiopaque implant (also called IMPLANON NXT outside of the US) and the redesigned applicator were approved by the Mutual Recognition Procedure (MRP) with the Netherlands as the Reference Member State in April 2010. Nexplanon or Implanon NXT, based on the Applicant's submission of April 2011, is approved for marketing in 23 countries, and is currently marketed in 12 countries outside the US.

### **2.3 Content of Current NDA Supplement**

The Application contained the necessary CMC, preclinical toxicology (primarily by cross-reference to the Applicant's original NDA for Implanon), clinical pharmacology, and clinical safety and efficacy information to support approval. Three year clinical pharmacology (bioequivalence) data were provided by multicenter Study 34528. Clinical safety and efficacy data were provided by Study 34528 and 3-year Study 34530.

### **2.4 Recommendation of Primary Clinical Reviewer/Cross-Discipline Team Leader regarding Approvability**

Theresa van der Vlugt MD, the primary Clinical Reviewer (who also was the Cross Discipline Team Leader/Clinical Team Leader for the review of this Application), stated the following in her Review signed on May 12, 2011:

*"This reviewer recommends approval of radiopaque NEXPLANON® (etonogestrel implant) containing 68 mg of etonogestrel and 15 mg of barium sulfate and the redesigned applicator for insertion for use by women to prevent pregnancy. A single radiopaque NEXPLANON® implant is inserted subdermally and may be used continuously (remain in place) for up to 3 years. Recommended approval is based on:*

- 1. The reanalysis of bioequivalence data in completed 3-year bioequivalence Study 34528.*
- 2. The interim report in the supplemental application for the ongoing 3-year applicator use Study 34530 reporting results of 301 radiopaque NEXPLANON® implant insertions using the redesigned applicator.*
- 3. Additional safety data requested for Study 34528 of all adverse events, other than insertion-related, with a start date within the first 60 days after implant insertion.*

4. *Additional validated safety data requested for the initial 12 months of ongoing 3-year Study 34530, and an additional focused listing of all adverse events by subjects (other than insertion-related) with an onset date within 60 days of the NEXPLANON® implant insertion.*
5. *Additional validated removal data requested for the now completed 3-year applicator use Study 34530.*
6. *Additional safety data requested for the now completed 3-year Study 34530 of all premature terminations for any reason, and all serious adverse events, other than insertion-related or removal-related.*
7. *The overall assessment by the Center for Devices and Radiological Health (CDRH) that the redesigned applicator is acceptable.*
8. *No outstanding CMC or nonclinical pharmacology/toxicology issues.*

*The review of the original safety data in the application and of the additional requested safety data did not demonstrate any overall safety concerns for the radiopaque NEXPLANON® implant nor did it demonstrate any safety concerns that might be related to the minimally higher upper limit of the 90% CI for the difference in Cmax values. The serious and common adverse events reported in clinical trials conducted to support the approval of radiopaque NEXPLANON® are consistent with those of approved IMPLANON®, other non-implantable progestin-only contraceptives, and with combination progestin plus estrogen contraceptives except for events related to the insertion and removal of the NEXPLANON® implant.*

*The effectiveness of NEXPLANON® for the prevention of pregnancy is also not an issue. No in-treatment pregnancies (pregnancies occurring after implant insertion and before implant removal) occurred in 3-year Study 34528. One (1) pregnancy occurred within 14 days of implant removal (estimated conception on day 7 following removal). No pregnancies occurred in ongoing 3-year Study 34530 as of the sNDA application Data Lock Point of March 12, 2010, which included, at a minimum, 2-year pregnancy data from all subjects who had not terminated prematurely. Therefore, sufficient evidence is provided in the application for me to conclude that the 68 mg radiopaque NEXPLANON® implant is equally effective for women for the prevention of pregnancy as the approved non-radiopaque IMPLANON®.*

*Sufficient evidence is also provided in the application in Study 34530 (interim report for 301 NEXPLANON® implant insertions using the redesigned applicator, 12 months of safety data, updated safety data for now completed Study 34530, and implant removal data for all subjects) for me to conclude that the redesigned applicator is an appropriate device for proper implant insertion.”*

Dr. van der Vlugt also recommended that the Applicant continue (1) to conduct for healthcare providers a clinical training program that focuses on proper insertion and removal of the implant, and (2) to report on a quarterly or semiannual basis postmarketing insertion- and removal-related events (IRREs) separately from the annual safety report.

Dr. van der Vlugt also recommended that the Applicant conduct, as part of a postmarketing commitment (PMC), a descriptive observational cohort study of insertion-, localization-, and removal-related events associated with Nexplanon use. The study should include at least 5,000 subjects who have had an insertion and removal of Nexplanon.

### Division Director's Comment

- *I concur with (1) the recommendation of Dr. van der Vlugt that the radiopaque etonogestrel implant (Nexplanon) and the new insertion applicator be approved for use by women to prevent pregnancy and (2) her recommendations regarding postmarketing activities.*

### 3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

Per the primary CMC Review, there are no changes to the manufacturing or quality control of the etonogestrel drug substance used in the radiopaque implant compared to that for the currently marketed non-radiopaque implant. Nevertheless, because barium sulfate is added to the core of the implant, an additional compatibility study was performed to demonstrate that etonogestrel is compatible with all excipients, including barium sulfate. Based on data provided by the Applicant, the CMC Reviewer stated:

*“It was demonstrated that etonogestrel is compatible with barium sulfate and ethylene vinylacetate copolymers. Etonogestrel content did not change after exposure to extreme heat and light conditions.* [REDACTED] (b) (4)

*[REDACTED] No unspecified degradation products were found. It can be concluded that addition of barium sulfate does not affect the stability of etonogestrel in the presence of the excipients.”*

*“Additional comparative dissolution tests with the approved Implanon® implant were carried out in different media to investigate whether both the approved and X-ray visible implant behave similarly in each of these media. .... there is hardly any difference observed for the release rate of the X-ray visible and current Implanon® implants when they are tested under identical conditions. This means that the in-vitro release of X-ray visible and current Implanon® implants is equivalent, irrespective of test conditions covering a wide range of release rates.”*

In his primary CMC Review signed on April 21, 2010, Dr. Hathaway stated:

*“The data and information submitted in the supplement are adequate to support the new formulation of Implanon® Implant. However, a number of labeling elements require revision.”*

The CMC Reviewer, however, focused on the implant, per se, and did not adequately address manufacturing and quality control issues that pertain to the redesigned applicator (inserter). Because of this oversight, a consult for inspection of the manufacturing site(s) for the redesigned applicator was made to the Office of Compliance (OC) for a combined Center for Drug Evaluation and Research (CDER)/Center for Devices and Radiological Health (CDRH) inspection of the manufacturing, assembly, and testing site(s) for the new applicator. The Division of Manufacturing and Product Control (DMPQ), International Compliance Branch (ICB), conducted an inspection of the Nexplanon drug manufacturing facility in the Netherlands on December 6 - 9, 2010. On February 10, 2011, the Office of Compliance issued an “Acceptable” recommendation for the facilities utilized in production and testing of the finished drug product and the insertion device.

In an addendum (signed on April 26, 2011) to his original primary review, Dr. Hathaway stated the following:

*“The chemistry, manufacturing, control and labeling information submitted in this supplement, as amended, is adequate for the proposed changes. Approval is recommended.”*

#### **Division Director’s Comment**

- *I concur with the assessments and final recommendation by Dr. Hathaway that from a CMC perspective this NDA can be approved.*

#### **4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY**

No new preclinical pharmacology/toxicology studies were submitted with this NDA supplement because the new implant is virtually identical to Implanon with the exception of the addition of barium sulfate. Dr. Raheja, the Pharmacology/Toxicology Reviewer, evaluated the safety implications of the addition of 15 mg barium sulfate ((b)(4)/6 v/v) to Implanon. In his safety assessment, Dr. Raheja considered the following information provided by the Applicant:

- Barium sulfate has very low solubility in water.
- X-ray visible products containing barium sulfate such as stents and IUDs are in widespread use and there are no barium sulfate-related safety concerns associated with the use of these products
- Large oral doses (grams) of barium sulfate are used on a routine basis for the purpose of radiologic diagnosis of GI tract disease without causing health problems.
- The daily release from the implant of barium ions is extremely low: (b)(4).
- Barium ions are natural constituents of the human body. Daily dietary and inhalatory exposure of the general population to barium is > 1 mg, and the normal body content of barium is about 22 mg.
- The worst case estimation of total release of barium sulfate particles from the open ends of the implant is (b)(4). These minute amounts will be phagocytosed at the application site by macrophages.

In his Pharmacology/Toxicology reviewer, Dr. Raheja states:

*“Based on the above information, the proposed use of barium sulfate in Radiopaque Etonogestrel Implant is acceptable. The extensive clinical experience with barium sulfate, the very low release of barium ions from barium sulfate containing rods, the pre-clinical studies with barium sulfate containing radiopaque IUD, as well as 6 months of safety data from clinical trial 34528 (including local tolerance), are sufficient to demonstrate the safety of barium sulfate.”*

Dr. Raheja made the following overall recommendations in his Review signed on December 14, 2009:

**Recommendations on approvability:** Pharmacology/toxicology recommends approval of sNDA 21-529 for contraception.

**Recommendations for nonclinical studies:** All preclinical studies have been previously submitted under the original NDA submission dated 9-30-03 and reviewed on 4-28-04. No new toxicology information is required.

Dr. Raheja reviewed final product labeling on May 11, 2011, and found it to be acceptable.

### **Division Director's Comment**

- *I concur with Dr. Raheja's (1) assessment that the addition of barium sulfate to the implant does not pose a safety concern and (2) overall recommendation that the Application be approved.*

## **5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS**

### **5.1 Overview of Study 34528**

The data supporting the efficacy and safety of Nexplanon (other than safety and performance data for the redesigned insertion applicator) were obtained largely from clinical trials that supported the approval of Implanon (the non-radiopaque implant) in the US in 2006. To bridge to these safety and efficacy data for Implanon, the Applicant conducted Study 34528. Study 34528 was a randomized, double-blind, parallel group, multicenter 3-year bioequivalence clinical trial. The study was conducted at a total of 9 clinical sites in Switzerland, France, and the Netherlands. The primary objective of Study 34528 was to demonstrate that Nexplanon was bioequivalent to Implanon. The main secondary objective was to assess the x-ray visibility of the Nexplanon implant following its subdermal insertion.

A total of 108 subjects were treated: 52 subjects received Nexplanon and 56 subjects received Implanon. Blood samples were collected at pre-dose, Days 3, 5, 7, 9, 11, 15, and 22, and Months 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 27, 30, 33, and 36. C<sub>max</sub> values and AUC values for different intervals [AUC (0-6 months), AUC (0-12 months), AUC (0-24 months), AUC (12-24 months), AUC (0-36 months), and AUC (24-36 months)] were calculated for the 2 implants.

### **Division Director's Comment**

- *A cross-over design was not feasible because of the 3-year duration of use for a single implant.*

### **5.2 Pharmacokinetic Findings**

Table 1 provides the Applicant's original pharmacokinetic (PK) values for etonogestrel and statistical analysis based on 103 of the 108 subjects in Study 34528. Five (5) subjects were excluded from the PK analysis submitted in the Application because they took prohibited contraceptive medications during the treatment period or the day before implant insertion.

**Table 1 Results of Bioequivalence Analysis Based on the Dataset Provided in the Original Submission (Study 34528)**

Parameter	Geometric mean [CV <sup>C</sup> ]		Ratio (Test/Reference)	90% Confidence Interval
	Implanon (Reference)	Nexplanon (Test)		
C <sub>max</sub> (pg/mL)	1,021.2 [50.4 %]	1,083.3 [50.4 %]	1.06	0.91-1.23
AUC (0-6 months) <sup>A</sup>	2,210.4 [27.2 %]	2,212.1 [28.4 %]	1.00	0.91-1.10
AUC (0-12 months)	3,594.0 [28.2 %]	3,495.4 [26.5 %]	0.97	0.88-1.07
AUC (0-24 months)	5,873.9 [31.1 %]	5,783.1 [25.1 %]	0.98	0.88-1.10
AUC (12-24 months)	2,355.5 [34.0 %]	2,207.3 [25.3 %]	0.94	0.84-1.05
AUC (0-36 months)	7,487.0 [31.9 %]	7,453.2 [24.9 %]	1.00	0.89-1.11
AUC (24-36 months)	1,652.5 [33.7 %]	1,613.0 [26.9 %]	0.98	0.87-1.10
t <sub>max</sub> (h) <sup>B</sup>	120.2 [29.1–232.8]	141.2 [47.4-334.5]	-	-

<sup>A</sup> Unit for AUC values is pg-month/mL.

<sup>B</sup> Data presented as median [range].

<sup>C</sup> Coefficient of variation.

Source: Table 1 of primary Clinical Pharmacology Review signed on July 23, 2010.

#### Division Director's Comment

- *Based on the Applicant's original analysis shown in Table 1, the 90% confidence intervals (CIs) for the ratios of the Test and Reference Least Square Means (LSMs) for etonogestrel for the parameters of C<sub>max</sub>, AUC (0-6 months), AUC (0-12 months), AUC (0-24 months), AUC (12-24 months), AUC (0-36 months), and AUC (24-36 months) are all within the 0.80 to 1.25 bioequivalence limits. These results, reported by the Applicant in the original Application of July 29, 2009, would indicate that Nexplanon and Implanon are bioequivalent.*

Based on an inspection of the Applicant's analytical site by the FDA's Division of Scientific Investigation (DSI), it was recommended that data from several subjects be excluded from the bioequivalence analysis because of assay quality control issues. In the FDA's final bioequivalence analysis, a total of 13 of the 108 subjects were excluded. In the FDA reanalysis, all AUC parameters [AUC (0-6 months), AUC (0-12 months), AUC (0-24 months), AUC (12-24 months), AUC (0-36 months), and AUC (24-36 months)] continued to meet the criteria for bioequivalence. The C<sub>max</sub> parameter, however, did not meet the criteria for bioequivalence because the upper limit of the 90% CI for the ratio of (C<sub>max</sub> Nexplanon/C<sub>max</sub> Implanon) for etonogestrel (1.264) minimally exceeded the generally accepted upper limit criterion of 1.25. The overall 90% CI for the ratio of (C<sub>max</sub> Nexplanon/C<sub>max</sub> Implanon) for etonogestrel based on the FDA reanalysis was 0.918-1.264.

#### Division Director's Comments

- *In his primary Clinical Pharmacology Review, Dr. Kim stated that although the upper limit of the 90% CI for the ratio of (C<sub>max</sub> Nexplanon/C<sub>max</sub> Implanon) was higher than 1.25, he believed that this finding is not clinically meaningful and that the efficacy and safety of Nexplanon can rely upon the efficacy and safety of Implanon.*
- *The Director of the Division of Clinical Pharmacology 3, Dr. Edward Bashaw, in a comment to the primary Clinical Pharmacology Review, stated "Given that C<sub>max</sub> represents a*

*transient time period for this product and that other measures over the entire "dosing" period meet their statistical tests, it is unlikely that this represents a meaningful difference."*

- *Nexplanon is to be inserted only once every 3 years. Therefore, C<sub>max</sub> values for etonogestrel occur only once every 3 years. There is little or no likelihood that the minimal and brief increase in C<sub>max</sub> values for etonogestrel in women treated with Nexplanon will pose any additional safety risk.*
- *To investigate further the possible clinical significance of the upper limit of the 90% CI minimally exceeding the generally accepted value of 1.25 for bioequivalence (the observed value was 1.264), Dr. van der Vlugt (the primary Clinical Reviewer) carefully reviewed all adverse events that occurred with 60 days after implant insertion in both treatment groups in Study 34528 and in the 301 subjects who received Nexplanon in Study 34530. She did not detect any findings that would suggest that the minimally increased C<sub>max</sub> was associated with any safety concerns.*
- *I concur with the conclusions of both Drs. Kim and van der Vlugt that the marginally increased upper limit of the 90% CI for the C<sub>max</sub> parameter will not pose any additional safety risk to women who use Nexplanon compared to the risk in women who use Implanon.*

### **5.3 Final Recommendation by Clinical Pharmacology Reviewer**

Dr. Hyunjin Kim stated the following in his primary Clinical Pharmacology Review signed on July 23, 2010:

*"The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in sNDA 021529 acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert."*

In an Addendum (signed on May 12, 2011) to his original review, Dr. Kim made the following statement:

*"The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the NDA 021529 acceptable and there are no pending issues."*

#### **Division Director's Comments**

- *I concur with (1) Dr. Kim's overall assessment that the failure of the upper limit of the C<sub>max</sub> PK parameter to meet fully the criteria for bioequivalence is not clinically meaningful and (2) his conclusion that NDA 021529 is acceptable.*
- *Dr. Kim did not recommend any Phase 4 commitments.*

## **6. CLINICAL MICROBIOLOGY**

The final drug product (the implant) and the inserter applicator are sterilized by [REDACTED] (b) (4). In his Product Quality Microbiology Review, signed on October 10, 2009, Dr. Steven Fong stated: "Recommended for approval from a microbiology quality standpoint." He did not request any Phase 4 commitments.

#### **Division Director's Comment**

- *I concur with Dr. Fong's recommendation.*

## 7. CLINICAL/STATISTICAL-EFFICACY

The primary support for the effectiveness of Nexplanon for prevention of pregnancy is provided by the PK findings from bioequivalence Study 34528 (see Section 5.2) via bridging to the original efficacy data that supported approval of Implanon in 2006. In the present Application, supportive efficacy data also were provided in Study 34528 and Study 34530.

### 7.1 Study 34528

An overview of the design and conduct of Study 34528 is presented in Section 5.1. The annual and cumulative Pearl Indices were calculated for the on-treatment pregnancies together with 95% CIs using the ITT population (all treated subjects). The Pearl Index was defined as the number of pregnancies per 100 woman years of exposure. As seen in Table 2, only one pregnancy, which occurred 7 days after removal of the Nexplanon implant, was reported.

**Table 2 Pearl Index Calculations based on Treatment Failures (Unplanned Pregnancies) – All Subjects Who Were Treated with Implanon or Nexplanon**

Treatment	N	Number of Pregnancies	Number of 28-Day Equivalent Cycles	Pearl Index	95% Confidence Interval
<b>Year 1, Year 2, Year 3, and cumulative 3-year results based only on pregnancies that occurred with implant in place</b>					
Year 1 (Day 1-365)					
Implanon	56	0	635.2	0	(0, 7.58)
Radiopaque etonogestrel	52	0	623.9	0	(0, 7.71)
Year 2 (Day 366-730)					
Implanon	42	0	481.1	0	(0, 10.00)
Radiopaque etonogestrel	45	0	542.1	0	(0, 8.88)
Year 3 (Day 731-1095)					
Implanon	33	0	418.8	0	(0, 11.49)
Radiopaque etonogestrel	38	0	446.1	0	(0, 10.79)
<b>Cumulative 3-Year (Day 1-1095)</b>					
<b>Implanon</b>	56	<b>0</b>	1535.1	<b>0</b>	<b>(0, 3.14)</b>
<b>Radiopaque etonogestrel</b>	52	<b>0</b>	1612.0	<b>0</b>	<b>(0, 2.98)</b>
<b>Year 3 and cumulative 3-year results based on pregnancies that occurred with implant in place or within 14 days after implant removal</b>					
Year 3 (Day 731-1095)					
Implanon	33	0	418.8	0	(0, 11.49)
Radiopaque etonogestrel	38	1	446.1	2.92	(0.074, 16.29)
<b>Cumulative 3-Year (Day 1-1095)</b>					
<b>Implanon</b>	56	<b>0</b>	1535.1	<b>0</b>	<b>(0, 3.14)</b>
<b>Radiopaque etonogestrel</b>	52	<b>1</b>	1612.0	<b>0.81</b>	<b>(0.020, 4.51)</b>

Source: Table 12 of the primary Clinical Review signed May 12, 2011.

#### Division Director's Comment

- *This efficacy information supports the bridging pharmacokinetic data. The absence of a pregnancy in 3-year Study 34528 while the implant was in place supports the contraceptive effectiveness of a single Nexplanon implant over 3 years of use.*

## 7.2 Study 34530

Study 34530 was an open-label, non-controlled, multicenter, 3-year trial designed primarily to evaluate the use characteristics of a new insertion device and the instructions for proper insertion of Nexplanon using the new device. A total of 301 healthy women of childbearing potential, aged 18 to 40 years, were treated with Nexplanon at a total of 23 clinical trial centers in Australia, France, Germany, Norway, Sweden, and the UK. In each country, approximately 2 “experienced” and 2 “non-experienced” investigators participated. “Experienced” was defined as an investigator having performing more than 10 Implanon insertions within the past year and “non-experienced” was defined as an investigator having performing 10 or less Implanon insertions within the past year. Secondary objectives of the clinical trial included: (1) to identify any complications/problems associated with removal of the Nexplanon implant, (2) to assess the x-ray visibility of the Nexplanon implant, and (3) to assess overall contraceptive efficacy and safety of Nexplanon.

### Division Director's Comments

- *In the Application, as originally submitted in July 2009, only information for the primary objective (assessment of the new insertion device) and the secondary objective of x-ray visibility of the implant at insertion were provided. This was in accord with the pre-NDA agreement between the Applicant and DRUP.*
- *During the review of this Application, the clinical component of Study 34530 was completed, thereby allowing DRUP to obtain additional safety and efficacy data. This additional information included:*
  - *Data on all unplanned pregnancies through at least 2 years after insertion of the implant.*
  - *Implant removal data from all removals.*
  - *A safety update that included all serious adverse events and premature terminations through the completion of the study.*

The Applicant reported in their submission of April 8, 2010, that as of March 12, 2010, no unplanned pregnancies had been reported in subjects enrolled in Study 34530. The annual and cumulative Pearl Indices for all on-treatment pregnancies, together with 95% CIs, for all subjects treated with Nexplanon in Study 34530 are shown in Table 3

**Table 3 Pearl Index Calculations Based on Treatment Failures (Unplanned Pregnancies) – All Subjects Who Were Treated with Nexplanon (Study 34530)**

Parameter	Year 1 (Day 1-365)	Year 2 (Day 366-730)	Cumulative (Day 1-730)
Number of subjects	301	243	301
On-treatment pregnancies	0	0	0
Women Years of exposure	276.753	211.431	488.183
Number of 28-day equivalent cycles	3,610.143	2,758.036	6,368.179
<b>Pearl Index estimates</b>	<b>0</b>	<b>0</b>	<b>0</b>
Lower limit of 95% Confidence Interval	0	0	0
Upper limit of 95% Confidence Interval	1.333	1.745	0.756

Source: Table 21 of the primary Clinical Review signed May 12, 2011.

### Division Director's Comment

- *The Applicant reported in their submission of April 8, 2010, that as of March 12, 2010, no unplanned pregnancies had been reported in subjects enrolled in Study 34530. Therefore, the Pearl Index for each of Years 1 and 2, as well as the cumulative Pearl Index was "0." These findings are consistent with a highly effective contraceptive.*

### 7.3 Overall Assessment of Efficacy

Based on the findings from bioequivalence Study 34528 and supportive efficacy data from Study 34530, it is anticipated that the efficacy of Nexplanon will be comparable to that of Implanon. The clinical trial data that supported the approval of Implanon in 2006 indicated that Implanon is a very effective contraceptive. In these studies with Implanon, 6 pregnancies during the equivalent of 20,648 28-day cycles of use over 3 years were reported. Two pregnancies occurred in each of years 1, 2, and 3. Each conception likely occurred shortly before or within 2 weeks after removal of the non-radiopaque etonogestrel implant. Considering these 6 pregnancies as treatment failures, the cumulative Pearl Index was 0.38 pregnancies per 100 women-years of use. Among women who were treated with Nexplanon for up to 3 years in Study 34528 and Study 34530, no pregnancies were reported to have occurred while the implant was in place. One pregnancy, which had an estimated date of conception 7 days after removal of Nexplanon, was reported in Study 34530.

## 8. SAFETY

### 8.1 Overview of Safety Database for Nexplanon and the New Insertion Device

The data to support the safety of the new radiopaque implant (Nexplanon) is derived primarily by bridging to the clinical trial database for Implanon. Such bridging is supported by the findings from 3-year bioequivalence Study 34528 in which Nexplanon was found to be (1) bioequivalent to Implanon in terms of the PK parameter AUC over all time intervals studied and (2) minimally above the upper limit for bioequivalence for the parameter of C<sub>max</sub> (see Section 5.2 for full information). Both the primary Clinical Pharmacology Reviewer and the primary Clinical Reviewer did not believe that the marginally increased upper limit of the 90% CI for the C<sub>max</sub> parameter would pose any additional safety risk to women who used Nexplanon compared to the risk in women who used Implanon (see Section 5.2, Division Director's Comments for a full discussion).

Additional data in support of the safety of the Nexplanon implant were obtained from Studies 34528 and 34530, in which 353 women were treated with Nexplanon for up to 3 years. Study 34530 also provided implant insertion and/or removal data from 301 women treated with Nexplanon, which was inserted using the new insertion device.

### Division Director's Comments

- *Although the Applicant has not yet submitted a Final Report for Study 34530, Dr. van der Vlugt reviewed the most critical safety data from Study 34530. These data were provided during the review cycle at the request of DRUP. These data included implant insertion and removal data from all subjects, all reported serious adverse events, and all reported adverse events leading to premature termination.*
- *The Applicant has provided adequate safety data to assess the likely safety profile of the Nexplanon implant inserted with the new insertion device. These data are also adequate to*

*support approval of this Application based on (1) the bioequivalence findings from Study 34528 that permit bridging to the well established safety profile for Implanon (2) implant insertion data from Study 34530 using the new applicator, (3) implant removal data from Study 34530, and (4) general safety data from Study 34528 and Study 34530.*

## 8.2 Subject Disposition

The disposition of subjects in Study 34528 and Study 34530 is summarized in Table 4.

**Table 4 Disposition of Subjects in Study 34528 and Study 34530**

Reason for Termination	Study 34528				Study 34530	
	Implanon		Nexplanon		Nexplanon	
	N	%	N	%	N	%
Treated subjects	56	100.0	52	100.0	301	100.0
Completed the study	32	57.1	32	61.5	156	51.8
Discontinued prematurely	24	42.9	20	38.5	145	48.2
Reason for discontinuation						
Bleeding irregularities	8	14.3	10	19.2	58	19.3
Adverse Event (non-bleeding)	9	16.1	5	9.6	46	15.3
Other reasons	6	10.7	4	7.7	37	12.3
Lost to follow-up	1	1.8	1	1.9	4	1.3

Source: Modified from Tables 7 and 8 of Primary Clinical Review signed May 12, 2011, and the Applicant's submission of April 25, 2011.

### Division Director's Comments

- *Premature termination rates of 38.5 % and 48.2% in Nexplanon-treated subjects are within the expected range for a 3-year contraceptive clinical trial. In the US Phase 3 clinical trial that supported the approval of Implanon, the percentage of subjects treated with Implanon who terminated prematurely was 48.8%, virtually identical to that for Study 34530.*
- *The percentage of Nexplanon treated subjects who terminated prematurely because of an adverse event or bleeding irregularities in Study 34530 was 34.6 % compared to 36.1 % of Implanon treated subjects who terminated for similar reasons in the US trial that supported approval of Implanon.*

## 8.3 Deaths and Non-fatal Serious Adverse Events

### 8.3.1 Deaths

No deaths were reported in either Study 34528 or Study 34530.

### 8.3.2 Nonfatal Serious Adverse Events

#### Study 34528

Ten (10) subjects reported a total of 12 serious adverse events (SAEs) in Study 34528 (6 subjects in the Implanon treatment group and 4 subjects in the Nexplanon treatment group). Of these 12 SAEs, only 3 were of concern: a single case of deep vein thrombosis (DVT) in each of the Implanon and Nexplanon treatment groups and a single case of peripheral arterial thrombosis (left femoral artery) in a Nexplanon-treated subject.

### Division Director's Comments

- *Three thrombotic events in a clinical trial in which only 108 subjects were treated with either Implanon (n=56) or Nexplanon (n=52) would normally raise significant concerns about the thrombotic risk of the drug product. Nevertheless, I do not believe that these events represent a true safety signal for either Implanon or Nexplanon, but rather a chance cluster of events. The basis for my assessment is provided in the following discussion:*
  - *Each of the 3 women had preexisting risk factors for a thrombotic event. Two of the women smoked cigarettes (approximately one pack per day). One of the smokers also was overweight and had a past history of a pulmonary embolus. The third woman was reported to have a protein C deficiency and a family history of thrombosis.*
  - *No thrombotic events were reported in Study 34530 in which 301 women were treated with Nexplanon for up to 3 years.*
  - *In the Phase 3 safety data that supported approval of Implanon in 2006, there was only one case of a DVT among 942 women that were treated with Implanon for up to 3 years.*
  - *Review of the FDA's Adverse Event Reporting System (AERS) database did not identify a signal for increase thrombotic events for users of Implanon, beyond that associated with other hormonal contraceptive products (see Section 8.7).*

### Study 34530

Seventeen (17) subjects reported a total of 19 SAEs in Study 34530. Although the investigators considered all of the SAEs as not related (n=13) or unlikely to be related (n=6), several were events that I believe might be related to treatment with Nexplanon. These included 2 cases of depression and one case each of attempted suicide and breast cancer.

### Division Director's Comments

- *Depression and breast cancer are both listed in the Warnings and Precautions section of to-be-approved Nexplanon labeling as well as in labeling for other progestin-only contraceptives.*
- *No thrombotic adverse events were reported in Study 34530.*
- *The reported SAEs do not raise any concerns about the safety profile of Nexplanon beyond those for other hormonal contraceptives.*

## 8.4 Radiographic Localization of Nexplanon

An objective of both Study 34528 and Study 34530 was to confirm that the addition of barium sulfate to the implant would allow localization of the implant by conventional x-ray techniques.

### Study 34528

Fifty (50) of the 52 radiopaque Nexplanon implants were visible on x-ray imaging immediately after their insertion. For the 2 subjects in which the implants were not clearly visible, the Applicant reported that the responsible radiologists stated that the X-rays were “technically not performed correctly.” For both of these latter subjects, their implants were clearly visible by x-ray prior to removal.

### Study 34530

An x-ray was performed for 61 subjects after implant insertion. All implants were clearly visible.

### **Division Director's Comment**

- *The ability to localize the Nexplanon implant using conventional x-ray techniques will be extremely helpful to facilitate removal of the implant in situations where the precise location of the implant cannot be identified via palpation (e.g., following inadvertent deep insertions or significant weight gain by the patient).*

## **8.5 Assessment of Performance of the New Inserter Device**

### **8.5.1 Investigator Assessment of the New Insertion Device in Study 34530**

Investigators completed a “User Satisfaction Questionnaire” that was designed to evaluate the ease of use and functionality of the new insertion device. The Questionnaire was completed by each investigator after the 4<sup>th</sup>, 8<sup>th</sup>, and 12<sup>th</sup> insertion. According to the primary Clinical Reviewer’s assessment of the information collected by the Questionnaire, the majority of investigators were either “very satisfied” or “satisfied” with the redesigned applicator by their 4<sup>th</sup> insertion. After 12 insertions, 16 of 23 investigators (69.6%) were “very satisfied” and 7 investigators (30.4%) were “satisfied” with the redesigned applicator. The reported findings also indicated that the majority of insertions were considered to be “easy” insertions by the investigators (295 of the 301 [98%] of the insertions).

### **Division Director's Comments**

- *All investigators participating in Study 34530 had previously performed Implanon insertions with the currently approved applicator. The assessment of the functionality and ease of use of the new applicator might have been less favorable had the study been conducted with investigators who had no prior experience with Implanon insertions.*
- *The new applicator appears to represent a significant improvement over the currently approved applicator that is used in the US for insertion of Implanon.*

### **8.5.2 CDRH Consultation**

The Center for Devices and Radiological Health (CDRH), Office of Device Evaluation, General Hospital Devices Branch (GHDB) was consulted to assist in evaluating the acceptability of the new implant insertion device (applicator). During the review of the new inserter by CDRH, there were several interactions and meetings between CDRH and DRUP and several information requests to the Applicant. Details of these interactions and the specific requests from CDRH and the Applicant’s responses to CDRH’s requests are well summarized by Dr. van der Vlugt in her primary Clinical Review/CDTL memo (see Section 6.1.4.3 of her Review).

In the final consult response from CDRH, signed by Nikhil Thakur, Combination Products Team Leader, General Hospital Devices Branch, the following information was conveyed to DRUP (referred to as CDER in the consult response):

- CDRH stated that they had indicated to CDER that the new insertion device would not totally prevent deep insertions from occurring. CDRH also stated that “based on their discussions with CDER, we defer to the CDER clinical team with regard to deep insertions.”
- Regarding “Human Factors deficiencies”: “Based on our discussion with CDER, it appears that the 2008 clinical study provided data that demonstrated that the Implanon device could be successfully used by multiple users in actual insertions of the Implanon rod into a patient’s arm. ... CDRH defers to CDER with regard to the clinical significance of deep

insertions.” (Note: The consult response incorrectly refers to the new insertion device for Nexplanon as the “Implanon device” and incorrectly refers to insertions of the “Implanon rod” instead of the “Nexplanon rod.”)

#### **Division Director's Comments**

- *Dr. van der Vlugt and I believe that deep insertions of the Nexplanon implant, which may lead to difficulties in locating and/or removing the implant, cannot be entirely eliminated. The addition of barium sulfate to the implant, however, will facilitate localization. Although yet to be demonstrated, the design of the new insertion device may reduce the likelihood of inadvertent deep insertions.*
- *The Applicant will sponsor company training for insertion and removal of Nexplanon as is currently being done for Implanon. The Applicant also intends to provide Nexplanon only to healthcare providers who have taken company sponsored training.*
- *To monitor the performance of the new insertion device, the Applicant will conduct as a post marketing commitment a descriptive observational cohort study of insertion-, localization-, and removal-related events associated with Nexplanon use. The study will include a minimum of 5,000 patients who receive Nexplanon.*

#### **8.6 Implant Removal-Related Adverse Events**

Investigators reported some degree of difficulty in 16 of 296 removals (5.4%) in Study 34530. Fourteen (14) of the 16 “difficult” cases were associated with the development of fibrotic tissue around the implant. Removal times for these cases ranged from 48 seconds to 8 minutes and 22 seconds.

#### **Division Director's Comment**

- *The small number of “difficult” removals is not unexpected and does not raise safety concerns regarding either the radiopaque Nexplanon implant, per se, or the redesigned insertion applicator.*

#### **8.7 Review of Postmarketing Safety Data for Implanon**

The FDA’s Division of Pharmacovigilance (DPV) II was requested to review the FDA’s AERS database with a focus on cases of death, thrombotic/thromboembolic events, stroke, and myocardial infarction in users of Implanon. A search of the AERS database by Mark Miller, PharmD, Safety Evaluator in DPV II on March 9, 2010, for all adverse events likely to fall within these categories retrieved 3 cases of fatality, 14 non-stroke cases of arterial or venous thrombosis/thromboembolism, 11 cases involving stroke-related events, and 4 cases of myocardial infarction.

Fatalities. Two of the 3 cases were non-US cases. Only one of the 2 non-US cases was possibly related to the use of Implanon (a fatal pulmonary embolus). Information for the single US cases was sparse, and the cause of death in this case was unclear based on available information.

Thrombotic/thromboembolic events. Among these 14 events were: 4 cases of pulmonary embolus, 9 cases of DVT, and one case of an arterial thromboembolism. According to the Safety Evaluator, all 14 cases had possible risk factors for a thrombotic event.

Stroke-related events: Among these 11 events were: 5 cases of possible stroke, 3 cases of transient ischemic attack, and one case each of a cerebral embolism, an occlusion of a cerebral

artery, and a carotid vessel thrombosis. According to the Safety Evaluator, 9 of the 11 cases included possible risk factors for stroke or thromboembolism.

Myocardial infarction: According to the Safety Evaluator, all 4 cases included possible risk factors.

### **Division Director's Comments**

- *According to the DPV II review, the Applicant reported that as of January 16, 2010, a total of (b) (4) Implanon rods had been distributed in the US since the US launch of the product in 2006. Based on the number of reported cases and the number of implants distributed in the US, the findings do not raise any new concerns about the safety of Implanon and the likely safety of Nexplanon.*
- *These thrombotic/thromboembolic events are labeled events currently described in the Warnings and Precautions section of Implanon labeling and are also included in to-be-approved labeling for Nexplanon. Based in part on these findings, the following statement will be included in the Warnings And Precautions section of to-be-approved labeling for Nexplanon:*  
*“There have been postmarketing reports of serious arterial and venous thromboembolic events, including cases of pulmonary emboli (some fatal), deep vein thrombosis, myocardial infarction, and strokes, in women using the non-radiopaque etonogestrel implant.”*

### **8.8 Overall Assessment of Safety**

It is anticipated, based on the findings from bioequivalence Study 34528, that the safety profile for Nexplanon, other than possibly for adverse events associated with insertion and removal of the implant, will be comparable to that of Implanon. Based on the clinical trial data that supported the approval of Implanon and DPV II's review of postmarketing safety reports for Implanon in the AERS database, the safety profile for Implanon is acceptable and does not raise any concerns, with one possible exception, beyond those associated with hormonal contraceptives in general. The exception is insertion- and removal-related adverse events. The Applicant has provided safety data, including insertion and/or removal data, from 3-year Study 34530 in which 301 subjects were treated with Nexplanon using the redesigned insertion applicator. These data did not raise any new concerns beyond those associated with the use of Implanon. Furthermore, it is anticipated that insertion- and removal-related adverse events will be reduced with the new insertion applicator. In summary, it is expected that the overall safety profile for Nexplanon inserted with the new insertion device will be acceptable.

### **9. ADVISORY COMMITTEE MEETING**

This NDA supplement was not presented to an advisory committee because no safety or efficacy issues were identified during the review that warranted discussion by an advisory committee.

### **10. PEDIATRICS**

A pediatric assessment of the safety and effectiveness of the radiopaque implant and new insertion applicator was not required because the Application did not involve a new active ingredient, a new indication, a new dosage form, a new dosing regimen, or a new route of administration.

## 11. OTHER RELEVANT REGULATORY ISSUES

### Certification of Financial Interests

The primary Clinical Reviewer stated the following in her review signed on May 12, 2011:

“Overall, no data integrity issues are identified in the financial disclosure information provided in the application.”

### Inspections by the Division of Scientific Investigation (DSI)

For Study 34528, the Clinical Pharmacology Reviewer requested that DSI inspect one of the clinical sites (Dinox BV, Netherlands) and the analytical site (MSD, Netherlands) that performed the etonogestrel plasma measurements.

No inspections were requested or conducted for Study 34530.

### Division Director's Comments

- *Deficiencies were identified at the clinical and analytical sites that were inspected for Study 34528.*
- *The deficiencies identified at the clinical site (i.e., failure to retain reserve samples of the study drug product and failure to use the most current version of the Informed Consent Form for some subjects) were not believed to impact on the integrity of the clinical data.*
- *The deficiencies identified at the analytical site were either (1) adequately addressed and resolved or (2) resulted in exclusion of analytical data for some subjects (see Section 5.2 for further details). In his Clinical Pharmacology Review, Dr. Kim made the following statement: “Overall, the sponsor’s response to the Form 483s for both clinical and analytical sites of the BE study addressed all the findings from the DSI inspection. Therefore, the sponsor’s data is valid to be reviewed....”*

## 12. LABELING

The Applicant initially proposed the proprietary name of “(b) (4).” This name was found to be unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA). The Applicant eventually proposed the name “NEXPLANON,” which DMEPA found to be acceptable.

Physician labeling was submitted in the format prescribed by the Physician Labeling Rule (PLR). Consultative reviews of proposed labeling were provided by the Division of Drug Marketing, Advertising and Communication (DDMAC), the Study Endpoints and Label Development (SEALD) team, and the Division of Risk Management (DRISK). Recommendations from these consultative reviews were incorporated into labeling as appropriate.

The content of labeling is based to a large extent on that for the approved product Implanon. It is anticipated, based on the findings from bioequivalence Study 34528, that the efficacy and safety profiles for Nexplanon, other than possibly for adverse events associated with insertion and removal of the implant, will be comparable to those for Implanon. Therefore, the clinical trial safety and efficacy data, as well as postmarketing safety data, in to-be-approved Nexplanon labeling are based primarily on information obtained from women treated with Implanon.

Information that has been revised or added to Nexplanon labeling includes:

- An updated description of the composition of the implant that states that the addition of barium sulfate allows the implant to be visualized by 2 dimensional x-ray.
- A full description of the proper use of the new inserter applicator.
- New information on insertion and removal events based on Nexplanon data using the new applicator.
- Three-year pharmacokinetic data for Nexplanon.
- Updated postmarketing safety data based on safety reports from women using Implanon.

After the final report for Study 34530 is submitted and reviewed, additional data, obtained with Nexplanon, may be added to product labeling for Nexplanon.

Carton labeling submitted on March 17, 2011, by the Applicant was found to be acceptable by DMEPA and the primary CMC Reviewer.

Physician and patient labeling submitted by the Applicant on May 9, 2011, was found to be acceptable by all review disciplines.

### **13. DECISION/ACTION/RISK BENEFIT ASSESSMENT**

#### **13.1 Regulatory Action**

This Application (NDA 021529/S007) will be approved for the use of (1) the radiopaque Nexplanon (etonogestrel) implant for the indication of “use by women to prevent pregnancy” and (2) the new device for insertion of the implant. The Applicant has provided sufficient information to allow me to conclude that Nexplanon will be a safe and effective hormonal contraceptive when used in accordance with to-be-approved labeling.

#### **13.2 Risk/Benefit Assessment**

It is anticipated, based on the findings from bioequivalence Study 34528, that the efficacy and safety profiles for Nexplanon, other than possibly for adverse events associated with insertion and removal of the implant, will be comparable to those for Implanon.

The clinical trial data that supported the approval of Implanon in 2006 indicated that Implanon is a very effective contraceptive. In these studies with Implanon, 6 pregnancies during the equivalent of 20,648 28-day cycles of use over 3 years were reported. Two pregnancies occurred in each of years 1, 2, and 3. Each conception likely occurred shortly before or within 2 weeks after removal of the non-radiopaque etonogestrel implant. Considering these 6 pregnancies as treatment failures, the cumulative Pearl Index was 0.38 pregnancies per 100 women-years of use. Among women who were treated with Nexplanon for up to 3 years in Study 34528 and Study 34530, no pregnancies were reported to have occurred while the implant was in place. One pregnancy, which had an estimated date of conception 7 days after removal of Nexplanon, was reported in Study 34530.

Based on the clinical trial data that supported the approval of Implanon and DPV II's review of postmarketing safety reports for Implanon in the AERS database, the safety profile for Implanon is acceptable and does not raise any concerns, with one possible exception, beyond those associated with hormonal contraceptives in general. The exception is insertion- and removal-related adverse events. The Applicant has provided safety data, including insertion

and/or removal data, from 3-year Study 34530, in which 301 subjects were treated with Nexplanon using the redesigned insertion applicator. These data did not raise any new concerns beyond those associated with the use of Implanon. Furthermore, it is anticipated that insertion- and removal-related adverse events will be reduced with the new insertion applicator.

In summary, it is expected that Nexplanon will be a very effective contraceptive with an acceptable safety profile.

### **13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)**

No postmarketing risk management activities beyond labeling and the Applicant's proposed risk management program are recommended. The Applicant's proposed risk management plan includes the following elements:

- The Applicant will continue the training program currently in place for Implanon with some modifications. Training will include both in person training for healthcare providers who have not had experience with Implanon insertions and removals and web based training for healthcare providers who have had experience with Implanon insertions and removals.
- The Applicant will also extend to Nexplanon their current policy of providing Implanon only to healthcare providers who have received company sponsored training regarding insertion and removal of the implant.
- The Applicant will conduct, in addition to standard pharmacovigilance monitoring, enhanced monitoring for Nexplanon insertion-, localization-, and removal-related events as is currently being done for Implanon. Reports of these events will be submitted quarterly for at least 3 years following the launch of Nexplanon in the US.

### **13.4 Recommendations for other Postmarketing Requirements and Commitments**

The Applicant has agreed to the following postmarketing commitment (PMC):

1754-1: A descriptive observational cohort study of insertion-, localization-, and removal-related events associated with Nexplanon use. The proposed protocol should include details on the study design, methodology, and analysis plan. This study will need to include a minimum of 5,000 patients who receive Nexplanon. Interim status reports will be submitted to the NDA at least annually.

The timetable submitted by the Applicant on May 4, 2011, states that the study will be conducted according to the following schedule:

Final Protocol Submission:	July 2011
Study Completion:	October 2017
Final Report Submission:	March 2018

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/s/  
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SCOTT E MONROE  
05/13/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021529Orig1s007**

**MEDICAL REVIEW(S)**

**CLINICAL REVIEW/CROSS DISCIPLINE TEAM LEADER  
REVIEW**

Application Type	Supplemental NDA
Application Number(s)	21-529/SES-007
Priority or Standard	Standard
Submit Date(s)	July 29, 2009
Received Date(s)	July 30, 2009
PDUFA Goal Date	August 30, 2010 (with 3-month extension)
Division / Office	Division of Reproductive and Urologic Products (DRUP)/Office of Drug Evaluation III (ODE III)
Reviewer Name(s)	Theresa H. van der Vlugt, M.D.
Review Completion Date	May 12, 2011
Established Name	Etonogestrel implant (Radiopaque)
Trade Name	NEXPLANON
Therapeutic Class	Hormonal Contraceptive
Applicant	Organon USA, Inc.
Formulation(s)	Implant (subdermal)
Dosing Regimen	One Implant Every Three Years
Indication(s)	Prevention of Pregnancy
Intended Population(s)	Reproductive Age Women

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>8</b>
1.1	Recommendation on Regulatory Action .....	8
1.2	Risk Benefit Assessment.....	11
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .	11
1.4	Recommendations for Postmarket Requirements and Commitments .....	12
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>15</b>
2.1	Product Information .....	15
2.2	Tables of Currently Available Treatments for Proposed Indications .....	18
2.3	Availability of Proposed Active Ingredient in the United States .....	18
2.4	Important Safety Issues With Consideration to Related Drugs.....	19
2.5	Summary of Presubmission Regulatory Activity Related to Submission .....	19
2.6	Other Relevant Background Information .....	21
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>25</b>
3.1	Submission Quality and Integrity .....	25
3.2	Compliance with Good Clinical Practices .....	29
3.3	Financial Disclosures.....	30
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>30</b>
4.1	Chemistry Manufacturing and Controls .....	30
4.2	Clinical Microbiology.....	33
4.3	Preclinical Pharmacology/Toxicology .....	34
4.4	Clinical Pharmacology .....	36
4.4.1	Mechanism of Action.....	36
4.4.2	Pharmacodynamics.....	36
4.4.3	Pharmacokinetics.....	36
<b>5</b>	<b>SOURCES OF CLINICAL DATA.....</b>	<b>44</b>
5.1	Tables of Studies/Clinical Trials .....	44
5.2	Review Strategy .....	44
5.3	Discussion of Individual Studies/Clinical Trials.....	45
<b>6</b>	<b>REVIEW OF EFFICACY .....</b>	<b>74</b>
	Efficacy Summary.....	74
6.1	Indication .....	74
6.1.1	Methods .....	74
6.1.2	Demographics.....	76
6.1.3	Subject Disposition.....	79
6.1.4	Analysis of Primary Endpoint(s).....	84
6.1.5	Analysis of Secondary Endpoint(s) .....	104

6.1.6	Other Endpoints .....	107
6.1.7	Subpopulations .....	111
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations ..	111
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	111
6.1.10	Additional Efficacy Issues/Analyses .....	111
<b>7</b>	<b>REVIEW OF SAFETY.....</b>	<b>112</b>
	Safety Summary .....	112
7.1	Methods.....	112
7.1.1	Studies/Clinical Trials Used to Evaluate Safety .....	112
7.1.2	Categorization of Adverse Events .....	115
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	116
7.2	Adequacy of Safety Assessments .....	117
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations .....	117
7.2.2	Explorations for Dose Response.....	119
7.2.3	Special Animal and/or In Vitro Testing .....	120
7.2.4	Routine Clinical Testing .....	121
7.2.5	Metabolic, Clearance, and Interaction Workup .....	121
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	121
7.3	Major Safety Results .....	121
7.3.1	Deaths.....	121
7.3.2	Nonfatal Serious Adverse Events .....	121
7.3.3	Dropouts and/or Discontinuations .....	127
7.3.4	Significant Adverse Events .....	131
7.3.5	Submission Specific Primary Safety Concerns .....	131
7.4	Supportive Safety Results .....	138
7.4.1	Common Adverse Events .....	138
7.4.2	Laboratory Findings .....	151
7.4.3	Vital Signs .....	151
7.4.4	Electrocardiograms (ECGs) .....	152
7.4.5	Special Safety Studies/Clinical Trials .....	152
7.4.6	Immunogenicity .....	152
7.5	Other Safety Explorations.....	152
7.5.1	Dose Dependency for Adverse Events .....	152
7.5.2	Time Dependency for Adverse Events.....	152
7.5.3	Drug-Demographic Interactions .....	153
7.5.4	Drug-Disease Interactions.....	153
7.5.5	Drug-Drug Interactions.....	153
7.6	Additional Safety Evaluations .....	153
7.6.1	Human Carcinogenicity .....	153
7.6.2	Human Reproduction and Pregnancy Data.....	153
7.6.3	Pediatrics and Assessment of Effects on Growth .....	153

7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	154
7.7	Additional Submissions / Safety Issues .....	154
<b>8</b>	<b>POSTMARKET EXPERIENCE.....</b>	<b>162</b>
<b>9</b>	<b>APPENDICES .....</b>	<b>177</b>
9.1	Literature Review/References .....	177
9.2	Labeling Recommendations .....	177
9.3	Advisory Committee Meeting.....	178

## Table of Tables

Table 1	Results of Bioequivalence Testing Using the Dataset Submitted in the Application (All-Subjects-Pharmacokinetically-Evaluable Group); Study 34528	37
Table 2	Applicant’s Results of Bioequivalence Testing Using the “Adapted” Dataset (All-Subjects-Pharmacokinetically-Evaluable Group); Study 34528	41
Table 3	List of Clinical Studies	44
Table 4	Composition of the IMPLANON® Implant and the NEXPLANON® Implant	46
Table 5	Demographics for Study 34528, All-Subjects-Treated Group	77
Table 6	Demographics for Study 345230, All-Subjects-Treated Group	78
Table 7	Disposition of Subjects in Study 34528	79
Table 8	Primary Reasons for Discontinuation, All-Subjects-Treated Group in Study 34528	80
Table 9	Primary Reasons for Discontinuation, All-Subjects-Treated Group in Study 34530 <sup>a</sup>	82
Table 10	Single Most Important Reason for Discontinuation (End of Trial Form), All-Subjects-Treated Group in Study 34530 <sup>a</sup>	83
Table 11	Overall Pearl Index With 95% Confidence Intervals in Study 34528, All-Subjects-Treated Group	85
Table 12	Pearl Index Calculations of Treatment Failure Rates for On-Treatment Pregnancies Occurring Before Implant Removal AND Occurring Before and Within 14 Days after Implant Removal: All Cycles for ITT Population – All Subjects	86
Table 13	Frequency Distribution (%) of the User Satisfaction Questionnaire by Domain and Assessment, Applicator User Group (N = 23)	88
Table 14	Frequency Distribution of the User Satisfaction Questionnaire Based on Investigator Level of Experience (More Than 10 Insertions Within the Past Year), Applicator User Group (N = 11)	90
Table 15	Frequency Distribution of the User Satisfaction Questionnaire Based on Investigator Level of Experience (10 or Less Insertions Within the Past Year), Applicator User Group (N = 12)	91
Table 16	NEXPLANON® Insertion Time (in Seconds), Applicator User Group (N = 23)	95
Table 17	Incidence of X-Ray Visibility and the 95% Confidence Interval for the NEXPLANON® Implant in Study 34528, All-Subjects-Treated Group	105
Table 18	Palpability of Study Implant in Study 34528, All-Subjects-Treated Group	106
Table 19	Implant Insertion Time (in Minutes) in Study 34528, All-Subjects-Treated Group	107
Table 20	Year-One Pearl Index and the Two-Sided 85% Confidence Interval for Study 34530, All-Subjects-Treated Group	109
Table 21	Year One and Year Two Pearl Indices and Two-Sided 95% Confidence Intervals in Study 34530, All-Subjects-Treated Group	110

Table 22	Pearl Index Calculations of Treatment Failure Rates for On-Treatment Pregnancies Occurring During the First Two Years of 3-Year Study 34530: All Cycles for ITT Population – Subjects 18-35 Years of Age AND Subjects Over 35 Years of Age .....	110
Table 23	Extent of Exposure: Summary of Total Exposure in Study 34528, All-Subjects-Treated Group .....	117
Table 24	Extent of Exposure: Summary of Treatment Duration in Study 34528, All-Subjects-Treated Group.....	118
Table 25	Listing of Subjects With Serious Adverse Events in Study 34530.....	124
Table 26	Number of Subjects With at Least One In-Treatment Serious Adverse Events Starting Within 365 Days of Implant Insertion in Study 34530, All-Subjects-Treated Group .....	126
Table 27	Primary Reason for Discontinuation in Study 34528, All-Subjects-Treated Group.....	128
Table 28	Number (%) of Subject Who Discontinued Study 34530 by Reason for Discontinuation, All-Subjects-Treated Group.....	129
Table 29	Number (%) of Subjects Who Discontinued from Study 34530 Due to In-Treatment Adverse Events Within 365 Day of Implant Insertion by MedDRA System-Organ Class, Preferred Term and Relationship to Study Product, All-Subjects-Treated Group.....	130
Table 30	Number (%) of Subjects With at Least One Adverse Event at Insertion	134
Table 31	Overview of Subjects With at Least One Adverse Event in Study 34528, All-Subject-Treated Group .....	138
Table 32	Number (%) of Subjects Reporting Treatment-Emergent Adverse Events $\geq$ 5% in Any Treatment Group in Study 34528, All-Subjects-Treated Group.....	139
Table 33	Number (%) of Subjects with at least One Adverse Event in Ongoing Study 34530, All-Subjects-Treated Group.....	142
Table 34	Number (%) of Subjects with Treatment-Emergent Adverse Events $\geq$ 5% in Study 34530, All-Subjects-Treated Group .....	143
Table 35	Number (%) of Subjects with Treatment-Emergent Adverse Events $>$ 1% in Study 34530, All-Subjects-Treated Group (One-year Verified Data).....	145
Table 36	Status at Site of the Radiopaque Etonogestrel Implant, All-Subjects-Treated Group in Study 34530 .....	148
Table 37	Number of Cases and Insertion and/or Removal Related Events per Number of Implants Distributed in the United States versus Other Countries in the 16 <sup>th</sup> Quarter.....	168
Table 38	Cumulative Number of Cases and Insertion and/or Removal Related Events Spontaneously Reported per Number of Implants Distributed in the United States versus Other Countries .....	168

## Table of Figures

Figure 1	Arithmetic mean ( $\pm$ SD) etonogestrel concentration-time profiles following implantation of IMPLANON® and NEXPLANON® over 36 months; Study 34528.....	38
Figure 2	Arithmetic mean ( $\pm$ SD) etonogestrel concentration-time profiles following implantation of IMPLANON® and NEXPLANON® over first 6 months; Study 34528.....	39
Figure 3	Schematic Drawing of the Current Approved IMPLANON® Applicator.....	53
Figure 4	Redesigned Next Generation Applicator (NGA).....	59

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

This reviewer recommends approval of radiopaque NEXPLANON® (etonogestrel implant) containing 68 mg of etonogestrel and 15 mg of barium sulfate and the redesigned applicator for insertion for use by women to prevent pregnancy. A single radiopaque NEXPLANON® implant is inserted subdermally and may be used continuously (remain in place) for up to 3 years. Recommended approval is based on:

1. The reanalysis of bioequivalence data in completed 3-year bioequivalence Study 34528.
2. The interim report in the supplemental application for the ongoing 3-year applicator use Study 34530 reporting results of 301 radiopaque NEXPLANON® implant insertions using the redesigned applicator.
3. Additional safety data requested for Study 34528 of all adverse events, other than insertion-related, with a start date within the first 60 days after implant insertion.
4. Additional validated safety data requested for the initial 12 months of ongoing 3-year Study 34530, and an additional focused listing of all adverse events by subjects (other than insertion-related) with an onset date within 60 days of the NEXPLANON® implant insertion.
5. Additional validated removal data requested for the now completed 3-year applicator use Study 34530.
6. Additional safety data requested for the now completed 3-year Study 34530 of all premature terminations for any reason, and all serious adverse events, other than insertion-related or removal-related.
7. The overall assessment by the Center for Devices and Radiological Health (CDRH) that the redesigned applicator is acceptable.
8. No outstanding CMC or nonclinical pharmacology/toxicology issues.

In the Supplemental New Drug Application (sNDA 21-529/SES-007), the Applicant, Organon USA Inc. (a subsidiary of Merck & Co., Inc., and formerly a subsidiary of Schering-Plough Corporation), reported that the radiopaque NEXPLANON® implant was bioequivalent to the currently approved non-radiopaque IMPLANON® [(etonogestrel implant) 68 mg approved in 2006 for women for the prevention of pregnancy], for both peak etonogestrel concentration and total etonogestrel exposure ( $C_{max}$ ,  $AUC_{0-6months}$ ,  $AUC_{0-24months}$ , and  $AUC_{0-36months}$ ).

Following the FDA's Division of Scientific Investigations (DSI) requested inspection of the analytical site for Study 34528 in The Netherlands and the issuance of a Form

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

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FDA 483 to MSD (Biopharmaceutical Analytical Facility), the Applicant created an “adapted” dataset with 4 additional subjects excluded from analysis (2 subjects in the IMPLANON® treatment group and 2 subjects in the NEXPLANON® treatment group for a total of 9 excluded subjects). Using the Applicant’s “adapted” dataset, the NEXPLANON® implant is bioequivalent to the currently approved non-radiopaque IMPLANON® for the pharmacokinetic parameters of  $AUC_{0-6\text{months}}$  to  $AUC_{0-36\text{months}}$ . However, using the Applicant’s “adapted” dataset, the NEXPLANON® implant does not meet the generally accepted criteria for bioequivalence to the currently approved IMPLANON® for the pharmacokinetic parameter  $C_{\text{max}}$ . The upper limit for the 90% confidence interval (CI) for the ratio of the  $C_{\text{max}}$  values for etonogestrel plasma concentrations for the NEXPLANON® implant compared to that for IMPLANON® was slightly above the upper limit of the general acceptance range of 0.80 to 1.25 for bioequivalence (90% CI: 0.92 to 1.26). The point estimate for the difference in etonogestrel  $C_{\text{max}}$  plasma concentrations for the NEXPLANON® implant compared to that for IMPLANON® was 1.08 and was not statistically significantly different from 1.0 (1 is contained within the 90% CI).

The Clinical Pharmacology reviewer reanalyzed the original data based on the DSI findings at the analytical site for Study 34528 and excluded 4 additional subjects with insufficient volume to confirm measurable pre-dose etonogestrel concentration. This reanalysis resulted in a total of 13 subjects being excluded from the bioequivalence dataset (12%, 13 of 108 treated subjects). The Clinical Pharmacology bioequivalence reanalysis showed that NEXPLANON® is bioequivalent to the currently approved non-radiopaque IMPLANON® for all of the pharmacokinetic parameters except  $C_{\text{max}}$ . The recalculated upper limit for the 90% CI for the ratio of the  $C_{\text{max}}$  values for etonogestrel plasma concentrations for the NEXPLANON® implant compared to IMPLANON® was again slightly above the upper limit of the general acceptance range for bioequivalence of 0.80 to 1.25 (90% CI: 0.918 to 1.264). This minimal increase in  $C_{\text{max}}$  plasma concentrations (an increase of only .014 above the criteria for bioequivalence) does not pose a safety concern, particularly because women who use the product will be exposed to this minimal increase only once every 3 years following insertion of the implant. To support this assessment and conclusion, the safety data were carefully reviewed for all adverse events that were reported to have an onset date within 60 days after insertion of the implant. The  $C_{\text{max}}$  for etonogestrel is reached approximately one week after insertion.

In the sNDA application, clinical trial safety data for 108 women treated for up to 3 years in Study 34528 was provided (56 subjects in the IMPLANON® treatment group and 52 subjects in the NEXPLANON® treatment group). This clinical trial safety data was supplemented by a requested additional analysis of all adverse events (listed by treatment group and subject), other than insertion-related, with a start date within the first 60 days after implant insertion. The sNDA application also contained, for the 301 subjects in ongoing 3-year Study 34530, clinical trial insertion-related adverse events (for the first 24 hours following insertion) for the radiopaque NEXPLANON® implant and

the redesigned applicator. This interim safety data was supplemented during the review cycle with validated safety data requested for all adverse events occurring within the first 12 months following implant insertion, and an additional focused listing by subjects of all adverse events (other than insertion-related) with an onset date within 60 days of implant insertion. All submitted safety data was reviewed. The safety information submitted in the Safety Update Report and in the updated Safety Update Report was also reviewed, as was the extensive safety database available since July 2006 in the U.S. for approved IMPLANON®.

The review of the original safety data in the application and of the additional requested safety data did not demonstrate any overall safety concerns for the radiopaque NEXPLANON® implant nor did it demonstrate any safety concerns that might be related to the minimally higher upper limit of the 90% CI for the difference in  $C_{max}$  values. The serious and common adverse events reported in clinical trials conducted to support the approval of radiopaque NEXPLANON® are consistent with those of approved IMPLANON®, other non-implantable progestin-only contraceptives, and with combination progestin plus estrogen contraceptives except for events related to the insertion and removal of the NEXPLANON® implant.

The effectiveness of NEXPLANON® for the prevention of pregnancy is also not an issue. No in-treatment pregnancies (pregnancies occurring after implant insertion and before implant removal) occurred in 3-year Study 34528. One (1) pregnancy occurred within 14 days of implant removal (estimated conception on day 7 following removal). No pregnancies occurred in ongoing 3-year Study 34530 as of the sNDA application Data Lock Point of March 12, 2010, which included, at a minimum, 2-year pregnancy data from all subjects who had not terminated prematurely. Therefore, sufficient evidence is provided in the application for me to conclude that the 68 mg radiopaque NEXPLANON® implant is equally effective for women for the prevention of pregnancy as the approved non-radiopaque IMPLANON®.

Sufficient evidence is also provided in the application in Study 34530 (interim report for 301 NEXPLANON® implant insertions using the redesigned applicator, 12 months of safety data, updated safety data for now completed Study 34530, and implant removal data for all subjects) for me to conclude that the redesigned applicator is an appropriate device for proper implant insertion. The Applicant's redesign objectives for the applicator have been met. These include to: 1) facilitate subdermal superficial insertion of the single rod implant by the shape and functionality of the device, 2) prevent the implant from dropping out prematurely from the applicator, and 3) allow single-handed handling of the applicator by healthcare providers during the insertion procedure.

## 1.2 Risk Benefit Assessment

IMPLANON® (etonogestrel implant) 68 mg (the currently marketed product in the U.S.) is a long-acting (up to 3 years), reversible, single rod, non-biodegradable, non-radiopaque hormonal contraceptive that was approved in the U.S. on July 17, 2006, for use by women for the prevention of pregnancy. The radiopaque NEXPLANON® single rod implant, one of the two components of this sNDA application (the other component being the redesigned applicator), differs from the approved non-radiopaque IMPLANON® in the composition of the rod core. The NEXPLANON® implant rod core contains the addition of 15 mg of barium sulfate [REDACTED] (b) (4) [REDACTED]. The addition of 15 mg of barium sulfate facilitates localization of the implant when the implant is not palpable after insertion, and extends the diagnostic modalities for localization to equipment more widely available, such as two-dimensional x-ray imaging.

The efficacy of the NEXPLANON® implant does not depend on the woman's self-administration or compliance to a daily, weekly or monthly dosing regimen.

Additional benefits of the radiopaque NEXPLANON® implant, which also apply to the approved non-radiopaque IMPLANON®, include the following:

1. Single rod
2. Highly effective (< 1% failure rate)
3. Rapid onset of action
4. Rapid reversibility and return to fertility after removal

The disadvantages of the NEXPLANON® implant, which also apply to the approved IMPLANON® implant, include the following:

1. Minor surgical procedure required for insertion and removal
2. High rate of frequent/prolonged vaginal bleeding
3. Insertion and removal-related adverse events in some women

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies (REMS) are recommended beyond the Applicant's proposed Pharmacovigilance Plan. The Pharmacovigilance Plan, proposed in the application, involves the following:

1. Postmarketing surveillance: Separate reporting for insertion and removal-related events (IRREs) related to insertion and removal of the radiopaque NEXPLANON® implant as is currently being done for approved IMPLANON®.

2. Periodic adverse drug event reporting including preparation of Periodic Adverse Drug Evaluation Reports (PADER).
3. Active follow-up (via questionnaires) of the following events to closely monitor the potential risks and to obtain as much information as possible about:
  - unintended pregnancy and pregnancy exposure
  - insertion and removal related events (IRREs).
3. Recommended healthcare provider (HCP) clinical training program (CTP) with availability of the Applicant's Global Medical Information (GMI) Center for follow-up calls.
4. Controlled distribution of the product by authorized distributors who will verify that the order or prescription is from a healthcare provider who has completed the CTP.
5. Appropriate product labeling that conveys important safety information including contraindications, warnings and precautions, and detailed instructions (including diagrams) on insertion and removal of the radiopaque NEXPLANON® implant.
6. USER Card provided to the woman so that she will have a record of the insertion location of the radiopaque NEXPLANON® implant in her upper arm, and the date when it should be removed.
7. Patient Consent Form.

More detailed information regarding the proposed Pharmacovigilance Plan for the radiopaque NEXPLANON® implant and the redesigned applicator can be viewed in Section 7.7 Additional Submissions/Safety Issues of this review.

#### **1.4 Recommendations for Postmarket Requirements and Commitments**

The Applicant was advised of a Postmarketing Commitment (PMC) for the radiopaque NEXPLANON® implant and the redesigned applicator in a teleconference on July 22, 2010, and in a regulatory letter dated July 27, 2010:

“We are requiring that you conduct a postmarketing study to assess insertion and removal events. The design of the study should be similar to that of your ongoing “Active Monitoring Program” (AMP) for Implanon. We request that the study include at least 5,000 insertions and removals with the radiopaque etonogestrel implant and the redesigned applicator.”

On August 20, 2010, Organon USA, Inc. submitted a preliminary AMP protocol for a postmarketing study to assess 5,000 insertion and removal events for NEXPLANON® (etonogestrel implant) 68 mg and the redesigned applicator.

The proposed design of the study is similar to that of the Applicant's ongoing AMP for approved IMPLANON®. A total of 5,000 insertions of the radiopaque NEXPLANON® implant with the redesigned applicator and the subsequent removals will be monitored in the AMP. The AMP will involve healthcare providers (HCP) who complete the clinical training program (CTP) and elect to register for the AMP. The AMP will monitor the effectiveness of the CTP for the radiopaque NEXPLANON® implant and the redesigned applicator. The Applicant estimates that up to 500 trained HCPs will need to participate. "These HCPs will be a subgroup assumed to be representative of the total group of trained clinicians across all practice types (clinics, groups, individuals)." These trained and registered HCPs will complete an Insertion Evaluation Form and a Removal Evaluation Form for each patient in whom they insert and/or remove NEXPLANON®. Per the Applicant, "A quarterly report on IRREs will be generated and submitted to the FDA for a period of 5 years after launch or until 5,000 insertion and removal forms have been received, at which time, a Final (or 5 Year) Report will be submitted."

The preliminary timetable that the Applicant submitted on August 20, 2010, states:

Study Start Date: March 2011  
Study Completion Date: November 2016  
Final Report Submission: Within 5 years after study launch

On January 19, 2011, the Applicant proposed changes to the design of the previously submitted AMP protocol for the radiopaque NEXPLANON® postmarketing study. In addition to collecting specific insertion, localization, and removal data from trained HCPs, the Applicant proposes to also collect data from patients themselves at regular intervals between implant insertion up to 3 months after the removal of the implant. Via a self-administered questionnaire, the patient will be asked "whether any actions have been taken to localize the implant, whether any attempts were made to remove the implant, whether removal was successful, and whether pregnancy or serious adverse events occurred."

Per the Applicant, the proposed changes for the NEXPLANON® implant AMP are based upon observations made during the AMP for approved IMPLANON®. The Applicant observed that following insertion of approved IMPLANON®, many patients changed address and/or changed HCP (possibly to a HCP who may not be participating in the Applicant's AMP) which may have contributed to a high loss to patient follow-up at the time of implant removal.

On March 16, 2011, the Applicant provided an amended timeline for the radiopaque NEXPLANON® postmarketing study:

- |                             |              |
|-----------------------------|--------------|
| ● Final Protocol Submission | July 2011    |
| ● Final Completion Date     | October 2017 |
| ● Recruitment period        | 28 months    |

- Last subject follow-up Q3 2017
- Study update reports to be submitted to FDA At 6 month intervals during the conduct of the study
- Final study report to be submitted to FDA Q1 2018

Per the Applicant, “All estimated timelines are dependent on the start date of the Clinical Training Program for Nexplanon as well as the actual market share of Nexplanon. In case the market share is lower than expected, this would lead to a reduction of monthly recruitment rates and thus an extension of the recruitment period, ultimately leading to a longer total study duration.”

A second amended timeline for the radiopaque NEXPLANON® postmarketing study was submitted by the Applicant on May 3, 2011:

Final Protocol Submission	July 2011
Study Completion Date	October 2017
Final Report Submission	March 2018

The Applicant agreed, in a submission dated May 10, 2011, to provide the Division with “quarterly reports of the postmarketing study data regarding insertion-, localization-, and removal-related events for three (3) years after launch of Nexplanon.”

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***The AMP protocol submitted on August 20, 2010 and the amended AMP protocols submitted on January 19, 2011 and March 16, 2011 are all considered preliminary. The Applicant has indicated, however, that the final AMP protocol for the postmarketing study for the radiopaque NEXPLANON® implant and the redesigned applicator will be submitted in July 2011.***

***This reviewer anticipates that the final protocol submission in July 2011 will include updated NEXPLANON® Clinical Training Program materials and updated material such as, but not limited to, the:***

- ***Insertion Evaluation Form***
- ***Removal Evaluation Form***
- ***Participation Registration Form***
- ***Active Monitoring Program (AMP) Instructions***
- ***AMP Description***
- ***Important Patient Information***

***This reviewer recommends that the Insertion Evaluation Form for the radiopaque NEXPLANON® implant and the redesigned applicator be modified. The question:***

***“Did you encounter any difficulties with the implant insertion procedure?  
If yes, please specify \_\_\_\_\_”***,

***should be expanded to ask:***

***1) if the HCP can identify the underlying basis for the “difficulties with the implant insertion procedure”, and***

***2) if the HCP can suggest a “solution” for the difficulties encountered during the insertion procedure.***

***The recommended change to the Insertion Evaluation Form was conveyed to the Applicant in a letter dated April 28, 2011. The Applicant indicated, in a submission dated May 2, 2011, that the recommended change to the Insertion Evaluation Form would be taken into account when designing the new data collection questionnaires.***

***The timeline for the postmarketing commitment proposed in the May 3, 2011 submission is acceptable.***

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

NDA 21-529/S-000 for IMPLANON® (etonogestrel implant) 68 mg was first submitted by Organon USA, Inc. on September 30, 2003 for the prevention of pregnancy in women of childbearing potential. IMPLANON® (etonogestrel implant) is a non-radiopaque, non-biodegradable, single rod implant consisting of an ethylene vinylacetate (EVA) copolymer core, containing 68 mg of etonogestrel, surrounded by a EVA copolymer skin. IMPLANON® is a progestin only subdermal implant that is replaced every 3 years.

Organon USA, Inc. received an Approvable action letter for NDA 21-529/S-000 on October 29, 2004 because of the following issues:

1. “Irregularities in study conduct identified by European regulatory authorities’ inspections of the clinical trial sites for Study 34507 (including its Canadian component)” which “raised concerns about the quality of the data from this study.” “These concerns are outlined in the October 11, 2004 letter from the Dutch

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

---

Medicines Evaluation Board to Concerned Member States and the summary comments of the September 23, 2004 Report of the Inspectorate of Health Care in the Netherlands (integrated Inspection Report IGZ 2004-015), which were included in your October 15, 2004 submission to the FDA.”

2. “---labeling can not be finalized at this time.”
3. “The inspection of the sterilization facility of [REDACTED] (b) (4) [REDACTED] has not been completed because the facility was not ready for inspection.”

To address these issues:

1. “---submit the Integrated Inspection Report IGZ 2004-015 entitled “Evaluation of Implanon Non-compliance Issues,” the independent audit report, and Organon’s response to the Dutch Medicines Evaluation Board to the NDA. You will also need to submit a detailed justification of why Study 34507 (including its Canadian component) are adequate and well-controlled trials that provide data sufficient to support (1) a conclusion that Implanon is safe and effective for prevention of pregnancy and (2) accurate product labeling. Alternatively, you can conduct another clinical trial to provide safety and efficacy data to support product labeling.”
2. “---, appropriate product labeling should be submitted to the FDA with the information requested in #1 above.”
3. “A satisfactory inspection report is required before this application may be approved.”

NDA 21-529 was re-submitted on December 13, 2004. The re-submission constituted a Complete Response to the October 29, 2004 Approvable letter. In the December 13, 2004 re-submission, the Applicant provided information they believed would establish that Study 34507 and Study 34507 Canada provided data sufficient to support the approval of IMPLANON® (etonogestrel implant).

Organon USA, Inc. received a second Approvable action letter on June 14, 2005 for NDA 21-529 because “---you have not established that the data from Studies 34507 are complete and accurate, we remain concerned that there is insufficient information about Implanon™ to determine whether the product is safe for use under the conditions prescribed in its proposed labeling and to precisely define its effectiveness in its labeling.” See the Approvable action letter, dated June 14, 2005, for a complete discussion of the data deemed to be insufficient.

To address the issue of the adequacy of the data to support approval of IMPLANON®, the Applicant was advised to “submit new clinical trial data from a clinical trial(s) that

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

---

has been conducted in accordance with Good Clinical Practice,” that includes “a sufficient number of subjects so that the assessment of safety and efficacy of Implanon™ can be derived from a clinical trial database containing the equivalent of at least 10,000 28-day cycles obtained during the first year of treatment.” “You will also need to submit an acceptable plan for post-marketing monitoring program for Implanon™-related insertion and removal adverse events in U.S. patients.”

A Complete Response to the June 14, 2005 Approvable action letter was submitted by Organon USA, Inc. on January 16, 2006. Included in the January 16, 2006 submission was a new analysis of efficacy and safety based on the Applicant’s audit program results. In total, Organon conducted 25 audits which supported the acceptance of data from 13 of the original 19 clinical sites. In the January 16, 2006 submission, the Applicant submitted integrated summaries of efficacy and safety using data from the “accepted” sites. In addition, the Applicant submitted: (1) a proposed training program for healthcare providers that would include training on implant insertion and removal techniques using model arms, information on implant localization techniques, and patient counseling. Only healthcare providers who completed the training program would be able to order IMPLANON® (Controlled Distribution), and (2) a proposed monitoring program for the insertion and removal-related events (IRREs) that included both a spontaneous reporting component (Pharmacovigilance Plan) and an Active Monitoring Program (AMP).

On July 12, 2006, Organon USA, Inc. confirmed its agreement regarding a Phase 4 commitment to conduct and submit interim and final study reports for a postmarketing study of insertion and removal complications involving at least 10,000 subjects.

The January 16, 2006 submission received an Approval action on July 17, 2006. Agreed-upon studies showed efficacy by detecting no pregnancies among 942 women in these studies. The safety profile of IMPLANON® was found to be similar to that of non-implantable progestin contraceptives except for events related to the insertion and removal of the implant.

See the following reviews for NDA 21-529 for a full discussion of the product’s regulatory history prior to the 2006 approval of IMPLANON® (etonogestrel implant): Primary Medical Officer’s review dated July 14, 2006, the Medical Team Leader review dated July 17, 2006, and the Division Director’s review dated July 17, 2006.

The current sNDA submission by Organon USA, Inc. (sNDA 21-529/SES-007), received on July 30, 2009, provides for a new radiopaque version of the original non-radiopaque implant rod, and a redesigned applicator, referred to in the submission as a Next Generation Applicator (NGA). Organon USA, Inc. is currently a subsidiary of Merck & Co., Inc. (formerly Schering-Plough Corporation).

## **2.2 Tables of Currently Available Treatments for Proposed Indications**

See the Primary Medical Officer's review of NDA 21-529/S-000, dated October 29, 2004, for a full discussion of available contraceptives for women for the prevention of pregnancy.

IMPLANON® (etonogestrel implant) 68 mg is currently the only approved subdermal implant marketed in the United States. U.S. approved six-rod (Norplant®) and two-rod (Jadelle®) implants, which contain the progestin levonorgestrel, are not marketed in the United States.

The U.S. market has other approved progestin-only contraceptives including Depo-Provera® (3-month injectable contraceptive that delivers 150 mg of medroxyprogesterone acetate), Micronor® and Nor-QD® tablets ("mini-pills" containing 0.35 mg norethindrone taken daily), Ovrette® (mini-pill" containing 0.075 mg of norgestrel), and Mirena® (intrauterine system containing levonorgestrel).

Numerous other hormonal contraceptive products are also available in the U.S. for women for the prevention of pregnancy, including combination oral contraceptive tablets (progestin plus ethinyl estradiol, and estradiol valerate plus dienogest), a vaginal ring (containing etonogestrel plus ethinyl estradiol), a transdermal patch (containing norelgestromin plus ethinyl estradiol), and a copper intrauterine system.

## **2.3 Availability of Proposed Active Ingredient in the United States**

Etonogestrel, which is a derivative of 19-nortestosterone, is the biologically active metabolite of desogestrel, the progestin component of several combination oral contraceptives approved for marketing in the U.S. Desogestrel is also approved and marketed as the progestin component in non-U.S. approved combination oral contraceptives.

Non-radiopaque IMPLANON® (etonogestrel implant) 68 mg has been marketed worldwide since 1998 and in the U.S. since 2006.

Etonogestrel is also approved and marketed in the U.S. in NuvaRing®, a vaginal contraceptive ring containing the combination of etonogestrel plus ethinyl estradiol.

IMPLANON NXT (68 mg) and the redesigned applicator was approved by the "Mutual Recognition Procedure" (MRP) with The Netherlands as the "Reference Member State" (RMS) on April 8, 2010 for contraception. IMPLANON NXT (in some countries also named NEXPLANON) is approved for marketing in 23 countries, and is currently marketed in 12 countries outside the United States.

## 2.4 Important Safety Issues With Consideration to Related Drugs

A major safety issue with one other approved hormonal contraceptive implant has been difficulty with insertions and removals. Norplant®, a six-rod implant, not currently marketed in the U.S., has been the subject of litigation related to injuries caused by difficult removals. Jadelle® (levonorgestrel implant), an approved two-rod implant, has never been marketed in the United States.

Progestin-only contraceptives include higher-dose injectable products that are administered once every 3 months such as Depo Provera Contraceptive Injection (medroxyprogesterone acetate), lower-dose oral progestin-only contraceptive products such as Ortho Micronor® and Ovrette® tablets, and the IMPLANON® implant. The risk profile of lower-dose progestin products, such as IMPLANON®, include but are not limited to:

- Irregular vaginal bleeding, a common reason for discontinuation of the product.
- Ovarian cysts, possibly the result of folliculogenesis without ovulation.
- Increased risk of ectopic pregnancy when the product fails, possibly because of depressed motility of the Fallopian tubes in the presence of progestin.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

On April 16, 2007, the Applicant requested a meeting with the Division to discuss a proposed marketing application for a radiopaque rod containing etonogestrel and a redesigned applicator for IMPLANON®. The pre-meeting information package, provided by the Applicant in preparation for the scheduled August 20, 2007 teleconference, contained the following proposal for the healthcare provider (HCP) training program for the radiopaque etonogestrel implant:

- Current HCP for IMPLANON® (etonogestrel implant) will be updated to provide training for the radiopaque NEXPLANON®.
- A re-training program will be developed for HCPs who have been trained with the original applicator and rod.
- All HCPs who undergo the re-training program will receive “the new materials”.
- Any HCP who has not received the re-training by a pre-determined time-frame will be removed from the trained HCP database and will not be able to order and insert NEXPLANON®.
- Any HCP not already trained in IMPLANON® will be offered the new Clinical Training Program (CTP) on the radiopaque NEXPLANON® implant.

The question from Organon USA, Inc. during the August 20, 2007 teleconference, regarding training was “Does FDA agree in principle with the proposed strategy for the HCP training program: i.e., the updates of the program and materials as well as the re-

training proposal for those HCPs who have already been trained on the current product?" FDA responded "Yes, the Division agrees in principle with the proposed strategy."

In the current submission, per the Applicant, "Upon careful review of the most currently available study results and data, since the meeting held with FDA on 20 August 2007, Schering-Plough (now Merck & Co., Inc.) is proposing (b) (4)

(b) (4) .” However, (b) (4)  
controlled distribution will continue.

(b) (4) initially  
proposed in the sNDA application.

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***This reviewer believes that it is advisable that all healthcare providers who will be inserting the radiopaque NEXPLANON® implant, including those previously trained for insertion of IMPLANON® with the currently approved applicator, should undergo Applicant-sponsored training with the redesigned applicator. The currently approved applicator and the redesigned applicator differ in their functionality and use. However, I do not believe that this should be a condition of approval of NEXPLANON®. In addition, the nature of the retraining for experienced users of IMPLANON® could be less extensive than the training never-trained healthcare providers would receive.***

The Applicant was advised, in a letter dated July 27, 2010, of the recommendation for training of all healthcare providers who will be inserting the NEXPLANON® implant with the redesigned applicator, including those who were previously trained for insertion of approved IMPLANON® with the currently approved applicator.

The Applicant stated in a communication dated August 17, 2010, that the Clinical Training Program (CTP) for the NEXPLANON® implant and the redesigned applicator will include recommended Applicant-sponsored training before a healthcare provider may order radiopaque NEXPLANON® and the redesigned applicator. "All healthcare providers (HCPs) who will be inserting the radiopaque etonogestrel implant ( (b) (4) ), including those who were previously trained on insertion of Implanon, will undergo company-sponsored training with the re-designed applicator."

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***This reviewer concurs with the Applicant’s plan to train all healthcare providers for insertion of the radiopaque NEXPLANON® implant with the redesigned applicator, including those healthcare providers previously trained for insertion of approved IMPLANON® and the currently approved applicator.***

***More detailed information regarding the proposed clinical training program for the radiopaque etonogestrel implant and the redesigned applicator can be viewed in Section 7.7 Additional Submissions/Safety Issues of this review***

**Controlled Distribution:**

Per the Applicant, the overall intent of the Applicant's "Controlled Distribution" (i.e., selling product only to Applicant-trained healthcare providers) will be maintained for NEXPLANON®. In order for a clinician to order NEXPLANON® and the redesigned applicator, the clinician will attend and complete an Applicant-sponsored Clinical Training Program (CTP) for the radiopaque implant with the redesigned applicator. Distribution of product will be controlled by authorized distributors who will verify that the order or prescription is from a clinician who has completed the CTP. Only by attending a Applicant-sponsored training session will clinicians be entered into the trained clinician database and have access to the radiopaque etonogestrel implant.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***This reviewer concurs with the Applicant's plan to establish and maintain "Controlled Distribution" for the radiopaque NEXPLANON® implant and the redesigned applicator.***

## **2.6 Other Relevant Background Information**

On September 24, 2009, prior to the sNDA submission, the Applicant submitted a "Request for Proprietary Name Review" for the proposed (b) (4)  
The Applicant indicated that the proposed (b) (4)

The Applicant also pointed out that both versions of the product (IMPLANON® and (b) (4)) would co-exist in the marketplace for several years since approved IMPLANON® can be used by the patient for up to 3 years after insertion. The Applicant contended that it was essential that the proprietary name of the new radiopaque etonogestrel implant product be differentiated from the current, non-radiopaque IMPLANON® to allow for proper pharmacovigilance tracking of the two versions of the product.

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.  
Supplemental NDA 21-529/SES-007  
Radiopaque Nexplanon® Implant

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Approved IMPLANON® has a Post-Approval Commitment (the Active Monitoring Program [AMP]) which requires close monitoring, data collection, evaluation and periodic reporting of “Insertion and Removal Related Events” [IRREs for 10,000 insertion and removals]) in addition to the routine pharmacovigilance monitoring requirements. Therefore, the Applicant considered it “essential” that the proprietary name of the new radiopaque implant be differentiated from IMPLANON® to allow for proper pharmacovigilance tracking of the two version of the implant.

The Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) informed the Applicant on December 23, 2009 that the “proposed proprietary name (b) (4) is unacceptable because (b) (4) (b) (4) may be a source of medication errors.”

On March 1, 2010, Organon USA, Inc. (now a subsidiary of Merck & Co., Inc.) submitted a Request for Reconsideration of Proprietary Name indicating that “Merck consider it highly unlikely that the proposed proprietary name (b) (4) would lead to medication errors and believes that the (b) (4) name complies with the requirements for labeling and promotion.” Their conclusions include, but are not limited to, the following:

- “As is the case for the currently approved (non-radiopaque) IMPLANON® product, a system of “Controlled Distribution” will be in place for the (b) (4) product.” Distribution of product will be controlled by authorized distributors who will verify (using the “Trained Clinician Database”) that the order or prescription is from an HCP who has completed the company-sponsored “CTP”.
- “There is no [subdermal] contraceptive implant product (other than IMPLANON) currently being marketed in the U.S. Also, a product-specific NDC# bar-code is prominently displayed on the unit product labeling (both the blister label and the unit carton).”
- “The primary difference between the old and new formulations is that the (newer) (b) (4) version will also contain a small amount of barium sulfate to make it radiopaque. Clinical studies have demonstrated that the two versions of the IMPLANON product are bioequivalent. Even in the unlikely event that a mix-up between the old/new versions of IMPLANON were to occur, women will be exposed to the same contraceptive dosage following subdermal insertion of the implant.”
- “The current IMPLANON® applicator and the newer (b) (4) applicator (and the unit packaging for each) are quite dissimilar from each other. Because these dedicated (single-use) disposable applicators make these products unique in appearance, it is unlikely that these products would be confused with any other medications, or with each other.”

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***This reviewer believes that it is essential that the insertion and removal-related events (IRREs) for the radiopaque NEXPLANON® implant and the redesigned applicator be differentiated from the IRREs reported with approved non-radiopaque IMPLANON® and the currently approved applicator.***

DMEPA reviewed the Applicant's Request for Reconsideration of the proposed proprietary name (b) (4). DMEPA concluded (communication dated May 21, 2010), "Our analysis of the data provided by Merck & Co., Inc. in support of the Request for Reconsideration of the proposed proprietary name, (b) (4), did not support that (b) (4) conveys its intended meaning and will not be a source of error. Thus, DMEPA continues to find the use of the proprietary name, (b) (4), unacceptable for the proposed product."

DMEPA and DRUP contacted the Applicant on April 27, 2010, regarding the proposed proprietary name. In summary, the Applicant was advised of the following two options for the proposed proprietary name: (b) (4)

A May 28, 2010 DMEPA letter, received by the Applicant on June 3, 2010, indicated "Proprietary Name Request Unacceptable".

The Applicant responded on July 6, 2010 with a Formal Dispute Resolution Request requesting "a formal review of the FDA (DMEPA) denial of our proposed proprietary (b) (4) at the Office Level (Office of Surveillance and Epidemiology)." The submission contained no new data or other information. The Applicant indicated that, "All data and information provided herein is intended to facilitate review, and has previously been provided to the Agency in prior submission (see "List of Documents" in the attached request)."

The Applicant's dispute appeal was denied on August 5, 2010 stating, "We have carefully reviewed your appeal and concluded that the Division of Medication Error Prevention and Analysis (DMEPA) acted appropriately in issuing the above referenced letters finding the proposed proprietary name, (b) (4), unacceptable. We believe that, (b) (4)

Therefore, your appeal is denied."

The Applicant submitted a second Formal Dispute Resolution Request on August 9, 2010 providing clarification for the Clinical Training Program (CTP) and the Controlled Distribution System. In the letter (page 3, last paragraph), it indicates that the "CTP"

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

---

and the “Controlled Distribution System” are “Voluntary Programs” which can be changed at any time, and which are not administered at FDA’s direction. “Although the CTP and Controlled Distribution System are not FDA requirements, it is very unlikely that either will be discontinued by the company.” The “CTP” is strongly recommended by the company, and no product is shipped to any healthcare provider who has not completed the company-sponsored “CTP”. “Product distribution is controlled using our “Trained Clinician Database” (i.e., “Controlled Distribution System”).”

“We disagree with the OSE findings. Therefore, in accordance with 21CFR: 10.75 and 314.103, and the FDA guidance for Industry: “Formal Dispute Resolution: Appeals Above the Division Level” (February 2000), we are hereby requesting a formal review of the FDA (OSE) denial of our proposed proprietary (b) (4) at the Center Level (Center for Drug Evaluation and Research).”

On September 21, 2010, the Deputy Director for Regulatory Affairs for CDER, Dr. Douglas C. Throckmorton, informed the Applicant, “I have now completed my review of the formal dispute resolution request and agree with the findings that (b) (4) is potentially false and misleading and could lead to medication errors. No data or responses presented by the company adequately address or alleviate these concerns. I therefore concur with Dr. Dal Pan’s decision dated August 5, 2010, and deny your appeal.” “If you wish to appeal this decision to the next level, your appeal should be directed to Dr. Margaret Hamburg, Commissioner, Food and Drug Administration.”

On November 30, 2010, the Applicant submitted a “Request for Proprietary Name Review” (amended on November 30, 2010) for a new proposed tradename Nexplanon®. The November 30, 2010 submission provided the report entitled “(b) (4) Research Findings for the Proposed Proprietary Name Nexplanon®”. Merck & Co., Inc. requested (b) (4), the research and regulatory assistance division of (b) (4), to conduct market research to assess the acceptability of NEXPLANON® as a proprietary name for the radiopaque etonogestrel implant. NEXPLANON® (pronounced Nex-plah-non) is considered to be a line extension of IMPLANON®.

“Combining NEX prefix with the PLANON letter sequence should convey a “next/next generation” version of IMPLANON® and distinguish it from the existing product. The “NEX” prefix is not intended to convey any superlative meaning: i.e. it is not intended to imply “better”, but rather, the next version. In other words, the brand name evolution using the “NEX” prefix is intended to clearly communicate a “next version” (or “next generation”) in a neutral manner while also avoiding proprietary name confusion with the current IMPLANON®.”

Based on the results of the (b) (4) believes NEXPLANON® is an acceptable proprietary name candidate that should be considered for the radiopaque etonogestrel implant.

A proprietary name review completed by DMEPA on January 31, 2011 and April 22, 2011 indicates, "The Proprietary Name Risk Assessment indicates that the proposed name, Nexplanon, is not vulnerable to name confusion that could lead to medication errors, nor is it considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name Nexplanon, for this product at this time."

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***This reviewer concurs with the proposed proprietary name NEXPLANON®.***

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

A request for a Biopharmaceutical Inspection was submitted to the Division of Scientific Inspections on September 18, 2009. The Office of Clinical Pharmacology identified the following sites for inspection.

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
FOR01C	Dinox BV, Hanzeplein 1, Entrance 53, 9713 GZ Groningen, The Netherlands  Principle Investigator Name: Tjeerd Lorver Address: NV Organon, PO Box 20, 5340 BH Oss, The Netherlands Phone: 31-412-661840	MSD, Molenstraat 110, PO Box 20, 5340 BH Oss, The Netherlands  Bioanalyst Name: W. Koslowksy Address: NV Organon PO Box 20 5340 BH Oss, The Netherlands

Per the Division of Scientific Inspections (DSI), a Form FDA 483 was issued on February 26, 2010 to Dinox BV (Biopharmaceutical Clinical Facility) indicating the following regarding the conduct of the clinical component of Study 34528. The observations were based on a review of study records including case histories for 32 subjects representing the total number of subjects enrolled and treated at this clinical site:

1. "The firm did not retain reserve samples for the study (No. 34528). The study drug products were provided in three shipments as follows. One shipment of four units was designated as back-up supplies and was returned to the sponsor. The other two shipments provided by the sponsor consisted of 24 units and eight units, 32 units in total, and were used for subjects dosing with none remaining."
2. "Administration of informed consent to the first 12 subjects utilized a current form version (15 March 2005) that had not been approved by the reviewing ethics committee. The approved version (8 April 2005) was administered to the subjects at a subsequent visit. The approved version included changes to information on study risks and information on subject confidentiality."

In regards to item number 1, DSI noted that the inspection confirmed that the Dinox-affiliated radiology unit maintained x-ray records independently, which revealed whether the individual implants were radiopaque. DSI recommended using the x-ray evidence as supportive evidence.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***This reviewer agrees that the x-ray evidence is supportive. The clinical investigator at Dinox also concurred with the DSI observation and stated in the response to Form FDA 483 that Dinox would maintain sample reserves in future bioequivalence studies.***

In regards to item number 2, DSI emphasized that these subjects later executed the correct informed consent and that both completed consent forms provided subject safety and protection.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***This reviewer concurs with the DSI observation. In the response to Form FDA 483 (dated March 3, 2010), Dinox stated that they will assure that consent forms are reviewed in proper and timely fashion in future studies.***

DSI also issued a Form FDA 483 to MSD (Biopharmaceutical Analytical Facility) indicating the following with regards to Study 34528 (analytical project 06009):

1. "Stability during long-term frozen storage was not validated pre-study for the same assay procedure used in study 34528 ( (b) (4) solid phase extraction with radioimmunoassay). Study samples were stored as long as 650 days (mean 231 days) before assay. However, within the study, stability of QCs was demonstrated for 105 days."
2. "Run acceptance/rejection decisions were made inappropriately, by averaging replicate determinations of QC sample concentrations. When QC data were

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

---

calculated in the same way as study sample data, the originally-failed run 27 would pass, and the passed runs 14 and 36 would fail.”

3. “Five serum samples (subjects (b) (6), (b) (6), (b) (6), (b) (6), and (b) (6)) with insufficient volume to confirm measurable pre-dose ENG concentrations were listed as “non reportable.” However, other measurable pre-dose ENG concentrations were confirmed to be accurate.”
4. “Failure to evaluate incurred sample reproducibility (ISR). Although 44 study samples in analytical run 27 were reassayed in run 31, because of the inappropriate process cited in observation #2, these 44 reassayed samples represent only about 2% of total study samples.”

DSI received a response from Organon USA, Inc. to the Form FDA 483 observations listed above for MSD on March 26, 2010. In regards to item number 1, MSD provided recent data on reassay of selected samples from Study 34528, in order to extend the period of acceptable stability and accuracy of samples from the original time of up to 105 days in storage to at least 650 days. The reassay used freshly-prepared calibrators. Storage stability for more than 2 years included combining quality control (QC) and reassay data. DSI recommended using this as evidence of stability during storage.

### **Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***This reviewer concurs with the DSI recommendation. The Clinical Pharmacology reviewer concurs with this recommendation. See the Clinical Pharmacology review dated July 23, 2010.***

In regards to item number 2, MSD responded with revised data combining data from both of these runs, but excluding data from runs # 14 and # 36. MSD pointed out that the concentration data in run # 27 and its repeated run # 31 are similar. DSI indicated that “this response is reasonable.”

### **Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***Per the Clinical Pharmacology reviewer, “In the original BE analysis, data from run 27 were rejected. However, samples for run 27 were reassayed in run 31 and accepted. Therefore, no adjustment in the evaluation of original BE analysis in regard to failed run 27 is necessary.”***

***Per the Clinical Pharmacology reviewer, “Data from 4 ( (b) (6), (b) (6), (b) (6), (b) (6) ) out of 34 subjects in runs 14 and 36 were for multiple data sets for period including first 2 months after implant insertion, during which  $C_{max}$  occurs and concentration of etonogestrel greatly varies and affects the AUC. Therefore, these four subjects listed above were excluded from the sponsor’s reanalysis of the BE data.” See the Clinical Pharmacology review dated July 23, 2010, and***

***Subsection 4.4 Clinical Pharmacology of this review for a more complete discussion.***

***This reviewer concurs with the removal of the data for the 4 subjects listed above.***

In regards to item number 3, DSI indicated that the five subjects with pre-dose etonogestrel concentrations unconfirmed by duplicate reassay are likely to have had true presence of drug, as was the case with several subjects with confirmed pre-dose concentrations. DSI notes that pre-dose samples for subjects (b) (6) and (b) (6) were reassayed only in singlet, confirming the original assay, but were nonetheless listed as “not reportable”. MSD agreed with the DSI observation in their response to FDA Form 483, and provided data from all assays in the revised study report. DSI recommended using all of the data.

*Medical Officer’s Comments:*

*The Clinical Pharmacology reviewer reassessed the data excluding subjects (b) (6), (b) (6), and (b) (6). See the Clinical Pharmacology review dated July 23, 2010, and Subsection 4.4 Clinical Pharmacology of this review for a more complete discussion.*

In regards to item number 4, MSD reassayed another 156 samples to meet the DSI recommended 10% for incurred sample reproducibility (ISR). Per DSI, the ISR results reported meet the acceptance criteria recommended. DSI recommended using these data to evaluate ISR for Study 34528.

*Medical Officer’s Comments:*

*Per the Clinical Pharmacology review, “The sponsor reestablished the ISR with more than 10% (which is the recommended % for ISR by DSI) of the total samples in response to this finding from DSI.”*

On March 30, 2010, DSI offered the following conclusions:

“Following the above inspections, the Division of Scientific Investigations recommends the following:

- Although Dinox and possibly other clinical sites for this study failed to retain reserve samples, there is partial confirmatory data in the independently-maintained x-rays. Despite this violation of the regulations, DSI recommends that the Biopharmaceutics review consider the weight-of-evidence.
- Deficiencies in informed consent had little or no consequence to subject protection and bioequivalence.

- Deficiencies in method validation (stability assessments) and study conduct (run acceptance/rejection, pre-study concentrations, ISR) were corrected in post-study experiments and report amendments.”

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

**See Subsection 4.4 Clinical Pharmacology of this review for a full discussion of the DSI findings at MSD (Biopharmaceutical Analytical Facility), Organon USA, Inc. responses to the DSI findings, and the resulting reanalysis of the pharmacokinetic data for Study 34528.**

**Per the Clinical Pharmacology review dated July 23, 2010, “Overall, the sponsor’s response to the form 483s for both clinical and analytical sites of the BE study addressed all the findings from the DSI inspection. Therefore, the sponsor’s data is valid to be reviewed and BE reanalysis showed that the efficacy and safety of (b) (4) can be relied upon the efficacy and safety of Implanon, although BE study between (b) (4) and Implanon did not meet the BE criteria for  $C_{max}$ .”**

**This reviewer agrees that the BE study data is valid to be reviewed.**

### **3.2 Compliance with Good Clinical Practices**

Both studies supporting the application (Study 34528 and Study 34530) appear to have been undertaken in accordance with the principles of Good Clinical Practice as set forth in the ICH-E6 Guidance. These studies were conducted with the approval of local Ethic Committees. Written informed consent was obtained for all subjects.

In the application, “the undersigned certifies that Organon USA, Inc. (formally a subsidiary of Schering-Plough Corporation, now a subsidiary of Merck & Co., Inc.) did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306 (a) or (b)].”

The Applicant conducted three site audits during the conduct of Study 34528. Copies of the audit certificates are available in the submission for:

1. Site # 104; Dr. G. Merki; Zurich, Switzerland.
2. Site # 107; Dr. H. Pas; Lens, France.
3. Site # 106; Dr. I. Duijkers; Dinoox BV, Netherlands.

No site audits were carried out for Study 34530.

### **3.3 Financial Disclosures**

Form FDA 3454 (4/06), dated July 28, 2009, and signed by Henk Jan Out, MD, Ph.D., Vice-President Women's Health, Global Clinical Research, Organon USA, Inc. is included in the submission

Per the application, each listed clinical investigator (Appendix 1 of the Financial Certification) did not disclose any "proprietary interest in this product or a significant equity in the Sponsor as defined in 21 CFR 542(b).

However, Organon USA, Inc. was unable to contact some investigators due to:

1. Investigator left the clinical trial site and attempts to locate and contact these investigators were unsuccessful.
2. Study and/or site personnel (for example, study coordinator, research nurse) were not required to complete a Financial Disclosure Form.
3. Clinical trial site did not respond to request to obtain necessary information.

#### **Medical Officer's/Cross Discipline Team Leader's Comments:**

***For Study 34528, all investigators and clinical sites responded with financial disclosure information. Study 34528 was conducted in Switzerland, France, and The Netherlands.***

***For Study 34530, 47.8% (11 of 23 participating clinical sites) of the clinical sites did not respond with the requested information. Study 34530 was conducted in Australia, Germany, France, United Kingdom, Norway, and Sweden.***

***Overall, no data integrity issues are identified in the financial disclosure information provided in the application.***

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

Per the primary Chemistry, Manufacturing, and Controls (CMC) review completed on April 21, 2010, there are no changes to the manufacturing or quality control of the etonogestrel drug substance used. A compatibility study was performed to demonstrate

that etonogestrel is compatible with all excipients, including barium sulfate added to the core of the implant.

For the final drug product, the application demonstrates that there is “hardly any difference observed for the release rates of the x-ray visible and current Implanon® implants when they are tested under identical conditions. This means that the *in-vitro* release of x-ray visible and current Implanon® implants is equivalent, irrespective of test conditions covering a wide range of release rates.”

The CMC reviewer indicates that the manufacturing process parameters and operating ranges have been adequately evaluated and are acceptable. In addition, the (b) (4) lidding film with an (b) (4) selected for the container closure was shown not to deteriorate during prolonged storage at accelerated conditions. See the CMC review, dated April 21, 2010, for a full discussion of manufacturing process development and the container closure system.

Per the application, a stability study was performed on core granulate to determine the compatibility of Org 3236 drug substance with the excipients barium sulfate and ethylene vinylacetate copolymer. The CMC reviewer concludes, “It was demonstrated that etonogestrel is compatible with barium sulfate and ethylene vinylacetate copolymers. Etonogestrel content did not change after exposure to extreme heat and light conditions. (b) (4)

(b) (4) No unspecified degradation products were found. It can be concluded that addition of barium sulfate does not affect the stability of etonogestrel in the presence of the excipients.”

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***The Chemistry, Manufacturing and Controls (CMC) reviewer states the following in his primary review of sNDA 21-529/SES-007 dated April 21, 2010:***

***“The data and information submitted in the supplement are adequate to support the new formulation of Implanon® Implant. However, a number of labeling elements require revision. The following comments have been revised in the draft labeling and have been communicated to the OND reviewers:***

- ***The proposed established name (non-proprietary name) is not acceptable; (b) (4) should be removed from labeling.***
- ***The proposed established name ‘(b) (4)’, is not acceptable. The Applicant may continue to use the currently approved established name, ‘etonogestrel implant’, (b) (4)***
- ***In Section 11 of the Physician’s Package Insert, the description of the applicator is incorrect. Change from ‘(b) (4)***

to

***The patient chart label, user card, blister label, carton label and package inserts should be revised to incorporate the above recommendations.”***

***The CMC reviewer subsequently concurred with the following designation for the final drug product: (b) (4) In addition, the CMC reviewer subsequently recommended approval of the NEXPLANON® carton, blister, chart and user card labeling (see the CMC review dated April 26, 2011).***

***This reviewer concurs with the CMC reviewer’s recommendations. All CMC labeling recommendations have been incorporated into the product labeling. See Subsection 9.2 Labeling Recommendations of this review.***

The primary CMC review, however, focused on the non-biodegradable single-rod implant, per se, and did not adequately address manufacturing and quality control issues that pertain to the redesigned applicator (insertor). Because of this oversight, a consult for inspection of the manufacturing site/processes for the redesigned applicator was made to the Office of Compliance (OC) for a combined Center for Drug Evaluation and Research (CDER)/Center for Devices and Radiological Health (CDRH) inspection of the applicator manufacturing/assembly site.

The Division of Manufacturing and Product Control (DMPQ), International Compliance Branch (ICB) conducted an inspection of the NEXPLANON® drug manufacturing facility in The Netherlands on December 6 - 9, 2010. A Form FDA 483(9/08) was issued on December 9, 2010 with 2 observations: OBSERVATION 1: “Sterilization dose audits are not performed every three months to monitor the resistance of the bioburden on the product. Instead, the firm has established an interval of one year between dose audits, as stated in Document ID INT00110020, Implanon/ (b) (4) – Revalidation of the (b) (4) process. The firm’s rationale for the one year interval is based in part on historical bioburden levels on the Implanon implant and applicator. However, the (b) (4) applicator design, applicator components supplier, blister packaging materials, and the filling/packaging line are different from those associated with the currently approved Implanon”, and OBSERVATION 2: “Preventive maintenance on the (b) (4) blister package heat seal platens, including confirmation of temperature ranges, was not performed at the 6 month interval designated in the preventive maintenance schedule. The last maintenance and temperature configuration was performed February 12, 2010.”

Per the OB/DMPQ/ICB Establishment Evaluation Request Summary Report, dated February 10, 2011, the Finished Dosage Manufacturing, the (b) (4) Sterilization Process, and the Control Testing Laboratory are acceptable.

In the second CMC review, dated April 26, 2011, the CMC reviewer indicates that the “facilities utilized in the production of the drug product (manufacturing, testing and sterilization sites) are acceptable.” The CMC reviewer states the following in the April 26, 2011 review: “The chemistry, manufacturing, control and labeling information submitted in this supplement, as amended, is adequate for the proposed changes. Approval is recommended.”

On May 11, 2011, the CMC reviewer concluded that the final agreed upon NEXPLANON® labeling was acceptable for all CMC-related issues.

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

**Based on NV Organon’s response to the Form FDA 483 issued on December 9, 2010, the OC/DMPQ/ICB inspection team confirmed on February 10, 2011 that the “overall recommendation for NV Organon is acceptable.” This reviewer concurs with the recommendation of the OC/DMPQ/ICB inspection team. This reviewer concurs with the CMC reviewer’s recommendation for approval.**

## **4.2 Clinical Microbiology**

The Clinical Microbiology reviewer states the following in his review of sNDA 21-529/SES-007 dated October 9, 2009:

1. “Recommendations
  - A. Recommendations on Approvability – Recommended for approval from a microbiology quality standpoint.
  - B. Recommendations on Phase 4 commitments and/or Agreements, if Applicable – N/A”
2. “Summary of Microbiology Assessments
  - A. Brief Description of the Manufacturing Processes that relate to product Quality Microbiology – The core of the proposed applicator rod differs from the approved rod in containing barium sulfate (15 mg/implant) in addition to etonogestrel drug substance (68 mg/implant) and ethylene vinylacetate copolymer (b) (4). The lidding material for container closure blister has been changes to a (b) (4). A novel product administration device for subdermal insertion of the rod, the NGIA, is also proposed.
  - B. Brief Description of Microbiology Deficiencies – None.
  - C. Assessment of Risk Due to Microbiology Deficiencies – Acceptable risk.”

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***This reviewer concurs with the Clinical Microbiology reviewer's recommendation on approvability. The risk due to microbiology deficiencies is acceptable.***

### **4.3 Preclinical Pharmacology/Toxicology**

No new preclinical pharmacology/toxicology studies were submitted with sNDA 21-529/SES-007. See the original Pharmacology/Toxicology Review and Evaluation, dated May 14, 2004, for a complete discussion of all genotoxicity, carcinogenicity, and reproductive and developmental toxicology studies conducted.

The Pharmacology/Toxicology reviewer evaluated the safety implications of the addition of barium sulfate to non-radiopaque IMPLANON®. The radiopaque etonogestrel implant has been made x-ray visible by incorporating 15 mg of barium sulfate ((b)(4)% v/v) per implant. The Applicant's risk assessment of possible local and systemic toxicity due to release of barium ions and barium particles was considered by the Pharmacology/Toxicology reviewer:

- Barium sulfate has very low solubility in water,
- X-ray visible products containing barium sulfate such as stents and IUDs have been approved and are in widespread use without barium sulfate-related safety concerns,
- Large oral doses (grams) of barium sulfate are used on a routine basis for the purpose of radiologic diagnosis of GI tract disease without causing significant health problems,
- The daily release from the implant of barium ions is extremely low: (b)(4),
- Barium ions are natural constituents of the human body. Daily dietary and inhalatory exposure of the general population is > 1 mg. Normal body content is about 22 mg. A normal blood value is 1.2 µg/L, and
- The worst case estimation of total release of barium sulfate particles from the open ends of the implant is (b)(4). These minute amounts will be phagocytosed at the application site by macrophages.

The Pharmacology/Toxicology reviewer considers the use of barium sulfate in the radiopaque etonogestrel implant acceptable, based on the above information. "The extensive clinical experience with barium sulfate, the very low release of barium ions from barium sulfate containing rods, the pre-clinical studies with barium sulfate containing radiopaque IUD, as well as 6 months of safety data from clinical trial 34528 (including local tolerance), are sufficient to demonstrate the safety of barium sulfate."

**Medical Officer's/Cross Discipline Team Leader's Comments:**

**The Pharmacology/Toxicology reviewer states the following in his review of sNDA 21-529/SES-007 dated December 14, 2009:**

- 1. "Recommendations**
  - A. Recommendation on approvability: Pharmacology/toxicology recommends approval of sNDA 21-529 for contraception.**
  - B. Recommendation for the nonclinical studies: All preclinical studies have been previously submitted under the original NDA submission dated 9-30-03 and reviewed on 4-28-04. No new toxicology information is required.**
  - C. Recommendation on labeling: As required the draft labeling is in accordance with PLR and provided in SPL format. The Carcinogenesis, Mutagenesis, Impairment of Fertility section is adequately described."**
- 2. "Summary of nonclinical findings**
  - A. Brief overview of nonclinical findings: Nonclinical findings were primarily related to progestational effects of etonogestrel.**
  - B. Pharmacologic activity: The pharmacological activity of etonogestrel is attributed to suppression of gonadotropins and inhibition of ovulation. Etonogestrel affects cervical mucus, which makes sperm penetration difficult, and also affects endometrial lining which prevents embryo implantation.**
  - C. Nonclinical safety issues relevant to clinical use: None."**

**The overall conclusions and recommendations are;**

**"Conclusions: The data provided supports the approval of [REDACTED] (b) (4) for contraception."**

**"Unresolved toxicology issues (if any): None"**

**"Recommendations: Pharmacology/Toxicology recommends approval of NDA 21-529."**

**"Suggested labeling: Draft labeling in accordance with PLR and presented in SPL format. The Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy sections are adequately described."**

**This reviewer concurs with the Pharmacology/Toxicology reviewer's recommendation on approvability. This reviewer agrees that the daily release of**

***barium ions from radiopaque NEXPLANON® is acceptable and does not present safety concerns.***

***On May 11, 2011, the Pharmacology/Toxicology reviewer indicated that final agreed upon NEXPLANON® labeling***

## **4.4 Clinical Pharmacology**

### **4.4.1 Mechanism of Action**

Etonogestrel, which is a derivative of 19-nortestosterone, is the biologically active metabolite of desogestrel, the progestin component of several combination oral contraceptive. The contraceptive effect NEXPLANON® is achieved by several mechanisms that include suppression of ovulation, increased viscosity of the cervical mucus, and alterations in the endometrium.

### **4.4.2 Pharmacodynamics**

No exposure-response relationship data for NEXPLANON® were submitted in this application. Dose finding studies were submitted with the original NDA submission. Data reported support the choice of dose for IMPLANON® (68 mg) and support the effectiveness of the drug product over a three year period.

#### *Medical Officer's Comments:*

*IMPLANON® (etonogestrel implant) 68 mg is a 3-year contraceptive implant approved for women for the prevention of pregnancy.*

### **4.4.3 Pharmacokinetics**

Study 34528 was conducted to demonstrate the bioequivalence of the approved non-radiopaque IMPLANON® (etonogestrel implant) 68 mg and radiopaque NEXPLANON® (etonogestrel implant) 68 mg.

A total of 108 healthy women between 18 and 40 years of age were randomized to two treatment groups: non-radiopaque IMPLANON® or radiopaque NEXPLANON®. Blood samples were collected at pre-dose, Days 3, 5, 7, 9, 11, 15, and 22, and Months 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 27, 30, 33, and 36.  $C_{max}$  and multiple AUCs from different periods ( $AUC_{0-6months}$ ,  $AUC_{0-12months}$ ,  $AUC_{0-24months}$ ,  $AUC_{12-24months}$ ,  $AUC_{24-36months}$ , and  $AUC_{0-36months}$ ) were calculated for the comparison of peak concentration and exposure of the two products.

Table 1 provides the Applicant's original calculated etonogestrel pharmacokinetic (PK) parameter values and statistical evaluation based on 103 out of 108 subjects in Study 34528. Five (5) subjects (Subjects (b) (6), (b) (6), (b) (6), (b) (6) and (b) (6)) were excluded from the PK analysis, submitted in the application, because they took prohibited contraceptive medications during the treatment period or the day before the implant insertion.

**Table 1 Results of Bioequivalence Testing Using the Dataset Submitted in the Original Application (All-Subjects-Pharmacokinetically-Evaluable Group); Study 34528**

Parameters	Geometric mean [CV]		Ratio (test/reference)	90% Confidence interval
	IMPLANON® (reference)	NEXPLANON® (test)		
C <sub>max</sub> <sup>a</sup> (pg/mL)	1,021.2 [50.4 %]	1,083.3 [50.4 %]	1.06	0.91-1.23
AUC <sub>0-6months</sub> <sup>b</sup> (pg·month/mL)	2,210.4 [27.2 %]	2,212.1 [28.4 %]	1.00	0.91-1.10
AUC <sub>0-12months</sub> <sup>c</sup> (pg·month/mL)	3,594.0 [28.2 %]	3,495.4 [26.5 %]	0.97	0.88-1.07
AUC <sub>0-24months</sub> <sup>d</sup> (pg·month/mL)	5,873.9 [31.1 %]	5,783.1 [25.1 %]	0.98	0.88-1.10
AUC <sub>12-24months</sub> <sup>d</sup> (pg·month/mL)	2,355.5 [34.0 %]	2,207.3 [25.3 %]	0.94	0.84-1.05
AUC <sub>0-36months</sub> <sup>e</sup> (pg·month/mL)	7,487.0 [31.9 %]	7,453.2 [24.9 %]	1.00	0.89-1.11
AUC <sub>24-36months</sub> <sup>e</sup> (pg·month/mL)	1,652.5 [33.7 %]	1,613.0 [26.9 %]	0.98	0.87-1.10
t <sub>max</sub> (h) <sup>a*</sup>	120.2 [29.1–232.8]	141.2 [47.4-334.5]	-	-

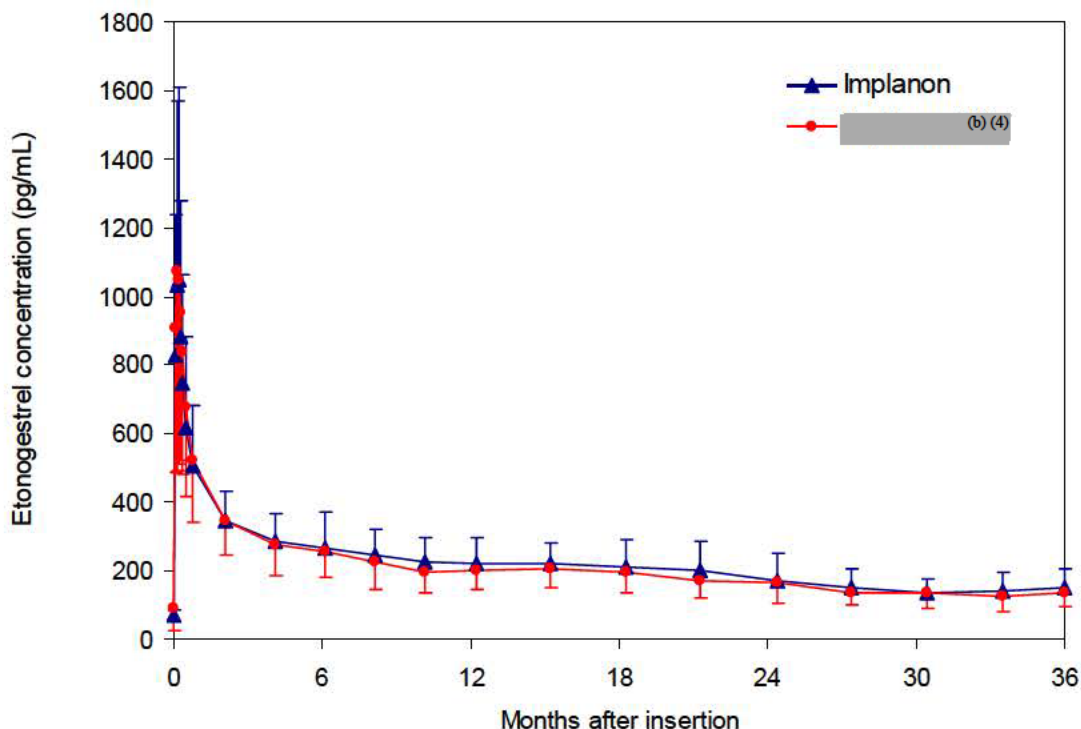
Source: Clinical Pharmacology review of sNDA 21-529/SES-007 dated July 23, 2010, page 3 of 30.  
n1: number of subjects implanted with Implanon, n2: number of subjects implanted with (b) (4);  
<sup>a</sup> n1=53, n2=50; <sup>b</sup> n1=46, n2=46; <sup>c</sup> n1=41, n2=42; <sup>d</sup> n1=32, n2=37; <sup>e</sup> n1=30, n2=32; \* Data presented as median [range].

**Medical Officer's/ Cross Discipline Team Leader's Comments:**

***As shown in Table 1, the 90% confidence intervals (CIs) for the difference between the Test and Reference Least Square Means (LSMs) for the parameters, C<sub>max</sub>, AUC<sub>0-6months</sub>, AUC<sub>0-12months</sub>, AUC<sub>0-24months</sub>, AUC<sub>12-24months</sub>, AUC<sub>24-36months</sub>, and AUC<sub>0-36months</sub> are all within the 0.80 to 1.25 bioequivalence limits for etonogestrel. These results, reported by the Applicant in the sNDA application, demonstrate the bioequivalence between the approved non-radiopaque IMPLANON® and the radiopaque NEXPLANON®.***

Figure 1, also provided in the sNDA application, graphically shows the serum concentration of etonogestrel time curves (arithmetic mean  $\pm$  standard deviation (SD)) serum etonogestrel concentration – time profiles) during the 36 months of Study 34528.

**Figure 1 Arithmetic mean ( $\pm$  SD) etonogestrel concentration-time profiles following implantation of IMPLANON® or NEXPLANON® over 36 months; Study 34528**



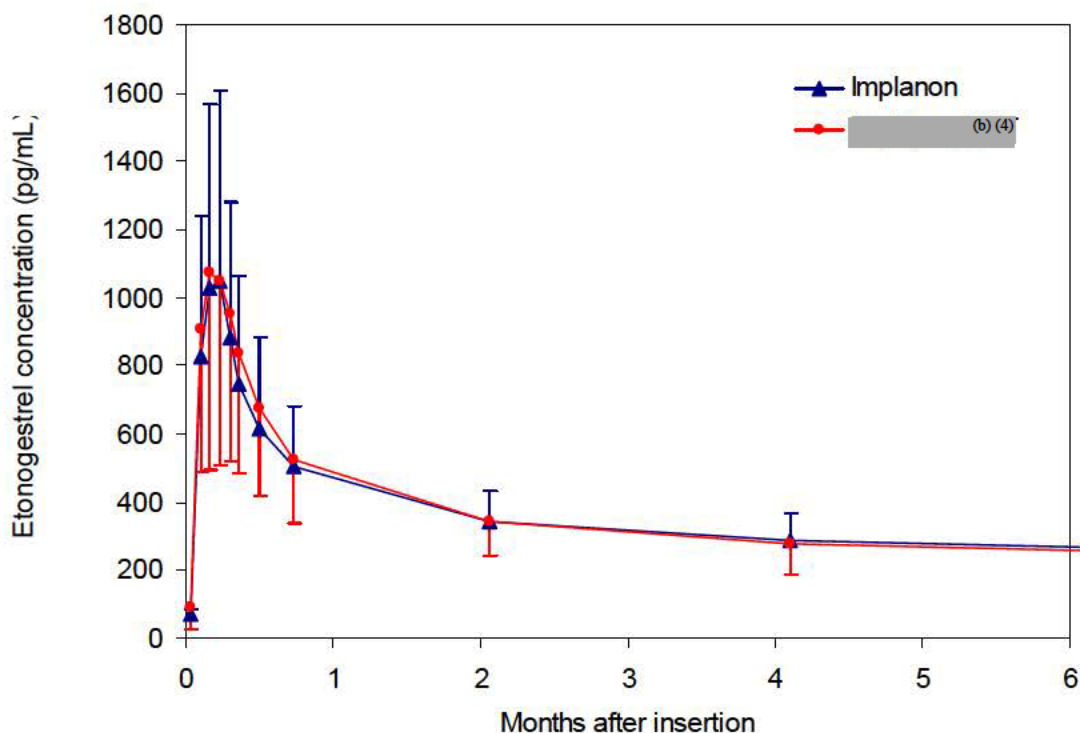
Source: Clinical Pharmacology review of sNDA 21-529/SES-007 dated July 23, 2010, page 7 of 30.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

**Figure 1 shows that the two serum etonogestrel concentration curves are similar during the entire 36 months of Study 34528, including the first 6 months in which the etonogestrel release is higher than in later time periods.**

Figure 2 shows that etonogestrel is rapidly released after the insertion of the IMPLANON® and NEXPLANON® implants. Maximum serum etonogestrel concentrations were reached within two weeks.

**Figure 2 Arithmetic mean ( $\pm$  SD) etonogestrel concentration-time profiles following implantation of IMPLANON® and NEXPLANON® over first 6 months; Study 34528**



Source: Clinical Pharmacology review of sNDA 21-529/SES-007 dated July 23, 2010, page 8 of 30.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***As shown in Figure 1 and Figure 2, approximately 30% of etonogestrel was released within first 6 months from both IMPLANON® and NEXPLANON®. Mean concentrations of etonogestrel after month 6 was relatively stable compared to mean concentration of etonogestrel over first few months. Mean concentrations of etonogestrel gradually decreased after month 6 (approximately 270 and 150 pg/mL at months 6 and 36, respectively).***

***Figure 1 shows that the two serum etonogestrel concentration curves are similar during the entire 36 months of Study 34528, including the first 6 months in which the etonogestrel release is the highest (Figure 2).***

Following the requested inspection of the analytical site MSD (Biopharmaceutical Analytical Facility) in The Netherlands by the Division of Scientific Investigations (DSI), DSI issued a Form FDA 483 regarding Study 34528 indicating, but not limited to, the following: (See Section 3 Ethics and Good Clinical Practices, Subsection 3.1

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.  
Supplemental NDA 21-529/SES-007  
Radiopaque Nexplanon® Implant

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Submission Quality and Integrity of this review for a full discussion of the content of the Form FDA 483 issued on March 3, 2010)

“Run/acceptance/rejection decisions were made inappropriately, by averaging replicate determinations of QC sample concentrations. When QC data were calculated in the same way as study sample data, the originally failed run 27 would pass and the passed runs 14 and 36 would fail.”

The Applicant established a new “adapted” dataset for Study 34528, based on this observation and the subsequent exclusion of runs 14 and 36 and inclusion of run 27. In the “adapted” dataset, etonogestrel concentrations were no longer available for the first 4 months after implant insertion for 2 subjects in the IMPLANON® treatment group (Subjects (b) (6) and (b) (6)) and 2 subjects in the NEXPLANON® treatment group (Subjects (b) (6) and (b) (6)) due to the exclusion of runs 14 and 36. Therefore, no pharmacokinetic parameters were determined for these 4 subjects (5 subjects had already been excluded in the original dataset who took prohibited medications before or at the time of implant insertion; 3 in the IMPLANON® treatment group [Subjects (b) (6), (b) (6), and (b) (6)] and 2 in the NEXPLANON® treatment group [Subjects (b) (6) and (b) (6)]). Overall, these additional exclusions resulted in 51 subjects available for analysis in the IMPLANON® treatment group (as compared to the 53 subjects included in the IMPLANON® All-Subjects-Pharmacokinetically-Evaluable [ASPE] group) and 48 subject available for analysis in the NEXPLANON® treatment group (as compared to the 50 subject included in the NEXPLANON® ASPE group). The results of the Applicant’s alternate PK analysis using the “adapted” dataset, which included a total of 99 subjects (92%, 99 of 108 treated subjects), are presented in Table 2.

**Table 2 Applicant’s Results of Bioequivalence Testing Using the “Adapted” Dataset (All-Subjects-Pharmacokinetically-Evaluable Group); Study 34528**

Parameters	Geometric mean [CV]		Ratio (test/reference)	90% Confidence interval
	Implanon (reference)	Nexplanon (test)		
C <sub>max</sub> (pg/mL)	1,020	1,099	1.08	0.92-1.26
AUC <sub>0-6months</sub> <sup>a</sup> (pg·month/mL)	2,248	2,290	1.02	0.92-1.12
AUC <sub>0-12months</sub> <sup>b</sup> (pg·month/mL)	3,621	3,610	1.00	0.90-1.10
AUC <sub>0-24months</sub> <sup>c</sup> (pg·month/mL)	5,825	5,875	1.01	0.90-1.13
AUC <sub>12-24months</sub> <sup>c</sup> (pg·month/mL)	2,281	2,177	0.95	0.85-1.07
AUC <sub>0-36months</sub> <sup>e</sup> (pg·month/mL)	7,387	7,597	1.03	0.91-1.16
AUC <sub>24-36months</sub> <sup>e</sup> (pg·month/mL)	1,610	1,638	1.02	0.90-1.15

Source: Adapted from sNDA 21-529/SES-007 Amendment dated March 24, 2010.

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***Using the Applicant’s “adapted” dataset demonstrated in Table 2, the radiopaque NEXPLANON® implant does not show bioequivalence to the currently approved IMPLANON® for the pharmacokinetic parameter C<sub>max</sub>. The upper limit of the 90% confidence interval (CI) for the radiopaque NEXPLANON® implant was slightly above the upper limit of the acceptance range of 0.80 to 1.25 bioequivalence for etonogestrel (90% CI of 0.92 to 1.26).***

***The effect shown in Table 2 was caused by the exclusion of 4 additional subjects in the “adapted” dataset. These exclusions resulted in a slight shift of the ratios of the point estimate from 1.06 to 1.08 and a corresponding shift in the upper bound of the 90% CI from 1.23 to 1.26.***

The Clinical Pharmacology review, dated July 23, 2010, reassessed the data in Study 34528. In addition to the 5 subjects excluded from analysis in the original dataset and the 4 subjects excluded from the Applicant’s reanalysis due to the DSI findings, the Clinical Pharmacology reviewer excluded 4 additional subjects (Subjects (b) (6), (b) (6), (b) (6), and (b) (6)) because of pre-dose concentrations of etonogestrel that were higher than 5% of each subject’s C<sub>max</sub>. This bioequivalence reanalysis, with a total of 95 subjects, showed that all the pharmacokinetic parameters except C<sub>max</sub> met the

bioequivalence criteria. Per the Clinical Pharmacology reviewer, the “90% CI for  $C_{max}$  was between 0.918 and 1.264.” The Clinical Pharmacology reviewer states the following in his review:

“Although the upper bound of 90% CI for  $C_{max}$  was higher than 1.25, this reviewer believes that this finding is not clinically meaningful for the following reasons.

- 1] (b) (4) is long term use contraceptive over 3 years. The 90% CI for not only AUC over 3 years, but also sectional AUCs ( $AUC_{0-6 \text{ months}}$ ,  $AUC_{0-12 \text{ months}}$ ,  $AUC_{0-24 \text{ months}}$ ,  $AUC_{12-24 \text{ months}}$ ,  $AUC_{24-36 \text{ months}}$ ) met the BE criteria.
- 2] Implanon is for single insertion over 3 years. Since there would be one time period during which  $C_{max}$  occurs over 3 years, there is less concern for 90% CI being over 1.25 by 0.14.
- 3] The review of the safety data in the application and of the requested safety data did not demonstrate safety concerns for the radiopaque etonogestrel implant related to the slightly higher upper limit of the 90% CI for  $C_{max}$  ---.”

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***Per the Clinical Pharmacology review, dated July 23, 2010, the following statement was made: “The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in sNDA 21-529 acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert.”***

***The Division of Clinical Pharmacology 3 Division Director concurred with the recommendation of the Clinical Pharmacology reviewer and made the following statement: “---, following the audit DSI indicated that some of the subjects should be removed from analysis and new statistics generated. When these subjects were removed, the 90% confidence interval for  $C_{max}$  exceeded by upper limit of 125% 1.4% (i.e., 126.4%). Even so, the point estimate for  $C_{max}$  was within the 80-125% limits and the overall confidence interval contained “1”. Given that  $C_{max}$  represents a transient time period for this product and that other measures over the entire “dosing “ period meet their statistical tests, it is unlikely that this represents a meaningful difference.” “I concur with the conclusion as written by the reviewer and his Team Leader in all aspects.”***

***An addendum to the Clinical Pharmacology July 23, 2010 review was completed May 12, 2011. Per the Clinical Pharmacology Addendum review, “agreement on the language in the package insert labeling between the sponsor and the Division was reached on 05/09/2011.” In addition, the Clinical Pharmacology Addendum review corrected the July 23, 2010 review as follows: “Implanon is for single insertion over 3 years. Since there would be one time period during which  $C_{max}$***

**occurs over 3 years, there is less concern for 90% CI being over 1.25 by 0.014 (see subsection 2.2 on page 8 and subsection 2.6 on page 18).**

**Per the May 12, 2011 Clinical Pharmacology Addendum review “The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the NDA 21529 acceptable and there are no pending issues.” This reviewer concurs with the Clinical Pharmacology reviewer’s and the Clinical Pharmacology Division Director’s assessments and recommendations.**

In the original NDA 21-529/S-000 application, an inverse relationship between body weight/body mass index (BMI) and etonogestrel serum concentration was observed (see the Clinical Pharmacology review dated October 27, 2004). In this sNDA application, the Clinical Pharmacology reviewer also evaluated the effect of body weight/BMI and serum etonogestrel concentrations in Study 34528. The mean etonogestrel concentration ( $\pm$  SD)-time profiles by 2 groups, BMI < 25 and BMI  $\geq$  25, following the insertion of approved IMPLANON® and the radiopaque NEXPLANON® were plotted.

In Study 34528, 8 of 53 subjects (15.1%) in the IMPLANON® treatment group and 10 of 50 subjects (20.0%) in the NEXPLANON® treatment group had BMI  $\geq$  25. Per the Clinical Pharmacology reviewer, the difference of mean serum concentrations of etonogestrel for both treatment groups in Study 34528 at each time point over 36 months (months 6, 12, 18, 24, and 36) are within the range of SD for each corresponding time point. The Clinical Pharmacology reviewer stated: “Therefore, there was no observed difference of etonogestrel concentration over 36 months in subjects with BMI <25 and subjects with BMI  $\geq$  25 who were implanted with either Implanon or

(b) (4) ”

Further analysis of the effect of BMI on etonogestrel serum concentration showed that there was neither the trend nor the statistical significance represented by P values of etonogestrel concentration versus BMI concentration in both treatment groups in Study 34528. The Clinical Pharmacology reviewer stated: “Therefore, the PK of

(b) (4)

was not influenced by BMI (18 – 29) in Study 34528.”

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

**See the Clinical Pharmacology review dated July 23, 2010. There is no observed difference in etonogestrel concentrations over 36 months in subjects with BMI < 25 and subjects with BMI between 25-29 in both treatment groups in Study 34528.**

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

**Table 3 List of Clinical Studies**

Study Number (number of study sites) Start Date End Date	Study Design	Age Range Years Mean (SD)	Treatment and Dose	Number of Subjects/Women Years of Exposure	Maximum Duration of Treatment
34528 (9) May 2005 February 2009	Randomized, double-blind, parallel group bioequivalence study	≥ 18 to 43 years 27.1 (6.7)	IMPLANON® (etonogestrel implant) 68 mg  Radiopaque NEXPLANON® implant 68 mg	56/120.7 women years  52 /121.5 women years	3 years (completed)
34530 (23) April 2007 Ongoing	Open-label, non-controlled, multicenter, redesigned applicator use study	≥ 18 to 40 years 28.2 (6.7)	Radiopaque NEXPLANON® implant 68 mg	301/630.6 women years <sup>a</sup>	3 years (ongoing)

Source: Adapted from sNDA 21-529/SES-007; Clinical Trial Report for Study 34528; Interim Report for Study 34530 and Safety Update dated April 8, 2010.

<sup>a</sup>. Study 34530 was ongoing at the time of submission of the sNDA application and the original Safety Update.

### 5.2 Review Strategy

The available clinical data from Study 34528 (3-year final clinical trial report) and Study 34530 (interim analysis of year 1 safety data and year 2 pregnancy outcome data of an ongoing 3-year study) have not been integrated, either between studies, or with the pre-existing clinical database which was the basis for approval of the currently marketed (non-radiopaque) IMPLANON® product.

Study 34528 provides a limited number of subjects (56 in the IMPLANON® treatment group and 52 in the NEXPLANON® treatment group). Therefore, integration of the new clinical data would not provide substantial additional information.

Study 34530 was ongoing at the time of the sNDA submission. The original sNDA application provided an interim analysis of insertion characteristics of the redesigned applicator for 301 insertions (July 2007 was date of last insertion), and safety data for

the insertion day after the implant insertion. A Safety Update, with a cut-off date of March 12, 2010, was submitted April 8, 2010.

DRUP requested and received additional analyses for safety data for Study 23428 and additional verified safety data through one year post insertion for Study 34530. All safety data was reviewed.

On October 13, 2010, the Applicant was requested to provide removal data for Study 34530 for the radiopaque etonogestrel implant. The requested removal data was received on November 30, 2010 and reviewed.

On April 15, 2011, the Applicant was requested to provide an updated Safety Update and an update on the regulatory status of the radiopaque implant outside of the U.S. The requested information was received on April 25, 2011.

### **5.3 Discussion of Individual Studies/Clinical Trials**

#### **Study 34528:**

Study 34528 titled “A randomized, double-blind, parallel group, bioequivalence study of Implanon® and Radiopaque Implanon” is a Phase 3b, randomized, double-blind, parallel group bioequivalence study conducted to demonstrate bioequivalence of IMPLANON® (etonogestrel implant) 68 mg and radiopaque NEXPLANON® (etonogestrel implant) 68 mg. The study protocol for Study 34528 was submitted to IND 42,877.

Non-radiopaque IMPLANON® (etonogestrel Implant) 68 mg is a single rod contraceptive implant of 4 cm length and 2 mm diameter approved July 17, 2006 for women for the prevention of pregnancy. IMPLANON® contains 68 mg etonogestrel (3-ketodesogestrel) dispersed in a matrix of ethylene vinyl acetate (EVA), surrounded by an EVA membrane. Etonogestrel is the active metabolite of desogestrel.

Per the IMPLANON® labeling last approved on February 19, 2009, the etonogestrel dose released by IMPLANON® amounts to “60-70 µg/day in week 5-6 and decreases to approximately 35-45 µg/day at the end of the first year, to approximately 30-40 µg/day at the end of the second year, and then to approximately 25-30 µg/day at the end of the third year.” (See the last approved IMPLANON® (etonogestrel implant) 68 mg labeling dated February 19, 2009.)

The radiopaque NEXPLANON® implant differs from IMPLANON® (etonogestrel implant) 68 mg in the composition of the core as shown in Table 4.

**Table 4 Composition of the IMPLANON® Implant and the NEXPLANON® Implant**

Composition	IMPLANON®	NEXPLANON®
<b>Core of the implant</b>		
Etonogestrel (Org 3236)	68 mg	68 mg
Barium sulfate	-	15 mg
EVA copolymer (28% vinyl acetate)	(b) (4)	(b) (4)
Core implant weight	(b) (4)	(b) (4)
<b>Skin of the implant</b>		
EVA copolymer (14% vinyl acetate)	(b) (4)	(b) (4)
<b>Total implant weight</b>	129 mg	141 mg

Source: Adapted from sNDA 21-529/SES-007, Clinical Overview, Table 1, page 8 of 43.

Definition: EVA = ethylene vinyl acetate.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***As shown in Table 4, in the core of the radiopaque etonogestrel implant, (b) (4) 15 mg of barium sulfate. This corresponds with (b) (4)% v/v BaSO<sub>4</sub>. The addition of barium sulfate serves to facilitate the detection of the implant by x-ray imaging, which is clinically important when the implant is not palpable following insertion.***

The primary objective of Study 34528 was to determine bioequivalence of the approved IMPLANON® implant and the radiopaque NEXPLANON® implant. The secondary objectives were to assess x-ray visibility and the palpability of the radiopaque etonogestrel implant. The applicator used in Study 34528 was the currently approved IMPLANON® applicator.

**Overall study design and plan:**

Inclusion Criteria:

To be included in Study 34528, all of the following inclusion criteria were to be fulfilled. Subjects were to:

- be at least 18 but not older than 40 years of age at the time of screening;
- be in good physical and mental health;
- have regular cycles with a usual length between 24 and 35 days;
- have a body mass index  $\geq 18$  and  $\leq 29$ ; and
- be willing to give informed consent in writing.

Exclusion Criteria:

Subjects met none of the exclusion criteria. Subjects were not to:

- have any of the following contraindications:
  - known or suspected pregnancy,
  - active venous thromboembolic disorders (e.g., deep vein thrombosis, pulmonary embolism),
  - presence or history of severe hepatic disease as long as liver function values had not returned to normal,
  - malignancy or pre-malignancy, if sex-steroid-influenced,
  - undiagnosed vaginal bleeding, or
  - hypersensitivity to any of the components of IMPLANON® or the radiopaque etonogestrel implant.
- have hypertension, i.e., systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg,
- have a history during pregnancy or during previous use of sex steroids of: jaundice and/or severe pruritis related to cholestasis, gallstone formation, porphyria, systemic lupus erythematosus, hemolytic uremic syndrome, Sydenham's chorea, herpes gestationis, or otosclerosis-related hearing loss,
- have present use or use during 2 months prior to the start of IMPLANON® or NEXPLANON®, one of the following drugs: phenytoin, phenobarbital, primidone, carbamazepine, rifampicin, oxcarbazepine, topiramate, felbamate, ritonavir, nelfinavir, griseofulvin or the herbal remedy St John's wort; or
- have administration of investigational drugs within 2 months prior to the start of study drug administration.

Study 34528 had two treatment groups: IMPLANON® (batch number CX 179 used) or NEXPLANON® (batch number CX 180 used). All subjects in each treatment group received trial medication from one batch.

At the implant insertion visit, provided the pregnancy test was negative, the subject was given a treatment number according to a randomization list. Randomization was performed in blocks for each center.

With regard to the day of insertion, the following types of women were identified and the following guidelines used:

- Not using a hormonal contraceptive: IMPLANON® or NEXPLANON® was inserted between days 1 and 5 of the menstrual period.
- After a combination oral contraceptive: IMPLANON® or NEXPLANON® was inserted on the first day after the tablet-free (or placebo) interval.
- After a progestogen-only pill or an implantable contraceptive: IMPLANON® or NEXPLANON® was inserted 7 days after the previous method was stopped. The

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

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woman used a condom during these 7 days plus for the first 7 days after implant insertion.

- After an injectable contraceptive: IMPLANON® or NEXPLANON® was inserted at least 6 months after the last injection. In the meantime, an adequate other method of contraception was used. If another steroid contraceptive was used in the meantime, the starting advice as indicated above was complied with. If no hormonal method was used in the meantime, the IMPLANON® or NEXPLANON® was inserted between days 1 and 5 of the menstrual period (but at least 6 months after the last injection).
- After a first trimester abortion: IMPLANON® or NEXPLANON® was inserted immediately.
- After a delivery or second trimester abortion: IMPLANON® or NEXPLANON® was inserted between days 21 and 28 after delivery/2<sup>nd</sup> trimester abortion. When the implant was inserted after 28 days, the woman was advised to use a condom for the first 7 days after study implant insertion. (If intercourse had already occurred, pregnancy was excluded, or the woman's first natural period was awaited before the actual insertion of the study implant.)

For efficacy measurements, contraceptive efficacy was assessed based on the occurrence of pregnancy with an estimated conception date within the treatment period. If an in-treatment pregnancy was diagnosed the study implant was removed. Data requested on the Pregnancy Data Form, including an ultrasound assessment to determine the location and the gestational age of the fetus, was collected. Pregnancies were categorized as pre-treatment when the estimated date of conception was before implant insertion. Pregnancies were considered in-treatment according to two definitions:

- In-treatment pregnancies were pregnancies with an estimated date of conception from the day of implant insertion up to and including the day of implant removal;
- In-treatment pregnancies were pregnancies with an estimated date of conception from the day of implant insertion up to and including the day of implant removal extended with a period of 14 days.

The efficacy analysis was performed for the All-Subjects-Treated (AST; defined as all subjects who had the study implant inserted) group and Intent-to-Treat (ITT; defined as all subjects allocated a randomization number) group. The efficacy results based on the AST group are presented in the clinical trial report. If the efficacy results in the ITT group differed from the AST group, those results are also presented in the clinical trial report.

Palpation of the inserted IMPLANON® or NEXPLANON® was performed at insertion, at the visits scheduled for Months 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 27, 30, 33, and 36 (prior to implant removal). Per the protocol, the analysis of palpability of the implant was conducted on the actual visit assessment. A  $\pm 1$  month visit window was allowed

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

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for each scheduled assessment in year 1 and a  $\pm 1.5$  month visit window for each scheduled assessment in the second and third year, except for the last window which was expanded to +2 months. Per the application, assessments falling outside the window were excluded from the analyses of that particular visit, but the data were used to determine a last in-treatment assessment. The number and percentage of subjects (and 95% confidence intervals [CI]) with palpability results “palpable” or “not palpable” is presented per assessment (including the last in-treatment assessment) and treatment group.

X-ray imaging was scheduled  $\leq 14$  days after implant insertion and  $\leq 14$  days before implant removal (month 36 or earlier in case of premature discontinuation). The consulting radiologist had the x-ray examination performed by taking at most two x-ray pictures from different angles (maximum of 4 images). The x-ray imaging results (i.e., “clearly visible” or “unclearly/not visible”) were reported using an Interactive Voice Response System (IVRS) and were not recorded in the case report form. Per the application, x-ray results were transferred to the clinical trial database after unblinding at trial end. Copies of x-ray results were made available to investigators after database lock for storage in the subject file.

The number and percentage of subjects (and 95% CI) with x-ray results “clearly visible” or “unclearly/not visible” is presented per assessment and treatment group.

Blood sampling for etonogestrel was collected just before implant insertion (before the actual insertion = Day 1), on Days 3 (2 days after insertion), 5, 7, 9, 11, 15, 22, and Months 2, 4, 6, 8, 10, and 12 in year 1; Months 15, 18, 21, and 24 in year 2; and Months 27, 30, 33, and 36 (or earlier in case of premature discontinuation) prior to implant removal. Per the application, data from the All-Subject-Pharmacokinetically-Evaluable (ASPE; defined as all treated subjects for whom at least one pharmacokinetic parameter could be calculated and who did not have any protocol deviations interfering with pharmacokinetics) group were used for the pharmacokinetic evaluation. Pharmacokinetic parameters were calculated from the concentrations of etonogestrel using the actual sample times:

- $C_{\max}$  and  $t_{\max}$  = the peak concentration ( $C_{\max}$ ) and the time of its first occurrence ( $t_{\max}$ ) were taken from the measured serum concentration data.
- $AUC_{0-6 \text{ months}}$  = the area under the concentration–time (C-t) curve from zero to 6 months was calculated by means of the linear trapezoidal rule. Pre-insertion concentrations above LLOQ were set to zero.
- $AUC_{0-24 \text{ months}}$  = the area under the C-t curve from zero to 24 months was calculated by means of the linear trapezoidal rule. Pre-insertion concentrations above LLOQ were set to zero.

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

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- $AUC_{0-36\text{ months}}$  = the area under the C-t curve from zero to 36 months was calculated by means of the linear trapezoidal rule. Pre-insertion concentrations above LLOQ were set to zero.

Bioequivalence testing was performed based on the above listed parameters. Parametric point estimates of the true ratio test/reference with their 90% and 95% parametric confidence limits (CLs) derived from an analysis of variance (ANCOVA) with factor group on the  $\log_e$ -transformed values were calculated. An acceptance range for bioequivalence testing 0.80-1.25 was used. Bioequivalence was to be concluded if the 90% CIs of  $C_{\max}$ ,  $AUC_{0-6\text{ months}}$ ,  $AUC_{0-24\text{ months}}$ , and  $AUC_{0-36\text{ months}}$  were fully contained within the acceptance range. For the 6-month, 12-month, 18-month, 24-month and 36-month etonogestrel concentrations, classical hypothesis testing on the  $\log_e$ -transformed values using the same ANCOVA model was performed. For  $t_{\max}$  a Wilcoxon rank-sum test was used on non-transformed values. Effects were considered statistically significant if  $p \leq 0.05$  ( $p$ : two-sided tail probability).

Information regarding adverse events was obtained by questioning and examining the subject. All adverse events (AEs) were to be coded using the dictionary of terms from the Medical Dictionary for Regulatory Activities (MedDRA) version 11.1. All Serious adverse events (SAEs) and serious trial procedure-related events (SPEs) were to be reported within 24 hours of awareness to Global Drug Safety (GDS) of Schering-Plough. A “drug related” AE was defined as an adverse event that is definitely, probably, or possibly related to the investigational product according to the investigator. A “non drug-related” AE was defined as unlikely or not related to the investigational product.

The safety analysis was performed for the AST group. Safety data from the in-treatment period (defined as the period between study implant insertion up to and including the day of study implant removal plus 5 days) were used for the statistical analysis.

Other safety assessments included physical examinations, gynecologic examinations, mammography, vital signs and body weight and height measurements. Frequency tables for occurrences of clinically significant findings are presented in the submission.

### Pharmacokinetic Bioequivalence:

See the Clinical Pharmacology Review of sNDA 21-529, dated July 23, 2010 for a complete description of the pharmacokinetic findings reported for Study 34528. See Subsection 4.4 Clinical Pharmacology of this review for a summary of the pharmacokinetic bioequivalence findings in Study 34528.

Contraceptive Effectiveness:

During the August 27, 2007 teleconference with the Applicant, the Division requested that Pearl Indices and life table estimates with 95% confidence intervals (based on the Poisson distribution) be calculated for the following time periods in Study 34528:

- Year 1 (Day 1 – 365)
- Year 2 (Day 366 – 750)
- Year 3 (Day 731 – 1095)
- Cumulative 3 Year (Day 1 – 1095)

The requested information is presented in the submission.

Medical Officer's Comments:

*See Subsection 6.1.4 Analysis of Primary Endpoint(s) of this review for contraceptive efficacy results reported in Study 34528.*

Safety Findings in Study 34528:

See Subsections 7.3 Major Safety Results and 7.4 Supportive Safety of this review for the safety findings in Study 34528.

**Study 34530:**

At the time of the sNDA submission, Study 34530 titled “An open-label, non-controlled multicentre trial to evaluate the insertion characteristics of the radiopaque etonogestrel implant using a next generation applicator” was an ongoing Phase 3b, 3-year, non-U.S. study conducted “to evaluate the use of the next generation applicator and its instructions for proper insertion” of the radiopaque etonogestrel implant (primary objective of Study 34530). The radiopaque NEXPLANON® implant contains 68 mg of etonogestrel and 15 mg of barium sulfate to assist with x-ray visibility when the single rod implant is not palpable following insertion or prior to removal. The redesigned applicator was developed to facilitate the insertion of the implant just below the skin.

The secondary objectives of Study 34530 are to:

- evaluate the removal of the radiopaque NEXPLANON® implant;
- assess overall contraceptive efficacy and safety of the radiopaque NEXPLANON® implant;
- assess x-ray visibility of the radiopaque NEXPLANON® implant; and
- assess subject's expectations and satisfaction with the radiopaque NEXPLANON® implant.

Per the application, only the primary objective and the secondary objective of x-ray visibility are addressed in the sNDA application. “The additional objectives will be addressed in the extension of this report after completion of this trial.” Study 34530 enrolled the first subject on April 27, 2007. The planned study completion (last subject completion) is estimated in October 2010.

According to the application, Study 34530 was initiated because postmarketing surveillance of IMPLANON® revealed that localization of non-radiopaque IMPLANON® *in situ* could be difficult.

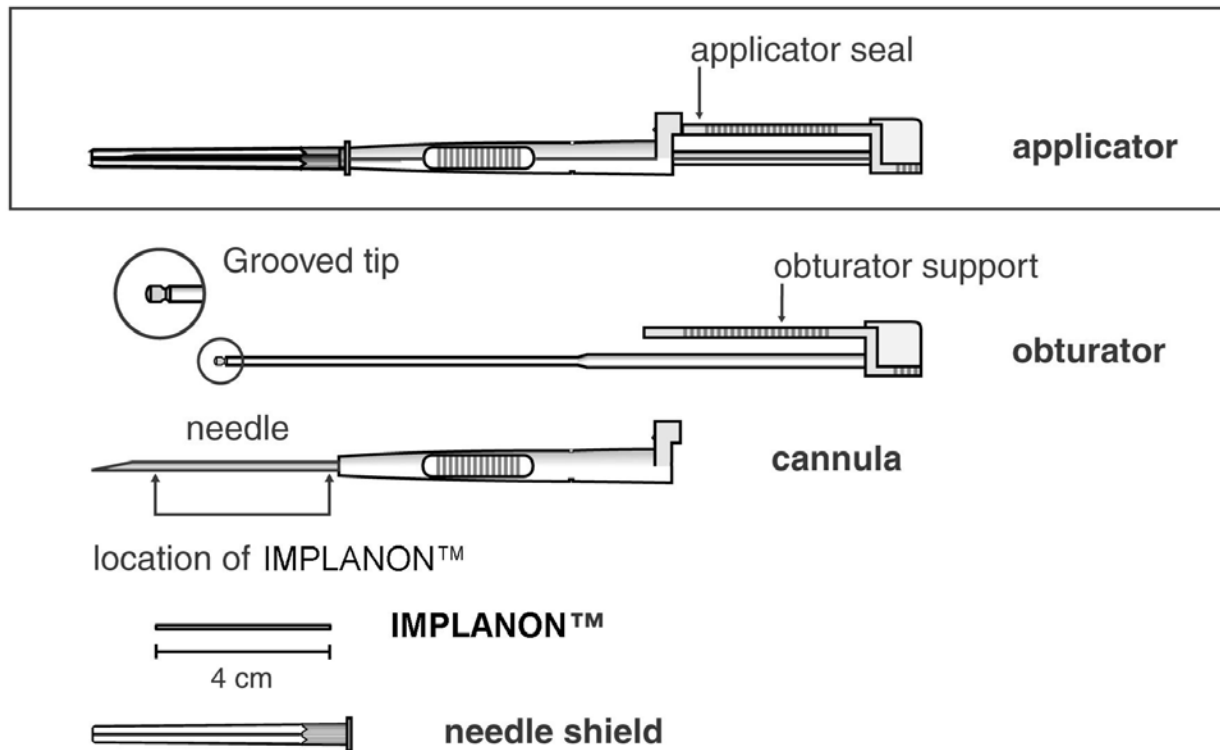
“This especially occurs when insertion has not been performed as instructed in the product physician’s labeling and includes errors such as wrong insertion site, too deep insertion and non-insertion. Techniques available to localize Implanon® *in situ* include palpation (which must be done routinely immediately after insertion) and if the implant is not palpable, ultrasound (US) and Magnetic Resonance Imaging (MRI). If all localization measures fail, serum ENG levels may be determined to verify the presence of an Implanon® implant in the body. However, this obviously does not reveal its localization. Besides, it is a time-consuming and specialized assay, which is only available in a limited number of (Organon) laboratories.”

Therefore, per the Applicant, to extend the diagnostic modalities with equipment that is more widely available (e.g., two-dimensional x-ray imaging), the radiopaque NEXPLANON® implant was developed.

Organon also developed a redesigned applicator for inserting the radiopaque NEXPLANON® implant, referred to as the Next Generation Applicator (NGA). The main goal of the NGA development was to facilitate the insertion of the implant just below the skin.

The current approved IMPLANON® product consists of a single etonogestrel-containing implant which is preloaded in the needle of a disposable applicator. The preloaded applicator is packed in a blister pack which is (b) (4) sterilized. Figure 3 shows the schematic drawing of the current approved IMPLANON® applicator.

**Figure 3 Schematic Drawing of the Current Approved IMPLANON® Applicator**



The following instructions, adapted by this reviewer from IMPLANON® approved labeling, outlines the procedure used for insertion with the current approved applicator. The procedure for the preparation of the patient before and after implant insertion, as well as the procedure for implant removal, can be viewed in IMPLANON® labeling.

1. Carefully remove the IMPLANON® applicator from its blister. Keep the shield on the needle and look for the IMPLANON® rod, seen as a white cylinder inside the needle-tip.
2. If you don't see the IMPLANON® rod, tap the top of the needle shield against a firm surface to bring the implant into the needle tip.
3. Following visual confirmation, lower the IMPLANON® rod back into the needle by tapping it back into the needle tip. Then remove the needle shield, while holding the applicator upright.
4. **Note that IMPLANON® can fall out of the needle.** Therefore, after you remove the needle shield, keep the applicator in the upright position until the moment of insertion.
5. Keep the IMPLANON® needle and rod sterile. If contamination occurs, use a new package of IMPLANON® with a new sterile applicator.
6. Apply counter-traction to the skin around the proposed insertion (Figure 6).

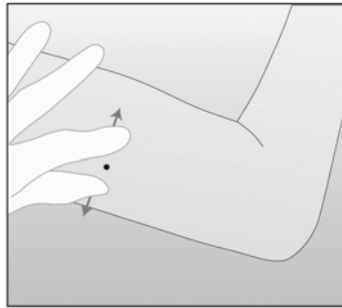


Figure 6

7. At a slight angle (not greater than  $20^\circ$ ), insert only the tip of the needle with the beveled side up into the insertion site (Figure 7).

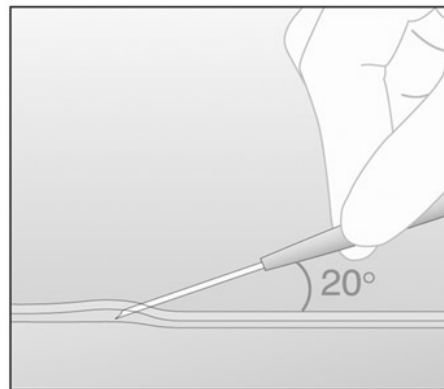


Figure 7

8. Lower the applicator to a horizontal position. Lift the skin up with the tip of the needle, but **keep the needle in the subdermal connective tissue** (Figure 8).

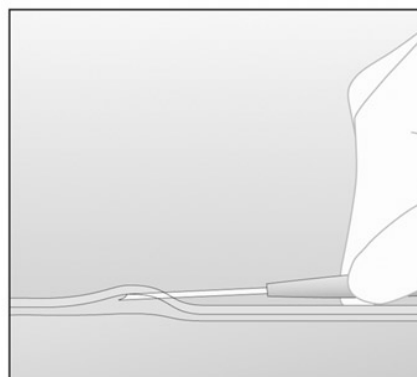


Figure 8

9. While “tenting” (lifting) the skin, gently insert the needle to its full length. Keep the needle parallel to the surface of the skin during insertion (Figure 9).

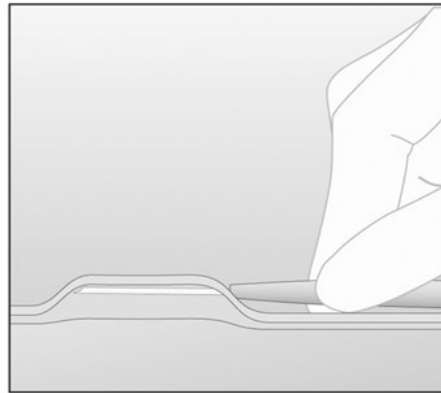


Figure 9

**10. If IMPLANON® is placed too deeply the removal process can be difficult or impossible. If the needle is not inserted to its full length, the implant may protrude from the insertion site and fall out.**

11. Break the seal of the applicator by pressing the obturator support (Figure 10).

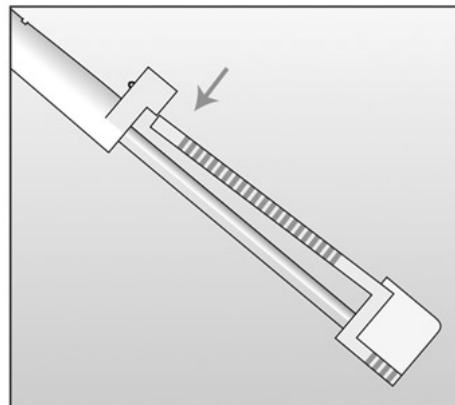


Figure 10

12. Turn the obturator 90° in either direction with respect to the needle (Figure 11).

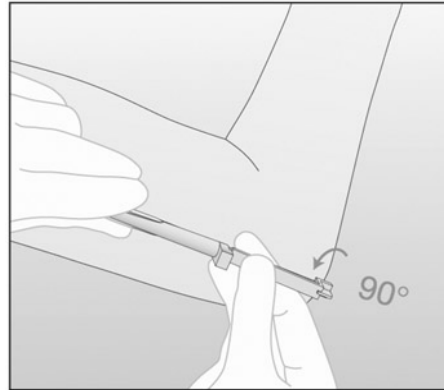


Figure 11

13. While holding the obturator fixed in place on the arm, fully retract the cannula (Figure 12). **Note: This procedure is opposite from an injection. Do not push the obturator. By holding the obturator fixed in place on the arm and fully retracting the cannula, IMPLANON® will be left in its correct subdermal position. Do not simultaneously retract the obturator and cannula from the patient's arm.**

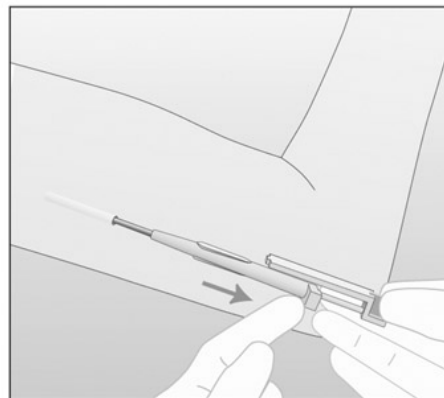


Figure 12

In this figure, the right hand is holding the obturator in place while the left hand is retracting the cannula.

14. Confirm that IMPLANON® has been inserted by checking the tip of the needle for the absence of IMPLANON®. After IMPLANON® insertion, the grooved tip of the obturator will be visible inside the needle (Figure 13).

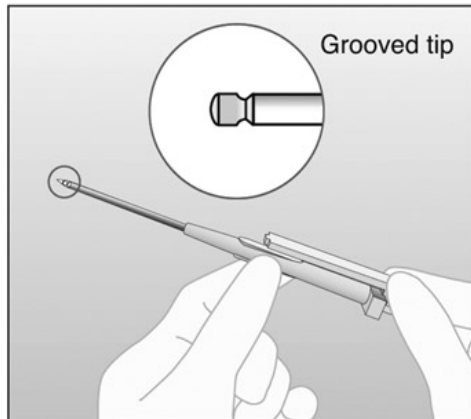


Figure 13

**15. Always verify the presence of IMPLANON® in the patient's arm immediately after insertion by palpation.** By palpating both ends of the implant, you should be able to confirm the presence of the 4 cm rod.

Medical Officer's Comments:

*The instructions for IMPLANON® insertion using the currently approved applicator appear clear.*

Per the sNDA application, the redesigned applicator was developed to:

- facilitate subdermal superficial insertion of the single rod implant by the shape of the applicator,
- prevent the implant from dropping out prematurely, and
- allow single-handed handling of the applicator by healthcare providers during the insertion procedure.

Per the Applicant, the redesigned applicator was developed in close consultation with medical doctors worldwide using pre-defined design requirements. The final design was evaluated in an international use test in Europe, North America, and Asia using an artificial arm (a total of 32 physicians with various levels of experience with IMPLANON® insertions). Study 34530 is testing the use of the redesigned applicator in human subjects.

To establish parameters that were likely to have the greatest impact on the safety and performance of the redesigned applicator, Organon risk management used Failure Mode Effect Analysis (FMEA) during the development process which included:

1. Design FMEA: looked at the applicator combined with a list of possible hazards.
2. Product Process Tree FMEA: looked at the risk per detailed steps of the process using the applicator.
3. Product Parts FMEA: looked at the risk of malfunction per part of the applicator.

Three residual risks with the redesigned applicator were identified:

- the needle protection cap gets loose after dropping the applicator,
- too deep insertions, and
- the user forgets to check whether the implant was inserted correctly.

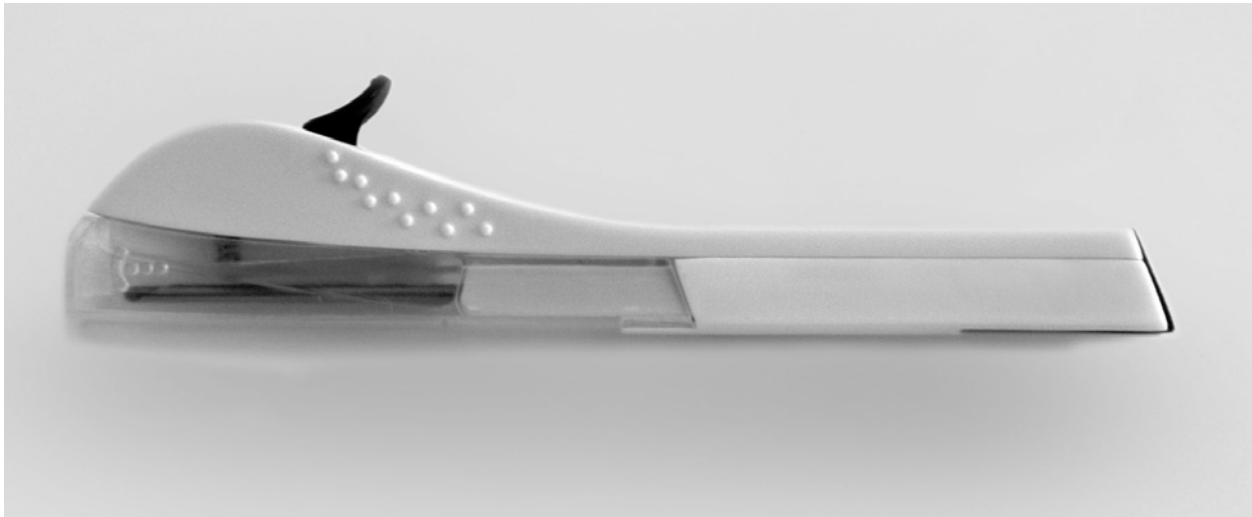
Per the Applicant, all of the information gained has led to the development of the redesigned applicator with the following functionalities:

- “Puncturing of the skin”;
- “Ensure a smooth gliding forward action of the whole needle strictly subdermally”;
- “Release of the implant from the needle in situ while retracting the needle in a one hand action”;
- “Furthermore the applicator further reduces the risk of non-insertions by:
  - making the applicator unusable if no implant is present in the applicator (needle protection cap can not be taken off);
  - holding the implant in the needle after the needle protection cap is taken off until the slider of the applicator is pushed down;
  - making the applicator unusable after complete insertion is performed (which also reduces the risk for accidental needle sticks since the needle is withdrawn entirely in the applicator housing and locked at that position).”

In addition, the new instructions for use and the new instruction video used for training stress: (1) discarding contaminated applicators; (2) how the applicator should be used to prevent too deep insertions; and (3) requires that the implant be checked by palpation following insertion.

As previously described, the redesigned applicator consists of (b) (4) housing, with an obturator made of (b) (4). The stainless steel needle is connected to an (b) (4) needle holder. The needle holder is protected by a needle cap made of (b) (4). In addition, the redesigned applicator has a “lever” which holds the implant in place after removal of the needle protection cap. Figure 4 is a photograph of the redesigned applicator.

**Figure 4 Redesigned Next Generation Applicator (NGA)**



As shown below, the functionalities of the redesigned applicator described in the application include:

- Step 1: The needle protection cap assures that the implant remains inside the needle (1). In case of absence of an implant in the needle, the needle protection cap can not easily be removed as the lever (3 in Step 2) will block the needle protection cap movement.

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- Step 2: Upon removal of the protection cap away from the needle (2) the lever (3) holds the implant in place in the needle.
- Step 3: The shape of the applicator and position of the handle relative to the needle should support proper subdermal insertion of the needle. Upon insertion the lever (4) is pushed upward thereby “unlocking” the implant.
- Step 4. While keeping the applicator in the same position after the needle has been inserted superficially into the subdermal connective tissue, the slider on top of the applicator can be unlocked by pushing down (5). By sliding the slider backwards until it is arrested in the back of the slider groove, the needle is retracted into the applicator housing and the implant (6), held in place by the obturator, is left behind under the skin.
- Step 5: After complete retraction of the slider, the purple tip of the obturator (7) is visible (out of the housing), and the needle is completely retracted into the housing and locked (8); this assures single use of the applicator and should prevent needle stick accidents.

The following instructions, adapted by this reviewer from the proposed insertion procedures in the application labeling, outlines the procedure for implant insertion using the redesigned applicator (not preparation of the patient).

1. Remove the sterile preloaded disposable radiopaque NEXPLANON® implant applicator from its blister.
2. Hold the applicator just above the needle at the textured surface area and remove the transparent protection cap from the needle which contains the implant (Figure 3). If the cap does not come off easily the applicator should not be used. You may see the white colored implant by looking into the tip of the needle. Do not touch the purple slider until you have fully inserted the needle subdermally, as it will retract the needle and release the implant from the applicator.

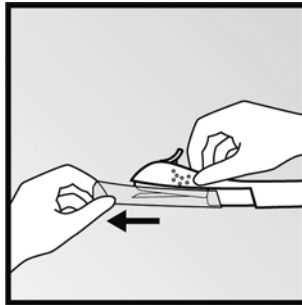


Figure 3

3. With your free hand, stretch the skin around the insertion site with the thumb and index finger (Figure 4).

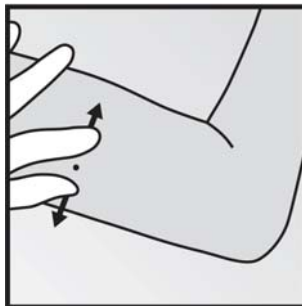


Figure 4

4. Puncture the skin with the tip of the needle angled about 30° (Figure 5)

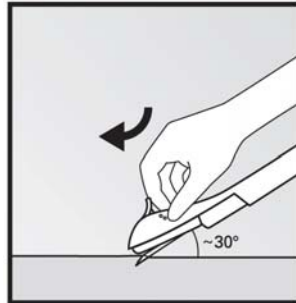


Figure 5

5. Lower the applicator to a horizontal position. While lifting the skin with the tip of the needle, slide the needle to its full length (Figure 6). You may feel slight resistance but do not exert excessive force. **If the needle is not inserted to its full length the implant will not be inserted properly.**

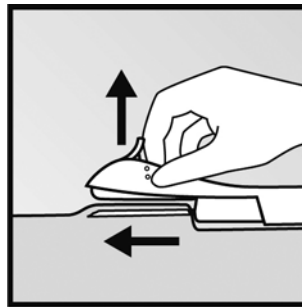


Figure 6

6. While keeping the applicator in the same position and the needle inserted to its full length, unlock the purple slider by pushing it slightly down. Move the slider back until it stops, leaving the implant in its final subdermal position and locking the needle inside the body of the applicator (Figure 7). **If the slider is not completely moved to the back, the needle will not be fully retracted and the implant will not be inserted properly.** The applicator can now be removed.

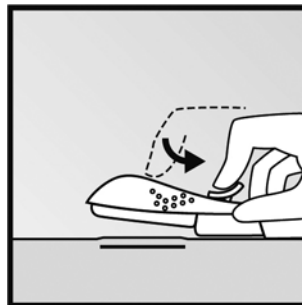


Figure 7

7. **Always verify the presence of the implant in the woman's arm immediately after insertion by palpation.** By palpating both ends of the implant, you should be able to confirm the presence of the 4 cm rod (Figure 8).

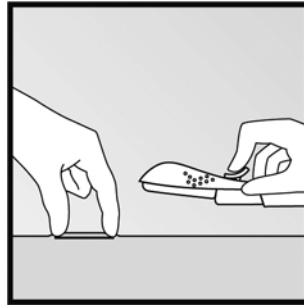


Figure 8

If you cannot feel the implant or are in doubt of its presence,

- Check the applicator. The needle should be fully retracted and only the purple tip of the obturator should be visible.
- Use other methods to confirm its presence. Suitable methods are: two-dimensional x-ray, x-ray computerized tomography (CT scan), ultrasound scanning (USS) with a high-frequency linear transducer (10 MHz or greater) or magnetic resonance imaging (MRI). If these methods fail, call 1-877-IMPLANON (1-877-467-5255) for information on the procedure for measuring etonogestrel blood levels.

**Until the presence of the implant has been verified, the woman should be advised to use a non-hormonal contraceptive method, such as condoms.**

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***In this reviewer's opinion, the redesigned applicator has several positive features which potentially could prevent previously described "shortcomings" of the currently approved IMPLANON® applicator. There include:***

- ***The applicator is unusable if no implant is present in the applicator (the needle cap can not be taken off).***
- ***After removal of the needle protection cap, the implant is held in place in the needle until the skin is punctured.***
- ***The position of the needle below the applicator reduces the risk of too deep insertions.***
- ***The position of the purple slider allows for one-hander retraction of the needle following implant insertion.***

- ***After the insertion, the applicator is not re-usable because the needle is withdrawn entirely in the applicator housing and locked in that position (reduced the risk of accidental needle sticks).***

#### **Overall study design and plan:**

A total of 301 healthy female subjects were treated at 23 clinical trial centers in Australia, France, Germany, Norway, Sweden and the UK. In each country, approximately two “experienced” and two “non-experienced” investigators participated in which “experienced” was defined as performing “more than 10 Implanon® insertions within the past year” and “non-experienced” was defined as performing “10 or less Implanon® insertions within the past year”. Per the application, the first subject entered Study 34530 on April 27, 2007 and the last insertion of the last subject was performed on July 19, 2007.

#### Inclusion Criteria:

To be included in Study 34530, all of the following inclusion criteria were to be fulfilled. Subjects were to:

- be at least 18 but not older than 40 years of age at the time of screening;
- be in good physical and mental health;
- have regular cycles with a usual length between 24 and 35 days;
- have a body mass index  $\geq 18$  and  $\leq 35$  kg/m<sup>2</sup>; and
- be willing to give informed consent in writing.

#### Exclusion Criteria:

Subjects met none of the exclusion criteria. Subjects were not to:

- have any of the following contraindications:
  - known or suspected pregnancy,
  - active venous thromboembolic disorders (e.g., deep vein thrombosis, pulmonary embolism),
  - presence or history of severe hepatic disease as long as liver function values had not returned to normal,
  - malignancy or pre-malignancy, if sex-steroid-influenced,
  - undiagnosed vaginal bleeding, or
  - hypersensitivity to any of the components of IMPLANON® or the etonogestrel radiopaque implant.
- have hypertension, i.e., systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mm Hg;
- have a history during pregnancy or during previous use of sex steroids of: jaundice and/or severe pruritis related to cholestasis, gallstone formation, porphyria, systemic

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

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lupus erythematosus, hemolytic uremic syndrome, Sydenham's chorea, herpes gestationis, or otosclerosis-related hearing loss;

- have present use or use during 2 months prior to the start of IMPLANON® or NEXPLANON®, one of the following drugs: phenytoin, phenobarbital, primidone, carbamazepine, rifampicin, oxcarbazepine, topiramate, felbamate, ritonavir, nelfinavir, griseofulvin or the herbal remedy St John's wort; or
- have administration of investigational drugs within 2 months prior to the start of study drug administration.

At the implant insertion visit, provided the pregnancy test was negative, the subject was given a treatment number according to a treatment list. The investigator was to assign the lowest treatment number available to the new subject who was being assigned. With regard to the day of insertion, the following types of women were identified and the following guidelines used:

- Not using a hormonal contraceptive: NEXPLANON® was inserted between days 1 and 5 of the menstrual period.
- After a combination oral contraceptive (COC), vaginal ring or transdermal patch: NEXPLANON® was inserted on the day after the last active tablet of her previous COC or on the day of removal of the vaginal ring or transdermal patch, but at the latest on the day following the usual tablet-free, ring-free, patch-free interval or following the last placebo tablet of her previous COC.
- After a progestogen-only method (minipill, injectable, an implantable contraceptive, or from a progestogen-releasing intrauterine system [IUS]): NEXPLANON® was inserted any day when the woman was switching from a minipill (from another implant or an IUS on the day of its removal, from an injectable when the next injection would be due).
- After a first trimester abortion: NEXPLANON® was inserted immediately.
- After a delivery or second trimester abortion: NEXPLANON® was inserted between days 21 and 28 after delivery/2<sup>nd</sup> trimester abortion. When the implant was inserted after 28 days, the woman was advised also to use a condom on the first 7 days after study implant insertion. (If intercourse had already occurred, pregnancy was excluded, or the woman's first natural period was awaited before the actual insertion of the study implant.)

The "non-experienced" investigators were not to be supervised by "experienced" investigators. The following checklist was to be followed at the insertion visit:

1. Check the use of any medication and the occurrence of (S)AEs since the screening assessment.
2. Perform urine pregnancy test before implant insertion.
3. Determine breastfeeding status.
4. Insert the implant.
5. Localize the implant by palpation:

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

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- For the first 50 subjects, except in France and Germany: localize the implant by two-dimensional x-ray also (within 1 day after insertion), the results of the x-ray performed were recorded on the CRF;
  - For the remaining subjects (as soon as 50 x-rays were obtained): if the implant is not palpable, the implant should be localized by two-dimensional x-ray and the results recorded on the CRF (if further information on the localization of the implant is needed, an x-ray computer tomogram, US, or MRI can be performed).  
Note: at the German sites, the implant was localized by means of US or MRI only.
6. Inspection of the implantation site.
  7. Fill in implant insertion CRF.
  8. Report any technical complaint related to the applicator (if applicable).
  9. Complete User Satisfaction Questionnaire; only to be completed by the investigator after the 4<sup>th</sup>, 8<sup>th</sup> and 12<sup>th</sup> insertion.

The User Satisfaction Questionnaire was completed and evaluated in order to be able to evaluate the efficacy and ease of use of the redesigned applicator. Before the investigator was allowed to perform the first insertion, he/she had to complete the training session on proper insertion and handling of the redesigned applicator. This training session was held at the Trial Initiation Training Meeting. During this training, the investigator received an instruction leaflet and needed to view an instruction video, both explaining the proper procedure for insertion. The instruction leaflet and video was translated and handed out in each investigator's native tongue (also applicable for the User Satisfaction Questionnaire). After having watched the video and having read the instruction leaflet, the investigator had to perform two successful insertions on a training arm.

All adverse events related to NEXPLANON® or the redesigned applicator were reported on the Adverse Event (AE) Case Report Form (CRF). The investigator could specify if the event was related to the drug, to the redesigned applicator, or both. Information regarding AEs was obtained by questioning or examining the subject and recording the information on the AE CRF. Serious events which could be associated with the trial procedure (rather than the investigational product) also were reported as serious adverse events (SAEs), even if they occurred outside the treatment procedure.

All SAEs were reported as soon as practical (within 24 hours of awareness) to the Drug Safety Surveillance Department (DSSD) of Organon.

A "technical complaint" was defined as any event or complaint relating to the quality or functioning of the investigational product (the radiopaque implant and its applicator) or its packaging. In all cases of a technical complaint, the concerned applicator was kept in order to make a technical investigation possible. The investigator completed a technical complaint CRF which was kept with the device.

Other safety assessments included physical examinations, gynecologic examinations, vital signs and body weight and height measurements. Frequency tables for occurrences of clinically significant findings are presented in the application.

Per the application, Organon has an independent Clinical Quality Assurance (CQA) department that conducts audits “to ensure that clinical trials are performed and the data are generated, documented (recorded) and reported in compliance with Good Clinical Practices, ---.” No audits had been conducted in relation to Study 34530 at the time of the sNDA submission.

The interim report for Study 34530 includes the results of descriptive statistics and supportive listings/figures for:

- demographic and other baseline characteristics,
- medication up to and including insertion day,
- user satisfaction questionnaire results,
- insertion characteristics,
- time for insertion,
- palpability and x-ray visibility following insertion, and
- safety data up to and inclusive of the insertion day.

Demographics are summarized for the All-Subjects-Treated (AST) group. Summary statistics for continuous variables include mean, median, standard deviation, minimum, and maximum. For categorical variables, frequency counts and percentages are presented. No statistical tests were performed.

All subjects who discontinued prematurely from Study 34530 are listed by center and reason for discontinuation. For the primary analysis, no premature discontinuation of treated subjects is presented, and the extent of exposure was not determined.

For the Applicator User (AU) group, major protocol violations (as determined by clinical and biometric personnel) are tabulated and listed per investigator. Investigators with any major protocol violations were excluded from the Per Protocol Applicator User (PPAU) group. The following were considered “major” protocol violations for the Applicator User group:

1. Not having attended the training session;
2. Not following the instructions for the applicator. This was considered to be the case when one of the following answers was given to a question from the Implant Insertion CRF for at least one insertion:
  - Answer “sitting” or “standing” instead of “lying down” on the question “Position of the subject at insertion?”
  - Answer “≥45 degrees” instead of “<45 degrees” on the question “At what angle was the skin punctured with the needle?”

- Answer “no, partial insertion of needle” to the question “Was the needle inserted to its full length into the subdermal connective tissue?”
  - Answer “no, it was not fully retracted and could still be seen” to the question “Was the needle fully retracted and invisible?”, and
  - Answer “no” to the question “Was the implant inserted in the non-dominant arm?”
3. Experienced supervisor present at time of insertion of the implant (only applicable for non-experienced investigators).

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***In total, five (5) investigators (21.7%, 5 of 23 investigators) had a major protocol violation and were excluded from the PPAU for not following the instructions of the applicator.***

**Primary Analysis:**

The analysis for the primary variable was performed for the Applicator User (AU) group. Only data up to and including the day of implant insertion was used. Reporting was scheduled at 1.5 months after the last subject had an implant inserted. In addition, an analysis for the Per Protocol Applicator User (PPAU) group was performed for Study 34530.

**User Satisfaction Questionnaire:**

For the AU group, the number and percentage of the score is presented by assessment (after the 4<sup>th</sup>, 8<sup>th</sup> and 12<sup>th</sup> insertion) and by level of experience for each domain (design, functionality, and safety). Data is also presented for reported overall applicator satisfaction (in response to the question “Taking all things into account, how satisfied or dissatisfied are you with the applicator?”) by assessment.

The User Satisfaction Questionnaire requests that the investigator identify his/her level of experience by providing the following information:

Level of experience with Implanon® insertions:

- more than 10 insertions within the past year
- 10 or less insertions within the past year

The User Satisfaction Questionnaire to be completed after the 4<sup>th</sup> and 8<sup>th</sup> insertion contained the following five questions. The investigator was requested to rate their response using the following classifications: very satisfied, satisfied, not satisfied nor dissatisfied, dissatisfied, or very dissatisfied.

Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

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1. How satisfied or dissatisfied are you with the design and technical aspects of the applicator? (please tick one box per item a-e)
  - a. The fit of the applicator in the hand
  - b. The size of the applicator
  - c. The weight of the applicator
  - d. The handling of the applicator
  - e. The color of the applicator
  
2. How satisfied or dissatisfied are you with the functional aspects of the applicator? (please tick one box per item a-d)
  - a. Verifying the presence of the implant in the needle before insertion
  - b. Guiding the needle into the correct subdermal position by:
    - puncturing the skin
    - lifting the skin to ensure subdermal position of the needle
    - horizontal lowering of the applicator ensuring the steering of the needle in the subdermal position
  - c. The one-hand action during retraction of the needle
  - d. Other, please specify:
  
3. How satisfied or dissatisfied are you with the safety aspects of the applicator? (please tick one box per item a-c)
  - a. The removal of the protection cap from the applicator
  - b. The full retraction of the needle into the applicator after insertion
  - c. The difference in colors of the obturator and the implant, to visually verify that the implant is no longer in the applicator
  
4. How satisfied or dissatisfied are you with the amount of time it takes to perform the insertion? (please tick one box)
  - a. I am .....
  
5. Taking all things into account, how satisfied or dissatisfied are you with the applicator? (please tick one box)
  - a. I am .....

The User Satisfaction Questionnaire to be completed after the 12<sup>th</sup> insertion contained the five questions mentioned above and four additional questions:

6. What would you consider to be the strong points of the applicator and points that could be improved? (In English)

Strong points:

Points for improvement:

7. How would you describe the development of your level of comfort when using the applicator from the first insertion to the current (12<sup>th</sup>) insertion? (In English)
8. How do you anticipate the impact the applicator will have on your practice for future insertions? (In English)
9. Would you recommend it to a colleague? (In English)

Insertion Characteristics:

The insertion characteristics form completed by the investigator at implant insertion contained the following five areas:

1. Preparation of subject for insertion of the implant

Position of the subject:  Lying down;  Sitting;  Standing

Was anything unusual noticed during anesthesia of the insertion site? =  No;  
 Yes, specify what:

2. Preparing the applicator for insertion

How was taking out of the applicator from its blister?  
 Easy;  Difficult, specify why:

Did you experience any difficulty in removing the protection cap from the applicator?  
 No;  Yes, Specify why:

Did you experience any difficulty in holding the applicator at the textured surface?  
 No;  Yes, specify why:

Was it easy to check the presence of the implant in the applicator?  
 Yes;  No, specify why not:

Did you experience any difficulty in keeping the needle and implant sterile?  
 No;  Yes, specify why:

3. Insertion of the implant

Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

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Did you experience any difficulty in puncturing the skin?

No;  Yes, specify why:

At what (estimated) angle was the skin punctured by the needle?

< 45 degrees;  ≥ 45 degrees

Did you experience any difficulty in sliding the needle superficially in the subdermal connective tissue?

No;  Yes, specify why:

To your opinion: was the needle inserted in the correct position into the subdermal connective tissue?

Yes;  No, specify:  Needle inserted too deep  
 Needle inserted too superficial (double puncture)  
 Not easy to determine correct insertion site  
 Other, specify:

Was the needle inserted to its full length into the subdermal connective tissue?

Yes;  No, partial insertion of needle

Did you experience any difficulty in unlocking the purple slider?

No;  Yes, specify why:

Was it clear to you when the slider was arrested in the back?

Yes;  No, specify why:

Did you experience any difficulty in removing the applicator?

No;  Yes, specify why:

Was the needle fully retracted and invisible?

Yes (purple tip of the obturator is visible)  
 No, it was not fully retracted and could still be seen. If no, was there in your opinion a reasonable chance of a needle stick injury?  Yes;  no

Any other remarks:

4. Outcome of the procedure

Date of insertion:

In which arm was the implant inserted?

Left;  Right

Was the implant inserted in the non-dominant arm?

Yes;  No

Where was the implant inserted?

- Above the sulcus bicipitalis medialis (i.e., over the biceps muscle)
- In the sulcus bicipitalis medialis
- Below the sulcus bicipitalis medialis (i.e., over the triceps muscle)
- Other, specify:

Was the implant clearly palpable:

Yes;  No

Was the implant inserted correctly?

- Yes;  No, specify:
- Non-insertion
  - Partial insertion
  - Implant is partly visible
  - (Suspected) deep insertion
  - Other, specify:

Was the overall insertion procedure easy or difficult?

Easy;  Difficult, please specify why:

Do you have any other remarks (suggestions for improvements, any unclear issues etc.) regarding (more than one tick box allowed)

- The applicator
- The (safety and ease of the) insertion procedure
- The packaging
- The instructions for use; specify:

Status at site of implant:  No abnormalities

- Swelling
- Redness
- Pain
- Haematoma
- Expulsion

## 5. Other

Time required for insertion: — (min) — (sec)  
(time for placement, excluding time for anesthesia)

Has subject emergency card been issued?

Yes;  No

Per the application, summary statistics for the AST group on the time for insertion (plus 95% CI) is presented for the AU and PPAU groups for each question per domain (preparation of the subject for insertion of the implant, preparation of the applicator for insertion, implant insertion, and outcome of the implant insertion procedure). In addition, summary statistics are presented by experience level of the investigator (“experienced” versus “non-experienced”).

Palpability and X-Ray Visibility:

The number and percentage of subjects with palpability results (“palpable” or “not palpable”) for the AST group are presented. The 95% CI for the incidence of palpability is also presented.

The number and percentage of subjects with x-ray results at insertion (“clearly visible” or “unclear/not visible”) are presented for the AST group. The 95% CI for the incidence of x-ray visibility is also presented.

Contraceptive Effectiveness:

During the August 27, 2007 teleconference with the Applicant, the Division requested that a year 1 Pearl Index (Day 1 - 365) be presented. The year 1 Pearl Index value is presented in the application.

In a request for information dated March 25, 2010, the Division requested that a year 2 Pearl Index (Day 366 – 750) be provided. This information was made available by the Applicant on April 8, 2010.

Per the application, “contraceptive effectiveness was calculated using only cycles at risk for pregnancy, this excluding cycles without intercourse and cycles with reported condom use during every intercourse.”

Medical Officer’s Comments:

*See Subsection 6.1.4 Analysis of Primary Endpoint(s) of this review for contraceptive efficacy results reported in year 1 and year 2 in Study 34530.*

Safety Findings in Study 34530:

See Subsections 7.3 Major Safety Results and 7.4 Supportive Safety of this review.

## 6 Review of Efficacy

### Efficacy Summary

#### 6.1 Indication

Approved non-radiopaque IMPLANON® (etonogestrel implant) 68 mg is indicated for women for the prevention of pregnancy. See the last approved labeling for IMPLANON® dated February 19, 2009.

Supplemental NDA 21-529/SES-007, submitted on July 29, 2009, proposes the same indication for radiopaque NEXPLANON® (etonogestrel implant) 68 mg.

#### 6.1.1 Methods

The clinical program submitted to evaluate the safety and efficacy of the 68 mg radiopaque NEXPLANON® implant included:

- Study 34528 is a 3-year randomized, double-blind, parallel group, Phase 3b, bioequivalence study of approved non-radiopaque IMPLANON® (etonogestrel implant) 68 mg and the radiopaque NEXPLANON® (etonogestrel implant) 68 mg. The primary study objective was to demonstrate bioequivalence of IMPLANON® and NEXPLANON®. The secondary study objective was to assess x-ray visibility of the radiopaque implant. Study 34528 was initiated on May 23, 2005. The last subject completed the study on February 25, 2009.

Per the Division's request in the August 20, 2007 teleconference with the Applicant, Pearl Index data is provided in this application including full 3-year Pearl Index data for completed Study 34528. However, "Life Table Estimates", also requested during the August 20, 2007 teleconference, are not included in this application. No in-treatment (occurring after implant insertion and before implant removal) pregnancies occurred in Study 34528.

#### **Medical Officer's/Cross Discipline Team Leader's Comments:**

***The available clinical data in completed Study 34528 has not been integrated with ongoing Study 34530, or with the pre-existing clinical database, which was the basis for approval of the currently marketed IMPLANON®. Although Study 34528 was a 3-year study, the number of subjects (56 in the IMPLANON® treatment group and 52 in the NEXPLANON® treatment group) is limited and integration of the new clinical data would not provide substantial additional information. Study 34528 is considered supportive of the original clinical efficacy data.***

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

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- Study 34530 is a 3-year open-label, non-controlled, multicenter, Phase 3 clinical trial conducted to evaluate the insertion characteristics of the radiopaque etonogestrel implant using a newly designed applicator, referred to as the Next Generation Applicator (NGA). Study 34530 was ongoing at the time of the sNDA submission.

The primary objective of Study 34530 is to evaluate the use of the redesigned applicator and its instructions for proper insertion of the radiopaque NEXPLANON® implant. The secondary objectives of the study are to:

- assess x-ray visibility of the radiopaque NEXPLANON® implant;
- evaluate the removal of the radiopaque NEXPLANON® implant;
- assess overall contraceptive efficacy and safety of the radiopaque NEXPLANON® implant; and
- assess subject's expectations and satisfaction with the radiopaque NEXPLANON® implant.

In the original sNDA application, only the primary objective in Study 34530 and the data for the secondary objective to assess x-ray visibility of the radiopaque etonogestrel implant is address. The interim report submitted covers the snapshot of the database taken on February 28, 2008. Per the Applicant, "All 3-month data were available as well as most of the 6 month data". "The 3-month data have been validated; the 6-month data have not been validated. Data on the implant palpability and on the implant site status have been taken from the Implant Insertion and the Follow-up Case Report Forms. Results are presented for the All-Subjects-Treated group and by planned assessment. In contrast to the described statistical analysis in the protocol, no visit windows have been applied on the implant site status data in order to present all available data for all subjects in this evaluation." Study 34530 was initiated on May 23, 2005. The planned last subject completion was projected as October 2010.

Per the Division's request in the August 20, 2007 teleconference with the Applicant, one-year Pearl Index data is provided in the sNDA application for on-going Study 34530. In a letter dated March 25, 2010, the Division requested that Pearl Index data for year 2 be provided given the estimated completion date of October 2010 for Study 34530.

The interim analysis of Study 34530 includes insertion data on 301 subjects along with x-ray data from 61 subjects.

Also included in the original sNDA 21-529/SES-007 application is a white paper "Risk Assessment of Barium Sulfate as an Excipient in the Radiopaque Etonogestrel Implant" to evaluate the safety of barium sulfate.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***DRUP requested and received additional analyses for safety data for Study 34528 and additional verified safety data through one year post insertion for Study 34530. All safety data was reviewed.***

***On October 13, 2010, the Applicant was requested to provide removal data for Study 34530 for the radiopaque etonogestrel implant. The requested removal data was received on November 30, 2010 and reviewed.***

***On April 19, 2011, the Applicant was requested to provide an updated Safety Update, primarily for Study 34530, to include all serious AEs and premature terminations through the completion of the study. The requested information was received on April 25, 2011.***

***See Section 7.3 Major Safety Results of this review for a full discussion of all safety data received and reviewed.***

## **6.1.2 Demographics**

### **Study 34528 Demographics:**

The demographics in Study 34528 are shown in Table 5.

**Table 5 Demographics for Study 34528, All-Subjects-Treated Group**

Parameter	Statistic	Treatment group		
		Implanon® N=56	Nexplanon® N=52	Combined <sup>a</sup> N=108
Age (years) n (%)	18-20	12 (21.4)	11 (21.2)	23 (21.3)
	21-25	18 (32.1)	9 (17.3)	27 (25.0)
	26-30	10 (17.9)	15 (28.8)	25 (23.1)
	31-35	12 (21.4)	6 (11.5)	18 (16.7)
	36-40	4 (7.1)	10 (19.2)	14 (13.0)
	41-45	-	1 (1.9)	1 (0.9)
Age (years)	Mean (SD)	26.2 (6.0)	28.0	27.1 (6.7)
	Median (Min-Max)	25.0 (18-40)	28.0 (18-43)	26.0 (18-43)
Body mass index (kg/m <sup>2</sup> ) n (%)	BMI <18	-	2 (3.8)	2 (1.9)
	BMI 18-≤20	6 (10.7)	5 (9.6)	11 (10.2)
	BMI 20-≤22	25 (44.6)	18 (34.6)	43 (39.8)
	BMI 22-≤24	12 (21.4)	13 (25.0)	25 (23.1)
	BMI 24-≤26	7 (12.5)	8 (15.4)	15 (13.9)
	BMI 26-≤29	6 (10.7)	6 (11.5)	12 (11.1)
Body mass index (kg/m <sup>2</sup> )	Mean (SD)	22.37 (2.31)	22.44 (2.56)	22.40 (2.42)
	Median (Min-Max)	21.50 (18.4-27.7)	22.18 (17.6-28.6)	21.74 (17.6-28.6)
Body weight (kg)	Mean (SD)	62.28 (8.08)	64.44 (8.41)	63.32 (8.27)
	Median (Min-Max)	60.85 (50.0-79.7)	64.40 (49.5-86.0)	62.40 (49.5-86.0)
Race n (%)	Asian	-	1 (1.9)	1 (0.9)
	Black	1 (1.8)	-	1 (0.9)
	Caucasian	53 (94.6)	50 (96.2)	103 (95.4)
	Other	2 (3.6)	1 (1.9)	3 (2.8)

<sup>a</sup> Both study treatment groups combined.

Source: Adapted from sNDA 21-529/SES-007, Study 34528 Clinical Trial Report, Table 7 Demographics at Screening All-Subject Treated Group, page 62 of 94.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***As shown in Table 5, the two treatment groups in Study 34528 were similar in respect to age, BMI, and race. The overall mean age was 27.1 (6.7) years. The majority of study participants in both study groups had a BMI between 20 and 24 (43 subjects [77%] in the IMPLANON® treatment group and 38 subjects [73%] in the NEXPLANON® treatment group). Similarities are also demonstrated for study subjects in both treatment groups with a BMI between 24 and 29 (13 subjects [23%] in the IMPLANON® treatment group and 14 subjects [27%] in the NEXPLANON® treatment group). The majority of subjects in Study 34528 were Caucasians (95.4%, 103 of 108 treated subjects).***

**Study 34530 Demographics:**

The demographics in Study 34530 are shown in Table 6.

**Table 6 Demographics for Study 345230, All-Subjects-Treated Group**

Parameters	Statistics	Nexplanon® (N=301)
Age (years) n (%)	18-20	43 (14.3)
	21-25	79 (26.2)
	26-30	64 (21.3)
	31-35	54 (17.9)
	36-40	61 (20.3)
Age (years)	Mean (SD)	28.2 (6.7)
	Median (Min-Max)	27.0 (18-40)
Body mass index (kg/m <sup>2</sup> ) n (%)	BMI < 18	2 (0.7)
	BMI ≥ 18-20	36 (12.0)
	BMI > 21-22	74 (24.6)
	BMI > 22-24	78 (25.9)
	BMI > 24-26	37 (12.3)
	BMI > 26-29	45 (15.0)
Body mass index (kg/m <sup>2</sup> )	Mean (SD)	23.76 (3.72)
	Median (Min-Max)	23.15 (16.9-35.2)
Body weight (kg)	Mean (SD)	66.11 (11.48)
	Median (Min-Max)	64.20 (41.0-11100)
Race n (%)	Asian	8 (2.7)
	Black or African American	2 (0.7)
	White	287 (95.3)
	Other	4 (1.3)

Source: Adapted from sNDA 21-529/SES-007, Study 34530 Clinical Trial Report, Table 4 Demographics All-Subject Treated Group, page 49 of 590.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***The majority of study subjects in Study 34530 had a BMI between 18 and 24 (63.1%, 190 of 301 subjects) which is similar to the study population in Study 34528. However, a larger percentage of the study population in Study 34530 had a BMI greater than 24 in this study as compared with Study 34528 (37%, 111 of 301 subjects in Study 34530 versus 25%, 27 of 108 subjects in Study 34528). This difference is largely accounted for by the inclusion of women with a BMI > 29 in Study 34530. Approximately 10% of the subjects in Study 34530 had a BMI > 29. This is important given the limited population of overweight women in the original efficacy studies submitted for approval of IMPLANON®. Current approved labeling for IMPLANON® states "The effectiveness of IMPLANON® in overweight women has not been defined because women who weighed more than 130% of their ideal body weight were not studied. However, serum concentrations of ENG are inversely related to body weight and decrease with time after insertion. It is therefore possible that with time IMPLANON® may be less effective in overweight women, especially in the presence of other factors that decrease etonogestrel concentrations such as concomitant use of hepatic enzyme inducers."***

**Overall, Studies 34528 and 34530 demonstrated similarities of age, BMI, weight, and race in their study populations. The majority of study participants in Study 34530 were also White (95%, 287 of 301 treated subjects).**

### 6.1.3 Subject Disposition

#### **Study 34528 Subject Disposition:**

A complete overview of the disposition of subjects by treatment groups in Study 34528 is shown in Table 7.

**Table 7 Disposition of Subjects in Study 34528**

Subjects	Implanon®		Nexplanon®		Combined <sup>a</sup>	
	N	%	N	%	N	%
Assigned a subject number	56	100.0	52	100.0	108	100.0
Treated	56	100.0	52	100.0	108	100.0
Completed the study	32	57.1	32	61.5	64	59.3
Discontinued prematurely	24	42.9	20	38.5	44	40.7

<sup>a</sup> Both study treatment groups combined.

Source: Adapted from sNDA 21-529/SES-007, Study 34528 Clinical Trial Report, Table 4 Disposition of Subjects All-Subjects-Allocated Group, page 56 of 590.

#### **Medical Officer's Comments:**

*In Study 34528, a total of 40.7% of treated subjects discontinued prematurely (44 of 108 subjects) over the 3 year trial. The discontinuations were similar between the two treatment groups (42.9% in the IMPLANON® treatment group versus 38.5% in the NEXPLANON® treatment group). Results from Study 34528 also show similarities in the reasons for discontinuation between the two treatment groups. See the following Table 8.*

**Table 8 Primary Reasons for Discontinuation, All-Subjects-Treated Group in Study 34528**

Primary reason for discontinuation	Implanon® (n = 56)		Nexplanon® (N = 52)		Combined <sup>a</sup> (N = 108)	
	n	%	n	%	n	%
Bleeding irregularities	8	14.3	10	19.2	18	16.7
AEs and other medical problems	9	16.1	5	9.6	14	13.0
Other reasons	6	10.7	4	7.7	10	9.3
Lost to follow-up	1	1.8	1	1.9	2	1.9
<i>Total</i>	<i>24</i>	<i>42.9</i>	<i>20</i>	<i>38.5</i>	<i>44</i>	<i>40.7</i>

<sup>a</sup> Both study treatment groups combined.

Source: Adapted from sNDA 21-529/SES-007, Study 34528 Clinical Trial Report, Table 5 Primary Reason for Discontinuation All-Subjects-Treated Group, page 58 of 590.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***Table 8 shows that the most frequently reported reasons for discontinuation were bleeding irregularities followed by AEs and other medical problems in Study 34528. Bleeding irregularities were also reported as the most common single reason for discontinuations in the original NDA 21-529 application. See the Primary Medical Officer's review dated July 14, 2004.***

***A total of 32 subjects (29.6%, 32 of 108 treated subjects) discontinued due to adverse events. Of these 32 subjects, 14 subjects experienced AEs other than bleeding irregularities (9 subjects in the IMPLANON® treatment group and 5 subjects in the NEXPLANON® treatment group; subjects may have reported more than 1 AE) including: acne (4 subjects), DVT (2 subjects), mood altered (2 subjects), and 1 subjects each for dysmenorrhea, dyspareunia, peripheral arterial occlusive disease, libido decreased, nausea/vomiting, chloasma, implant site sensitivity, skin irritation and weight increased.***

***Overall, 40.7% of subjects in Study 34528 discontinued treatment. This discontinuation rate in non-U.S. Study 34528 is higher than the reported discontinuation rate for non-U.S. studies submitted with the original NDA application (27.6%, 169 of 612 treated subjects in non-U.S. studies). A 40.7% discontinuation rate in Study 34528, however, is slightly less than the discontinuation rate reported in U.S. studies submitted with the original NDA application (48.8%, 161 of 330 treated subjects in U.S. studies). A discontinuation rate of 40% in a 3-year contraceptive study is not excessive and is comparable to, or lower than, that generally observed in studies of combination oral contraceptives.***

***One explanation for this observed difference in discontinuation rates between non-U.S. Study 34528 and non-U.S. studies with "accepted" data in the original***

***NDA application could be differences in the study populations. Six of the 10 non-U.S. studies with “accepted” data in the original NDA application were conducted in Southeast Asia. It is possible that an Asian study population is more “accepting” of irregular bleeding than the European study population participating is Study 34528. Likewise, it appears that a U.S. study population and a European study population are equally “unaccepting” of irregular bleeding.***

***In Study 34528, two subjects were lost to follow-up with the implant in place (Subject (b) (6) in the IMPLANON® treatment group and Subject (b) (6) in the NEXPLANON® treatment group). No further information is available for these two subjects.***

#### **Study 34530 Subject Disposition:**

In the interim report in the sNDA application, only the results of the “in-treatment period” (defined as the insertion day after the implant insertion) are described. For this analysis, the extent of exposure was not determined or tabulated.

No subjects discontinued during this reporting period.

#### **Safety Update:**

The Safety Update submitted April 8, 2010, presented information regarding subject disposition, as of the cut-off date of March 12, 2010, in ongoing Study 34530. Subject discontinuations were based on information derived from the Removal, Termination, and End of Trial (EoT) forms and summarized. Discontinued subjects for whom the EoT Form was not available or incomplete are listed as missing reason for discontinuation. However, the Applicant indicated that this data was “unverified”.

Per the Safety Update, 301 subjects were treated with the radiopaque NEXPLANON®. One hundred twenty-three (123) subjects (40.9%, 123 of 301 treated subjects) have discontinued Study 34530 (Table 9).

**Table 9 Primary Reasons for Discontinuation, All-Subjects-Treated Group in Study 34530<sup>a</sup>**

Reason for Discontinuation	Nexplanon® N = 301 n (%)
AE	89 (29.6)
Pregnancy	0 (0.0)
Withdrawal of consent	1 (0.3)
Other reason	20 (6.6)
Missing	13 (4.3)
<i>Total</i>	<i>123 (40.9)</i>

<sup>a</sup>. Note: Table includes unverified data.

Definition: AE = adverse event.

Source: Adapted from sNDA 21-529/SES-007; Safety Update Report dated April 8, 2010; Table 3 Number (%) of subjects who discontinued by reason for discontinuation in Study 34530 (All-Subjects-Treated Group).

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***In the Safety Update Report, the number of subjects discontinuing Study 34530 (40.9%, 123 of 301 treated subjects) is the same as the discontinuation rate reported in Study 34528 (40.7%, 44 of 108 treated subjects). Likewise, similarity is noted between these two studies for the number of subjects with adverse events (29.6%, 89 of 301 treated subjects with AEs in Study 34530 [including bleeding irregularities] and 29.7%, 32 of 108 treated subjects in Study 34528 [including bleeding irregularities and AEs]).***

**One-Year "Verified" Safety Date:**

On June 21, 2010, the Applicant was requested to provide "verified" safety data through at least one year of treatment for Study 34530. The Applicant responded with the requested information on July 23, 2010. Fifty-eight subjects discontinued for any reason before and including Day 365 in Study 34530. See Table 10 adapted from the information provided.

**Table 10 Single Most Important Reason for Discontinuation (End of Trial Form), All-Subjects-Treated Group in Study 34530<sup>a</sup> (Includes all Discontinuations through Study Day 365)**

Reason for Discontinuation	Nexplanon® N = 301 n (%)
AE	48 (15.9)
Planned pregnancy	6 (2.0)
Other reason	3 (1.0)
Loss to follow-up	1 (0.3)
<i>Total</i>	<i>58 (19.2)</i>

<sup>a</sup> The removal data is taken from the EOT form. In case the EOT form was not present, the removal date was taken from the Removal form.

Source: Adapted from sNDA 21-529/SES-007, One-Year ‘Verified’ Safety Information of Trial 34530, Listing 4 Subjects who discontinued from the trial for any reason before and including Day 365 (Study 34530, All-subject-Treated Group), page 141.

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***The “verified” safety data for Study 34530 demonstrates that subjects with AE accounted for the majority of discontinuation in study year 1. An examination of the single most important reason for discontinuation showed that vaginal spotting, menorrhagia, and metrorrhagia was reported by 18 of 48 subjects (37.5%) with adverse events. This reported occurrence is similar to Study 34528, and does not raise any new safety concerns.***

**Updated Safety Update Report:**

On April 19, 2011, the Applicant was requested to provide an update to the previously submitted Safety Update Report (dated April 8, 2010) for completed Study 34530. The Applicant responded with the requested information on April 25, 2011. In total, 145 subjects (48.2%) prematurely discontinued Study 34530. The adverse events most commonly reported as the reason for premature discontinuation were: metrorrhagia (38.7%), menorrhagia and weight gain (13.2% each), acne (11.3%), vaginal hemorrhage (10.4%), and mood altered (9.4%).

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

**Bleeding irregularities, including metrorrhagia, menorrhagia, and vaginal hemorrhage, was the most commonly reported reason for discontinuations in completed Study 34530. This finding is similar to the commonly reported reason for discontinuations in Study 34528 and in the original NDA 21-529 application. This finding does not raise any new safety concerns.**

#### **6.1.4 Analysis of Primary Endpoint(s)**

The primary objective of Study 34528 was to determine the bioequivalence of IMPLANON® (etonogestrel implant) 68 mg and the radiopaque NEXPLANON® (etonogestrel implant) 68 mg.

The primary objective of Study 34530 is to evaluate the use of the redesigned applicator and its instruction for proper insertion of the radiopaque etonogestrel implant.

##### **6.1.4.1 Study 34528 Analysis of Primary Endpoint(s):**

See the Clinical Pharmacology Review of sNDA 21-529/SES-007, dated July 23, 2010, for a full discussion of the pharmacokinetic findings reported for Study 34528. See Subsection 4.4 of this review for this reviewer's summary of the pharmacokinetic findings in Study 34528.

Although Study 34528 was designed as a bioequivalence study, the Division requested that the Applicant provide Pearl Indices and life table estimates with 95% confidence intervals (based on the Poisson distribution) for the following time periods in Study 34528:

- Year 1 (Day 1 – 365)
- Year 2 (Day 366 – 750)
- Year 3 (Day 731 – 1095)
- Cumulative 3 Year (Day 1 – 1095)

##### Contraceptive Efficacy in Study 34528:

No pregnancies occurred after implant insertion and before implant removal in Study 34528. Therefore, the application does not include life table estimates. After removal of the implant, however, one (1) subject in the NEXPLANON® treatment group became pregnant within 14 days after implant removal (Subject (b) (6); discontinuation on Day 835; pregnancy wish; estimated day of conception was day 7 after implant removal). Three (3) subjects became pregnant 15 or more days after implant removal (1 in the IMPLANON® treatment group [Subject (b) (6), estimated day of conception was day 15] and 2 in the NEXPLANON® treatment group [Subject (b) (6), estimated conception was day 38 after implant removal, and Subject (b) (6), estimated conception was day 302 after implant removal]).

##### *Overall Pearl Index Estimate*

With 1 pregnancy occurring in the period after implant removal up to and including 14 days thereafter in the NEXPLANON® treatment group, the estimated overall Pearl Index (PI) with the 95% confidence interval (CI) for the All-Subjects-Treated (AST)

group equals 0.41, 95% CI (0.01, 2.30) for both treatment groups combined (IMPLANON® plus the NEXPLANON® treatment groups) and 0.82, 95% CI (0.02, 4.59) for the NEXPLANON® treatment group alone. See Table 11 reported by the Applicant.

**Table 11 Overall Pearl Index With 95% Confidence Intervals in Study 34528, All-Subjects-Treated Group (Based on Cumulative 3-Year Data (Day 1 through Day 1095))**

Type of in-treatment pregnancy	Treatment group as randomized	Number of Subjects	Number of 28-day cycles	Number of women-years	Number of pregnancies	Pearl Index estimate	95% confidence interval
Occurring before implant removal	Implanon® implant	56	1574.3	120.7	0	0.000	0, 3.06
	Radiopaque Nexplanon® implant	52	1585.1	121.5	0	0.000	0, 3.04
	Combined	108	3159.4	242.2	0	0.000	0, 1.52
Occurring before removal + 14 days after removal	Implanon® implant	56	1574.3	120.7	0	0.000	0, 3.05
	Radiopaque Nexplanon® implant	52	1585.1	121.5	1	0.823	0.02, 4.58
	Combined	108	3159.4	242.2	1	0.413	0.01, 2.30

Note: Two sided 95% CI for Pearl Index was calculated by assuming underlying Poisson distribution. If PI=0 (no pregnancies), an upper confidence limit of 97.5% was used.

Source: sNDA 21-529/SES-007 Final Study Report, Module 2.5 Clinical Overview, Table 14.2.1-1.5 Overall Pearl Index with 95% confidence intervals, All-Subjects-Treated group, page 192 of 590.

In the FDA Statistical Review, dated April 9, 2010, the Statistical reviewer calculated Pearl Index values for all subjects in Study 34528. Pearl Index values based separately on each of study years 1, 2, and 3 and cumulative data over the 3-year study are provided in Table 12.

**Table 12 Pearl Index Calculations of Treatment Failure Rates for On-Treatment Pregnancies Occurring Before Implant Removal AND Occurring Before and Within 14 Days after Implant Removal: All Cycles for ITT Population – All Subjects**

Treatment	N	Number of Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Year 1, Year 2, and Year 3 and Cumulative 3-Year Results not including pregnancy that occurred within 14 days after implant removal					
Year 1 (Day 1-365)					
IMPLANON	56	0	635.2	0	(0, 7.58)
Radiopaque etonogestrel	52	0	623.9	0	(0, 7.71)
Year 2 (Day 366-730)					
IMPLANON	42	0	481.1	0	(0, 10.00)
Radiopaque etonogestrel	45	0	542.1	0	(0, 8.88)
Year 3 (Day 731-1095)					
IMPLANON	33	0	418.8	0	(0, 11.49)
Radiopaque etonogestrel	38	0	446.1	0	(0, 10.79)
Cumulative 3-Year (Day 1-1095)					
IMPLANON	56	0	1535.1	0	(0, 3.14)
Radiopaque etonogestrel	52	0	1612.0	0	(0, 2.98)
Year 3 and Cumulative 3-Year Results including pregnancy that occurred within 14 days after implant removed					
Year 3 (Day 731-1095)					
IMPLANON	33	0	418.8	0	(0, 11.49)
Radiopaque etonogestrel	38	1	446.1	2.92	(0.074, 16.29)
Cumulative 3-Year (Day 1-1095)					
IMPLANON	56	0	1535.1	0	(0, 3.14)
Radiopaque etonogestrel	52	1	1612.0	0.81	(0, 0.020, 4.51)

Source: Adapted from Statistical Review of sNDA 21-529/SES-007, dated April 9, 2010.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***As shown in Table 11 and Table 12, in 3-year Study 34528, one pregnancy occurred in the period after implant removal up to and including 14 days thereafter resulting in an estimated overall Pearl Index of 0.41 with 95% CI: (0.01, 2.30) for both treatment groups combined. This compares favorably with the cumulative Pearl Index of 0.38 pregnancies per 100 women-years of use reported for approval of IMPLANON® (etonogestrel implant) 68 mg. The Pearl Index reported in the Statistical Review for the NEXPLANON® treatment group (0.81) supports the Pearl Index reported by the Applicant for the same treatment group (0.823). See the Statistical Review of sNDA 21-529/SES-007, dated April 9, 2010.***

***This effectiveness information is reported only in support of the original efficacy data for IMPLANON®. The absence of a pregnancy in 3-year Study 34528 (no pregnancies occurred after implant insertion and before implant removal)***

***indicates that contraceptive effectiveness is sustained across the three years of recommended implant use.***

#### **6.1.4.2 Study 34530 Analysis of Primary Endpoint(s)**

The primary objective of Study 34530 was to evaluate the use of the redesigned applicator and its instruction for proper insertion of the radiopaque NEXPLANON® implant. In total, 23 investigators (classified as “experienced” [more than 10 implant insertions within the past year] or “non-experienced” [10 or less implant insertions in the past year]) performed 301 insertions. Study 34530 was ongoing at the time of submission of the sNDA application. An analysis of insertion characteristics are provided in this submission which includes data from all subjects regarding screening, implant insertion, status of implant site after insertion, technical complaints, and User Satisfaction Questionnaire responses (completed to evaluate the efficacy and ease of use of the redesigned applicator after each investigator’s 4<sup>th</sup>, 8<sup>th</sup>, and 12<sup>th</sup> insertion). The specific content of the User Satisfaction Questionnaire can be viewed beginning on page 68 of this review. Table 13 summarizes the results of the User Satisfaction Questionnaire for each domain for all 23 investigators.

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**Table 13 Frequency Distribution (%) of the Responses from the User Satisfaction Questionnaire by Domain and Assessment, Applicator User Group (N = 23)**

Domain <sup>a</sup>	Number of Insertions Completed <sup>b</sup>	Investigator Assessment					
		Missing	Very Satisfied	Satisfied	Not Satisfied nor Dissatisfied	Dissatisfied	Very Dissatisfied
Design and technical aspect	4	0	73.0	23.5	2.6	0.9	0.0
	8	0	73.9	23.5	2.6	0.0	0.0
	12	0	79.1	20.0	0.9	0.0	0.0
Functionality <sup>c</sup>	4	0.0	53.8	32.8	7.6	4.2	1.7
	8	0.0	64.2	28.3	4.2	2.5	0.8
	12	0.9	69.0	25.9	2.6	1.7	0.0
Safety	4	0.0	87.0	11.6	0.0	0.0	1.4
	8	0.0	91.3	7.2	1.4	0.0	0.0
	12	0.0	89.9	8.7	1.4	0.0	0.0
Used time (Insertion Time)	4	0.0	82.6	17.4	0.0	0.0	0.0
	8	0.0	91.3	8.7	0.0	0.0	0.0
	12	0.0	82.6	17.4	0.0	0.0	0.0
Applicator satisfaction	4	0.0	60.9	30.4	4.3	4.3	0.0
	8	0.0	69.6	26.1	4.3	0.0	0.0
	12	0.0	69.6	30.4	0.0	0.0	0.0

<sup>a</sup>. The different domains consist of a different number of questions: “Design/technical aspects” consists of five questions, “Functionality” consists of six questions, and “Safety” consists of three questions. “Used time” and “Applicator satisfaction” are single questions. The domain frequency of a score (for example, “Satisfied”) is the sum across all questions in that particular domain for that score over all investigators.

<sup>b</sup>. Number of insertions completed by the investigator before completing the questionnaire.

<sup>c</sup>. If the question “Other” in the domain “Functionality” was not answered by an investigator, this question for that particular investigator did not contribute to the percentage of that domain.

Source: Adapted from sNDA 21-529/SES-007, Clinical Trial Report for Study 34530, Table 6 Frequency distribution (%) of the User Satisfaction Questionnaire by domain and assessment, Applicator User Group (N = 23), page 52 of 298.

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***Overall, the majority of investigators were either very satisfied or satisfied with the redesigned applicator by the 4<sup>th</sup> insertion (“Applicator satisfaction” domain) and this reported result was sustained through the 12<sup>th</sup> insertion. See Table 13 above. After 12 insertions, 16 investigators (69.6%, 16 of 23 investigators) were very satisfied and 7 investigators were satisfied (30.4%) with the redesigned applicator. For the two investigators who were either dissatisfied or not satisfied nor dissatisfied at the 4<sup>th</sup> insertion, their satisfaction with the redesigned applicator improved by the 8<sup>th</sup> and 12<sup>th</sup> insertions, respectively.***

***Table 13 also shows that all of the investigators were either very satisfied or satisfied with the insertion time from the 4<sup>th</sup> insertion onward to the 12<sup>th</sup> insertion. See Table 16 in this review for insertion times reported in Study 34530.***

***In the “Safety” domain, one investigator answered at the 8<sup>th</sup> insertion not satisfied nor dissatisfied because she indicated that removal of the protection cap from the applicator was difficult. For the other two questions in the “Safety” domain [(1) full retraction of the needle into the applicator after insertion, and (2) difference in colors of the obturator and implant to visually verify that the implant is no longer in the applicator), investigators answered with their satisfaction.***

***In the “Functionality” domain, investigators were satisfied with verifying the presence of the implant in the needle before insertion and with the one-hand action during retraction of the needle. However, not all investigators were satisfied with other aspects of the “Functionality” domain or with the “Design and Technical aspect” domain. Specific reasons for dissatisfaction are discussed in the Medical Officer’s Comments following Table 15.***

The findings of the User Satisfaction Questionnaire were also reported based on the “experience” levels of the investigator to better explore any noted differences in responses. Overall, the more experienced investigators (N = 11; defined as having done more than 10 insertions of IMPLANON® within the past year with the currently approved applicator) were more satisfied with all aspects of the new applicator and its procedure for insertion than less experienced investigators (N = 12, defined as having done 10 or less insertions of IMPLANON® within the past year with the currently approved applicator). See the reported frequency differences in Table 14 and Table 15.

**Table 14 Frequency Distribution of the Responses from the User Satisfaction Questionnaire Based on Investigator Level of Experience (More Than 10 Insertions Within the Past Year), Applicator User Group (N = 11)**

<b>Assessment Domain</b>	<b>Very Satisfied %</b>	<b>Satisfied %</b>	<b>Not Satisfied nor Dissatisfied %</b>	<b>Dissatisfied %</b>
<u>After 4th Insertion</u>				
- Design and technical aspects	80.0	14.5	3.6	1.8
- Functionality	56.7	29.8	5.3	5.3
- Safety	93.9	6.1	-	-
- Used time (Insertion Time)	100.0	-	-	-
- Applicator satisfaction	72.7	18.2	9.1	-
<u>After 8th Insertion</u>				
- Design and technical aspects	85.5	10.9	3.6	-
- Functionality	71.9	24.6	3.5	-
- Safety	97.0	3.0	-	-
- Used time (Insertion Time)	100.0	-	-	-
- Applicator satisfaction	81.8	18.2	-	-
<u>After 12th Insertion</u>				
- Design and technical aspects	90.9	9.1	-	-
- Functionality	75.0	23.2	-	1.8
- Safety	97.0	3.0	-	-
- Used time (Insertion Time)	90.9	9.1	-	-
- Applicator satisfaction	81.8	18.2	-	-

Source: Adapted from sNDA 21-529/SES-007, Clinical Trial Report for Study 34530, Table 14.2-1.1.1.

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**Table 15 Frequency Distribution of the Responses from the User Satisfaction Questionnaire Based on Investigator Level of Experience (10 or Less Insertions Within the Past Year), Applicator User Group (N = 12)**

Assessment Domain	Missing %	Very Satisfied %	Satisfied %	Not Satisfied Nor Dissatisfied %	Dissatisfied %	Very Dissatisfied %
<u>After 4th Insertion</u>						
- Design and technical aspects	-	66.7	31.7	1.7	-	-
- Functionality	-	48.4	35.5	9.7	3.2	3.2
- Safety	-	80.6	16.7	-	-	2.8
- Used time	-	66.7	33.3	-	-	-
- Applicator satisfaction	-	50.0	41.7	-	8.3	-
<u>After 8th Insertion</u>						
- Design and technical aspects	-	63.3	35.0	1.7	-	-
- Functionality	-	57.1	31.7	4.8	4.8	1.6
- Safety	-	86.1	11.1	2.8	-	-
- Used time	-	83.3	16.7	-	-	-
- Applicator satisfaction	-	58.3	33.3	8.3	-	-
<u>After 12th Insertion</u>						
- Design and technical aspects	-	68.3	30.0	1.7	-	-
- Functionality	1.7	63.3	28.3	5.0	1.7	-
- Safety	-	83.3	13.9	2.8	-	-
- Used time	-	75.0	25.0	-	-	-
- Applicator satisfaction	-	58.3	41.7	-	-	-

Source: Adapted from sNDA 21-529/SES-007, Clinical Trial Report for Study 34530, Table 14.2-1.1.1.

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***As shown in Table 14 and Table 15, not all “experienced” and “non-experienced” investigators were satisfied with aspects of the “Functionality” domain and with aspects of the “Design and technical aspect” domain. Reasons given for very dissatisfied and dissatisfied in the “Functionality” domain include:***

**Puncturing of the skin (“Functionality” domain):**

***Three “non-experienced” investigators answered dissatisfaction (one at the 4<sup>th</sup> insertion [Investigator 103], one at the 4<sup>th</sup> and 8<sup>th</sup> insertions [Investigator 125], and one at all three insertions times [Investigator 102]).***

**Lifting the skin to ensure subdermal position of the needle (“Functionality” domain):**

***Two investigators were very dissatisfied at the 4<sup>th</sup> insertion (Investigators 103 [“non-experienced”] and 109 [“experienced”]), but their satisfaction increased to***

***not satisfied nor dissatisfied and very satisfied at the 8<sup>th</sup> and 12<sup>th</sup> insertions, respectively.***

**Horizontal lowering of the applicator to ensure placement of the needle in the subdermal position (“Functionality” domain):**

***Two investigators were very dissatisfied at the 4<sup>th</sup> insertion (Investigators 103 [“non-experienced”] and 109 [“experienced”]), but their satisfaction (both Investigators) increased to very satisfied at the 12<sup>th</sup> insertions.***

**Subdermal sliding of the needle (“Functionality” domain):**

***Three investigators indicated dissatisfaction (Investigators 111 [“non-experienced”; 4 insertions], 112 [“experienced”; 12 insertions], and 125 [“non-experienced”; 8 insertions]). Only Investigator 112 has data present at all three insertion times. Dissatisfaction at the 4<sup>th</sup> insertion remained through the 12<sup>th</sup> insertion for this Investigator.***

***In the “Design and technical aspect of the applicator” domain, more than 95% of the 5 questions were answered very satisfied or satisfied. All investigators reported satisfaction with the fit of the applicator in the hand, the weight, and the handling of the applicator. However, one “experienced” investigator was dissatisfied with the size of the applicator and three investigators (one “experienced” and two “non-experienced”) were “not satisfied nor dissatisfied” with the color of the applicator.***

After the 12<sup>th</sup> insertion, investigators were asked to list strong points and points for improvement of the redesigned applicator:

Strong points listed include:

- One-hand action (9 of 23 investigators)
- Ease of use (8 of 23 investigators)
- Full retraction of the needle into the applicator after insertion (7 of 23 investigators)
- Less chance to perform too deep or wrong insertion (6 of 23 investigators)
- Fast insertion time (3 of 23 investigators)
- Implant can not fall out of the needle before insertion (3 of 23 investigators)

Points for improvement listed include:

- Easier subdermal sliding (4 of 23 investigators)
- Sharpness of the needle (3 of 23 investigators)
- Better visualization of the needle during insertion (3 of 23 investigators reported that it was not easy to see the needle puncturing the skin if the needle in the applicator was not viewed from the side)

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***One of the 3 investigators who recommended “better visualization of the needle during insertion” inserted the radiopaque NEXPLANON® implant while standing, not sitting as per instructions. It is not clear from the information provided if the other two investigators were seated or standing.***

***Final agreed upon labeling recommends: “You can best see movement of the needle if you are seated and are looking at the applicator from the side and NOT from above. In this position, you can clearly see the insertion site and the movement of the needle just under the skin.”***

**Insertion Characteristics:**

At each insertion, the investigators were asked to complete the Implant Insertion Case Report Form (CRF). The content of the Implant Insertion CRF can be viewed beginning on page 70 of this review.

None of the investigators were supervised during implant insertions in Study 34530. The overall insertion procedure was considered “easy” in 100% of the insertions, performed by “experienced” investigators (11 “experienced” investigators performed 141 insertions), per the interim report. Out of the 160 insertions performed by 12 “non-experienced” investigators, 6 insertions were reported as “difficult” (3.8%, 6 out of 160 insertions). The reported reasons were difficulty in puncturing the skin and/or sliding the needle superficially (4 insertions) or because it was one of the first insertions for the investigator (2 insertions).

Some of the difficulties with the redesigned applicator that investigators reported included:

- difficult to take the applicator out from its blister: reported by 1 “non-experienced” investigator
- difficult to remove the protection cap from the applicator: reported by 6 “non-experienced” investigators and 1 “experienced” investigator
- difficult to keep the needle and implant sterile due to wet gloves; reported by 1 “non-experienced” investigator
- difficult to check the presence of the implant in the applicator because it is located deep in the needle: reported by 1 “experienced” investigator
- difficult to hold the applicator at textured surface: reported by 1 “non-experienced” investigator
- difficult to puncture the skin: reported by 8 “non-experienced” investigators and 6 “experienced” investigators. Investigators reported that the needle “seemed not

- sharp or that there was some resistance.” Per the application, technical inspections at Organon did not show any damage to the needle tips
- difficult to puncture the skin at a < 45 degree angle: reported by 16 “non-experienced” investigators and 8 “experienced” investigators
  - difficult to slide the needle superficially in the subdermal tissue: reported by 14 “non-experienced” investigators and 27 “experienced” investigators. It was reported by investigators that they encountered “resistance” in sliding the needle superficially in the subdermal tissue. They sometimes added that this “resistance” increased halfway through the insertions. Per the application, Organon inspected several of these applicators but failed to find damage on the needle tips that could explain extra resistance. (See *Medical Officer’s/Cross Discipline Team Leader’s Comments* below for additional information.)
  - difficult to insert the needle in the correct position into the subdermal tissue: reported by 1 “non-experienced” investigator and 1 “experienced” investigator. In both instances the implant was reported as being inserted too deep
  - difficult to unlock the purple slider: reported by 2 “non-experienced” investigators

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***The reported findings in Study 34530 indicate that the majority of insertions were considered to be “easy” insertions by the investigators participating in Study 34530 (98%, 295 of the 301 insertions performed). All investigators participating in Study 34530 had previously performed IMPLANON® insertions (at least 1 insertion) with the currently approved applicator, however. Although it is apparent that the redesigned applicator for insertion may not be “ideal,” it represents a significant improvement over the currently approved applicator that is used in the U.S.***

***The redesigned applicator contains a “lever locking mechanism” that prevents the implant from falling out of the needle when the protection cap is removed. This lever locking mechanism is “released” when approximately one-half of the length of the needle is inserted subdermally. The force needed to release the lever locking mechanism may account for the reported “resistance” in sliding the needle superficially in the subdermal tissue that increased halfway through the insertion procedure.***

***The two investigators who reported the implant as being inserted too deep both reported that it was “difficult to push the needle through the subdermal tissue.” Both implants were palpable after insertion, however, and no complications were reported at the time of implant removal (Subject (b) (6) on Day 16, and Subject (b) (6) on Day 1115).***

Time for Insertion:

Table 16 shows the implant insertion time (defined as the time from removal of the protection cap from the applicator until retraction of the needle from the arm after insertion). Insertion times were analyzed for 291 insertions (96.7%, 291 of 301 insertions).

**Table 16 NEXPLANON® Insertion Time (in Seconds), Applicator User Group (N = 23)**

	NEXPLANON® Insertions Times (Seconds)							
	n	Mean	SD	Min	P25	Median	P75	Max
Experienced Investigator (N = 11)	141	18.7	15.1	2	10	15.0	21	95
Non-Experienced Investigator (N = 12)	150	36.6	36.1	7	15	25.0	45	300
All Investigators (N = 23)	291	27.9	29.3	2	12	19.0	32	300

Source: Adapted from sNDA 21-529/SES-007, Clinical Study Report for Study 34530, Table 8 Implant insertion time (in seconds). Applicator User Group (N = 23), page 57 of 298 and Table 14.2-3.2 Implant insertion times (in seconds), Applicator User Group (N = 23), Section 14.2, page 74 of 84.

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***On average (SD), 18.7 (15.1) seconds were needed by the “experienced” investigators for insertion of the radiopaque NEXPLANON® implant using the redesigned applicator. This is compared with an average of 36.6 (36.1) seconds reported for the “non-experienced” investigators. Per the application, a total of three “non-experienced” investigators reported at least once an insertion time of two minutes or more.***

***A mean (SD) insertion time of 1.33 (1.35) minutes (range of 0.3 minutes to 7.5 minutes) was reported in Study 34528 with the use of the currently approved applicator. See Table 19 of this review.***

***The one hand action of the redesigned applicator may be a factor in the reduced insertion time reported in Study 34530.***

**6.1.4.3 Center for Devices and Radiological Health Consult**

A Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), General Hospital Devices Branch consult was requested to evaluate the redesigned insertion applicator for the NEXPLANON® implant on February 18, 2010.

CDRH first responded to the consult request on April 29, 2010. There were several subsequent interactions between CDRH and DRUP and information requests to the Applicant.

The CDRH reviewer initially identified several deficiencies in the original materials provided and requested the following additional information from the Applicant “related to your device component”:

- Risk Management Report
- Design Verification test protocols and reports
- Design Validation protocols and reports
- Explicitly state the functional tests and the quantitative endpoints for release specification

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***CDRH was not initially provided the interim report of Study 34530 included in the application in the February 18, 2010 consult request. At the time of the sNDA application, Study 34530 was an ongoing applicator use study conducted to report the results of 301 implant insertions with the redesigned applicator and the radiopaque implant. On May 11, 2010, a second CDRH consult was requested providing the absent interim report.***

As previously noted, the CDRH initial evaluation of the sNDA application identified several protocols and reports for the redesigned applicator that had not been included in the original NDA submission. These included:

- Risk Management Report
- Design Verification Test Protocols and Reports
- Design Validation Protocols and Reports

The Applicant was requested to provide the missing information on May 11, 2010 and responded with the requested information on June 4, 2010.

In the Risk Management Report, the Applicant identified the following residual risks and the associated risk/benefit analysis:

Residual risk	Risk benefit analysis
Cap coming loose after dropping the applicator	Cap needs to be easily removable during the procedure because otherwise the physician might cut himself when the cap suddenly comes off after using more force. This contradicts with the cap staying in place when the applicator is dropped. Therefore, it is accepted that the cap can come loose when the applicator is dropped. The physician is obliged to and urged to discard contaminated applicators. The instructions are clear on this point.
Too deep insertions	Due to the design of the next generation applicator, too deep insertions are less likely to occur compared to the current applicator. However, it is still possible to insert the implant too deep, which may result in a situation that the presence of the implant cannot be checked by palpation and might lead to problems at removal. The Clinical Trial Report (Study 34530) concludes: "The Next Generation Applicator is an appropriate device." Considering the change of the applicator design, the situation for this scenario with the NGIA is definitely improved, compared to the current applicator. In addition, since the implant is now made radiopaque, the presence of the implant can easily be verified by x-ray. The user test results also show that the instruction video is a good complementary way of instruction for the physician. As a result of this clinical study, a recommendation to perform the insertion in a sitting position and a warning that the needle needs to be inserted completely has been added to the insertion instructions.
User forgets to check if Implanon is correctly inserted	A check by palpation for the presence and position of the implant in the arm of the patient shall remain an important part of the instructions for the physician. Use test results show that the instruction video is a good complimentary way of instruction for the physician. In addition the SmPC (approved foreign labeling for IMPLANON NXT), which includes the insertion instructions, also clearly states that the presence of the implant should always be checked by palpation.

The CDRH reviewer indicated his acceptance, in his consultative review signed on July 7, 2010, of the Applicant's analysis of the first and third residual risk, but expressed concern for the second residual risk – too deep insertions.

Per the CDRH reviewer, “In your risk management report, you identify several risks. One of these is identified as “too deep insertions” whereby the implant is delivered at a greater than desired depth into the tissue.”

“Your FMEA states that the applicator is designed to prevent incorrect positioning of the applicator relative to the skin. However, the FMEA also documents clinical results, which demonstrate that the implant may be delivered deeper than desired. You conclude that the residual risks are acceptable. However, you have not provided an analysis of the risks to health from a deep insertion. Rather, your report concludes that the implant may be imaged on x-ray. It is unclear what further steps are to be taken after imaging the deep implant. Your report identifies several labeling mitigations. However, no data or information is presented to demonstrate that these mitigations are effective”

“We are unable to conclude that the residual risks are acceptable, because you have not provided an analysis of the associated risks to health. Please provide validation that labeling mitigations are effective and provide a full analysis of the risks to health associated with deep insertions (including risks associated with x-ray and additional steps to correct the deep insertion), which provides a supportable conclusion that the residual risks are acceptable.”

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***As stated by the Applicant, it is still possible to insert the implant too deep with the redesigned applicator. In this reviewer’s opinion, insertions that are too deep are probably less likely to occur with the redesigned applicator as compared to the currently approved applicator. In addition, because the new implant is radiopaque, one complication of a too deep insertion (localization of the implant) should be significantly reduced.***

The July 7, 2010 CDRH review also identified the following two additional deficiencies:

- “For the design verification test, “Force to disassemble protection cap from housing (Implant not inserted in needle)” [SOP 0002 (document # 3-0271-TREP-0049, v.3.0)], the requirement is Force (b) (4). The test results demonstrate several results (b) (4). It does not appear that you have addressed these failures.”
- “For the drop test, your stated design requirements are no device deformation and device functionality. The results demonstrate several test samples with deformation, which were also non-functional. You have not addressed these failures.”

“Please address failures for both tests, including the cause of the failures, corrections to prevent recurrence of the failures, and provide verification that the corrections are effective.”

The Applicant was requested to respond to the CDRH deficiency, and responded on August 9, 2010 regarding too deep Insertions, and on July 7, 2010 regarding the design verification test and the drop test.

Per the information received regarding the design verification test, the CDRH reviewer states in his review dated August 19, 2010 that it was unclear to him why the Applicant asserted that the failures were likely due to manufacturing defect. Per the CDRH review, the Applicant “states that since the failed samples met the specification when retested, it implies the assembly error.” The Applicant also provided a test of an additional (b) (4) samples (all pass), which was performed (b) (4) to exclude test artifact, but failed to provide the protocol/report for the test. The CDRH reviewer requested that the Applicant, “Provide an analysis detailing the potential failure mechanisms that could lead to the lock-out feature failing, define (b) (4) testing, and provide the test protocol/report for the (b) (4) additional samples.”

Regarding the information received on the drop test failures, the Applicant stated that the redesigned applicator would not be used if dropped. The CDRH reviewer recommends in the review dated August 19, 2010 that “--- it is appropriate to include statements in the labeling warning that dropped applicators should not be used” because “--- data demonstrate functional damage may occur and non-aseptic conditions may occur.”

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***This reviewer concurs with the CDRH recommendation that product training and labeling must clearly instruct the healthcare provider to perform the entire insertion procedure under aseptic conditions. Final agreed upon labeling recommends: “Insert NEXPLANON under aseptic conditions” and lists the equipment needed for implant insertion under aseptic conditions.***

On August 9, 2010, the Applicant responded with information regarding deep implant insertions with use of the currently approved applicator. The redesigned applicator has only been used in the current ongoing applicator use Study 34530. Per the information received, deep insertions reported with the currently approved applicator (not the proposed redesigned applicator) are low. A total of (b) (4) Insertion Evaluation Forms have been received from Applicant-trained healthcare professionals participating in the Active Monitoring Program (AMP) since product launch in 2006. Nineteen (19) cases of deep insertions have been reported in the approved IMPLANON® AMP for a reporting rate of (b) (4)%. The Applicant estimates that (b) (4) IMPLANON® implants have been inserted by healthcare providers not registered for the AMP. Through spontaneous reporting, a total of 121 U.S. cases of deep insertions have been reported for approved IMPLANON® for a reporting rate of (b) (4)%.

Per the Applicant, deep insertions can be associated with:

- “possible nerve injury resulting in local neurosensory changes such as paresthesia and hypoesthesia”
- “difficulty localizing an implant, via palpation, because it is too far from the surface necessitating further localization methods”
- “implant migration which can result in difficult localization”
- “difficult implant localization can lead to the risk of an implant not found”
- “difficulty removing the implant which may require surgical removal in an operating room under general anesthesia”

One (1) of the 19 deep insertions reported in the approved IMPLANON® AMP was associated with paresthesia reported as non-serious. Seven (7) of the 121 spontaneous reports of deep insertions for approved IMPLANON® were associated with possible nerve injury and local neurosensory changes, also reported as non-serious.

“Removal problems” were reported for 15 of the 19 cases of deep insertions originating from the AMP. None of these cases required general anesthesia, but involved, “enlarging the incision, difficulty dissecting the fibrous tissue surrounding the implant, difficulty in grasping the implant, failed first attempts and/or took longer than normal.” Fifty-two (52) of the 121 cases of deep insertions spontaneously reported had “removal problems”. “Removal problems” were similar as stated above, but 4 of these 52 cases required general anesthesia with successful removal of the implant.

Per the Applicant, “Based upon these low numbers of non-serious cases, it can be concluded that the health risk is very small when compared with the unique contraceptive compliance benefit.” The redesigned applicator “is designed to facilitate correct insertion.”

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***This reviewer acknowledges that it is still possible to insert the implant too deeply with the redesigned applicator. As previously discussed, Study 34530 results demonstrate that two investigators (8.7%, 2 of 23 investigators) had difficulty inserting the needle in the correct position into the subdermal tissue which resulted in the radiopaque etonogestrel implant being inserted “too deep” (0.7%, 2 of 301 total insertions; Subjects (b) (6) and (b) (6)). These two investigators answered the question, “Was the implant inserted correctly?” with a no response and checked “(Suspected) deep insertion”. Both implants were palpable following insertion, however, and remained palpable at the 3- and 6-month evaluation of implant palpability. One of the “too deep” insertions was performed by an investigator classified as “experienced” (defined as having performed 10 or more IMPLANON® insertions in the previous year), and one was***

**performed by an investigator classified as “non-experienced” (defined as having performed 10 or less IMPLANON® insertions in the previous year).**

**Additional safety data for these two subjects in the One-Year “Verified” Safety Data submitted on July 26, 2010 for Study 34530 shows that Subject (b) (6) had the radiopaque etonogestrel implant removed without difficulty on (b) (6) (study Day 16). No removal adverse event was reported for this subject. Subject (b) (6) terminated study participation due to “mood change”. Subject (b) (6) reported headaches, increased appetite, and weight gain within the first 60 days following implant insertion, and continues study participation. No removal adverse event was reported for this subject (NEXPLANON® was removed on study Day 1115).**

**The U.S. Steering Committee’s (established by the Applicant to review the data from spontaneous reporting of insertion and removal-related events and the AMP on a quarterly basis) review of the approved IMPLANON® insertion and removal-related events across 16 reporting periods since approval in 2006, reports no evident trends for neurovascular injury cases due to deep insertions. Per the U.S. Steering Committee’s review, the 6 cases describing possible nerve or vascular damage in the 16<sup>th</sup> IRRE report (covering April 17, 2010 through July 16, 2010) “were not serious” and do not necessitate any modifications to the CTP or the AMP or product labeling. This reviewer agrees.**

A CDRH Human Factors Review was completed on July 22, 2010 and amended on August 4, 2010. Per the Human Factors Review:

“Based on subsequent review of a later clinical trial that focused on the insertion characteristics of the “next generation applicator” (Study 34530, July 2008) it appears that good performance was obtained for multiple users and actual insertions. It is, however, not clear in that study whether the modifications to the training video and the design of the applicator were made prior to the 2008 study, and whether improvements in terms of use-error reduction can be demonstrated from the results of that study. Please provide a summary of the modifications to the device and the training video that were made prior to the 2008 clinical trial and a clarification of their effectiveness based on the results of that study.”

The Applicant was requested to provide this information on August 9, 2010 and responded initially on August 11, 2010 with a follow-up response on August 17, 2010. The following summarizes the information provided by the Applicant:

Modification to the device:

- Suggestion: Consider making a prominent, audible, click when unlocking the knob. The suggestion was made to the design team to make the

- healthcare provider more aware in case the implant was accidentally unlocked before insertion of the needle.
- Response: “The applicator parts that were used for the applicator in the clinical study were made in (b) (4) and from the final part materials (b) (4). The use of the final (b) (4) and (b) (4) materials resulted in more exact shaped detailed applicator parts and much smaller tolerances. These changes resulted in a more constant unlocking force, a noticeable resistance and a slight click when the needle is unlocked.”
- Suggestion: Consider a more colorful applicator for the Asian countries ---.
- Response: “--- one single presentation in the whole market would be preferable.”
- Suggestion: Consider communicating the improvements of the NGIA to experienced Implanon users to inform them why the applicator is an important improvement for them too.
- Response: “The Marketing Authorization Holder decided that the NGIA would be put into the market rather neutral, i.e. the NGIA further facilitates the correct insertion of the implant.”

#### Modification to training materials:

- Suggestion: During training, users could be provided with an empty applicator (unannounced, at random) as well to have them experience the effect and reason of the cap blocking mechanism.
- Response: “The MAH decided not to follow this suggestion, since the force to remove the cap is very high in case there is no implant present in the needle (acceptance criterion (b) (4)). In the instruction for use (step 7) and in the instruction video it is stated: **“If the cap does not come off easily, the applicator should not be used.”**”
- Suggestion: Tenting/lifting the skin should be emphasized. The video should explain the applicator’s design (shape and gripping area) can be used during the “mouse under the carpet movement” of the needle.
- Response: “This is included both in the video (included in this response) and in the instructions for use ---.”
- Suggestions: The video should state more clearly what to do if the needle protection cap does not come off with ease.
- Response: “The instructions for use and the video used in trial 34530 clearly explain that the applicator should not be used.”
- Suggestion: Emphasize palpation after insertion.
- Response: “The importance of palpation was recognized and has been emphasized both in the video and in the instructions. It is clearly

shown in the video that both the inserter and the woman should verify the presence of the implant by palpation.”

A final CDRH consult response dated August 24, 2010, and signed by Richard C. Chapman, Acting Branch Chief, General Hospital Devices Branch, updates CDRH's position regarding the previously mentioned deficiencies.

- Regarding the device performance deficiencies, specifically deep insertion, which “---, CDER explained their belief that the risk of deep insertion could not really be mitigated to “zero.”, the consult response states: “Based on our discussion with CDER, we defer to the CDER clinical team with regards to deep insertions.”
- Regarding the device performance deficiencies, specifically force to disassemble protection cap from housing (implant not inserted in needle), “CDRH agrees with CDER that the protection cap is a secondary mechanism to prevent unintended needle sticks with the Implanon needle.” “CDRH recommends that the labeling for the Implanon device be updated to reflect the appropriate disposal of the applicator in a sharps container or other needle stick prevention receptacle.”
- Regarding the Human Factors deficiencies: “Based on our discussion with CDER, it appears that the 2008 clinical study provided data that demonstrated that the Implanon device could be successfully used by multiple users in actual insertions of the Implanon rod into a patient’s arm.” “CDRH defers to CDER with regard to the clinical significance of deep insertions.” CDRH recommended that an advisory statement be conveyed to the Applicant regarding Human Factors/Usability validation testing for all medical devices for future use.

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***The advisory statement regarding Human Factors/Usability validation testing for all medical devices was conveyed to the Applicant on May 9, 2011.***

***Final agreed upon labeling for the radiopaque etonogestrel implant states, “The applicator is for single use only and should be disposed in accordance with the Center for Disease Control and Prevention guidelines for handling of hazardous waste.” This reviewer concurs with the inclusion of this statement in labeling for the radiopaque NEXPLANON® implant.***

***The reported adverse events associated with “deep insertions” with approved IMPLANON® and the currently approved applicator are well documented and tracked in the Applicant’s Active Monitoring Program (AMP) and quarterly reports of spontaneously reported Insertion and/or Removal Related Events (IRREs). All data are reviewed by the Applicant’s established U.S. Steering Committee. This reviewer agrees with the U.S. Steering Committee’s assessment that no medically***

***significant nerve or vascular injury cases, due to deep or wrongly placed implant insertions, are evident across 16 reporting periods since IMPLANON® approval in 2006 that would necessitate any modifications to the CTP or the AMP or product labeling.***

***N.V. Organon, Oss, The Netherlands, a subsidiary of Merck and Co., Inc. will continue to use a controlled distribution system for NEXPLANON®. Spontaneously reported IRREs for NEXPLANON® will be submitted to the Agency quarterly. In addition, the Applicant has agreed to institute an AMP for NEXPLANON® to include 5,000 insertions and removals.***

***This reviewer agrees with the overall assessment by the Center for Devices and Radiological Health (CDRH) that the redesigned applicator is acceptable for insertion of the radiopaque NEXPLANON® implant.***

### **6.1.5 Analysis of Secondary Endpoint(s)**

#### **Study 34528 Analysis of Secondary Endpoint(s)**

The secondary objectives in Study 34528 were to assess x-ray visibility of the radiopaque etonogestrel implant and to assess the palpability of NEXPLANON®.

#### **X-Ray Visibility of Implant in Study 34528:**

Approved IMPLANON® (etonogestrel implant) 68 mg is not radiopaque and is not visible on x-ray imaging.

In Study 34528, fifty (50) of the radiopaque NEXPLANON® implants were clearly visible on x-ray imaging after implant insertion (96.2%, 50 of 52 subjects treated with the radiopaque implant). For 2 subjects in the NEXPLANON® treatment group (3.8%, 2 of 52 treated subjects), the implant was reported as not clearly visible on x-ray imaging (Subject (b) (6) on Day 8 after implant insertion, and Subject (b) (6) on Day 4 after implant insertion). Per the sNDA application, the responsible radiologists reported that the x-rays taken were “technically not performed correctly.” For both Subject (b) (6) and Subject (b) (6), the radiopaque implants were clearly visible on x-ray imaging before implant removal.

The two-sided 95% CIs for the incidence of visibility (i.e., clearly visible results) are presented in Table 17 for radiopaque NEXPLANON®.

**Table 17 Incidence of X-Ray Visibility and the 95% Confidence Interval for the NEXPLANON® Implant in Study 34528, All-Subjects-Treated Group**

Assessment	Nexplanon®	
	Estimated incidence	95% Confidence Interval
After implant insertion	0.962	0.868 – 0.995
Before implant removal <sup>a</sup>	1.000	0.929 – 1.000

a. Two subjects did not have x-ray imaging before implant removal.

Source: Adapted from sNDA 21-529/SES-007, Study 34528 Clinical Study Report, Table 12

Incidence of x-ray visibility and the 95% confidence intervals, All-Subjects-Treated Group, page 70 of 590.

Palpability of Implant Following Insertion in Study 34528:

As a secondary objective in Study 34528, the implant was to be palpated at each visit assessment. Overall, the percentage of subjects with a palpable implant was 100% except for the 12-month and 30-month assessment in the IMPLANON® treatment group. The implant in Subject (b) (6) in the IMPLANON® treatment group was not palpable at the 12-month assessment (Day 355), but was palpable at her early termination assessment on Day 421. The implant in Subject (b) (6) in the same treatment group was not palpable at the 30-month assessment, but was palpable at the 33-month assessment (Day 913) and at removal (Day 1101).

The information presented in the following table includes only non-missing results. If the question “Was the implant palpable” was answered with “not done” the assessment was considered as missing. None of the implants represented in Table 18, however, was inserted with the redesigned insertion device.

**Table 18 Palpability of Study Implant in Study 34528, All-Subjects-Treated Group**

Actual Assessment	Treatment Group					
	Implanon® (N = 56)		Nexplanon® (N = 52)		Combined <sup>a</sup> (N = 108)	
	n	%	n	%	n	%
Implant Insertion	56	100.0	52	100.0	108	100.0
2 months	56	100.0	51	100.0	107	100.0
4 months	53	100.0	48	100.0	101	100.0
6 months	51	100.0	50	100.0	101	100.0
8 months	47	100.0	47	100.0	94	100.0
10 months	47	100.0	41	100.0	88	100.0
12 months	42	97.7	42	100.0	84	98.8
15 months	42	100.0	40	100.0	82	100.0
18 months	38	100.0	42	100.0	80	100.0
21 months	36	100.0	38	100.0	74	100.0
24 months	35	100.0	38	100.0	73	100.0
27 months	33	100.0	36	100.0	69	100.0
30 months	34	97.1	33	100.0	67	98.5
33 months	33	100.0	32	100.0	65	100.0
36 months	32	100.0	34	100.0	66	100.0

<sup>a</sup> Both study treatment groups combined.

Source: Adapted from sNDA 21-529/SES-007, Clinical Study Report for Study 34528, Table 10 Palpability, All-Subjects-Treated Group, Page 69 of 590.

### **Study 34530 Analysis of Secondary Endpoint(s):**

The single secondary objective reported in the sNDA application for Study 34530 was to assess the x-ray visibility of the radiopaque NEXPLANON® implant. Per the application, the additional secondary objectives in this study will be reported upon in the forthcoming final clinical study report following the completion of Study 34530.

#### **X-ray Visibility of NEXPLANON®:**

An x-ray was performed for 61 subjects after implant insertion in Study 34530. All implants were clearly visible [100%, 95% CI using Clopper Pearson approach (0.942-1.000)].

#### **Palpability of Implant Following Insertion in Study 34530:**

The palpability of NEXPLANON® was also reported in the sNDA application. For 300 of the 301 treated subject in Study 34530, the implant was clearly palpable after insertion [99.7%, 95% CI using Clopper Pearson approach (0.982-1.000)]. Per the application, insertion of the non-palpable implant (Subject (b) (6)) was performed by a “non-experienced) investigator who performed the insertion standing rather than sitting (as

instructed) in a poorly lit room. This information was received from personal communication. Although this one implant was non-palpable, it was clearly visible on the two-dimensional x-ray.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***For Subject (b) (6), the implant was not palpable at month 3 or month 6 following insertion. However, no removal complication was reported for this subject. Subject (b) (6) had her implant removed on study Day 1142.***

### 6.1.6 Other Endpoints

**Study 34528 Other Endpoints:**

Insertion time and the outcome of a post-treatment evaluation were reported in Study 34528.

Insertion Time:

In Study 34528, insertion times reported in minutes ranged from 0.3 to 7.5 minutes with a median of 1.0 minutes. The currently approved applicator was used in both treatment groups. See Table 19.

**Table 19 Implant Insertion Time (in Minutes) in Study 34528, All-Subjects-Treated Group**

Treatment Group	n	Mean	SD	Min	P25	Median	P75	Max
IMPLANON®	56	1.21	1.06	0.3	0.33	0.79	2.00	5.0
NEXPLANON®	52	1.46	1.60	0.3	0.31	1.00	2.00	7.5
Combined	108	1.33	1.35	0.3	0.33	1.00	2.00	7.5

Source: Adapted from sNDA 21-529/S-007, Clinical Study Report, Table 14.3.6-2-A Implant insertion time (in minutes), Section 14.3.6 Vital signs, physical findings and other observations related to safety, page 30 of 46.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***Insertion times reported in Study 34528 using the currently approved applicator exceed the insertion times reported in Study 34530 (mean of 1.46 minutes for 108 insertions in Study 34528 versus a mean of 27.9 seconds for 291 insertions in Study 34530). The one-hand operation of the redesigned applicator may be a contributing factor in this reduced insertion time.***

Post-Treatment Evaluation:

Per the study protocol, a post-treatment assessment was conducted 3 months ( $\pm$  1 month) after implant removal for 105 subjects in Study 34528 (97.2%, 105 of 108 treated subjects). Information tabulated includes the following:

- 21% (22 subjects) did not use a post-treatment contraceptive method
- 28% (30 subjects) reported implant use as a post-treatment contraceptive method
- 26% (28 subjects) reported oral contraceptive use as a post-treatment contraceptive method
- 25% (27 subjects) reported either/and IUD, condom, diaphragm, spermicide, or "other" contraceptive methods
- Return of menses to pre-trial pattern was seen in 36 of 39 subjects (92.3%) who were not pregnant and were not using post-treatment hormonal contraceptives

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***As previously reported, three (3) subjects became pregnant 15 or more days after implant removal (1 in the IMPLANON® treatment group [Subject (b) (6)], estimated day of conception was day 15] and 2 in the NEXPLANON® treatment group [Subject (b) (6), conception was day 38 after implant removal, and Subject (b) (6), conception was day 302 after implant removal]). No additional information is available regarding post-treatment evaluation events.***

***From the post-treatment evaluation information presented, less than 30% of subjects elected to continue implant use for contraception.***

**Study 34530 Other Endpoints:**

Contraceptive effectiveness is reported for year 1 and year 2 in ongoing Study 34530.

**Contraceptive Efficacy in Study 34530:**

At the time of the submission of sNDA 21-529/SES-007, Study 34530 was ongoing with an expected completion date of October 2010. The Applicant included the year one Pearl Index data for this study as requested by the Division in the August 20, 2007 meeting. Per the application, the full efficacy analysis for Pearl Index data will be included in the Final Study Report for Study 34530. The year-one Pearl Index estimate included in the application is presented in Table 20.

**Table 20 Year-One Pearl Index and the Two-Sided 85% Confidence Interval for Study 34530, All-Subjects-Treated Group**

Group	Parameter	Year 1 (Day 1-365)
All subjects	Number of subjects	301
	In-treatment pregnancies	0
	Women Years	276.75
	28-day cycles	3610.14
	Pearl Index estimate	0
	95% CI of Pearl Index	(0, 1.33)

Source: Adapted from sNDA 21-529/SES-007, Clinical Overview, Table 10 Year-One Pearl Index and the Two-Sided 95% CI (Study 34530) All Subject Treated Group.  
 Data Lock Point – May 1, 2009.

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***At the request of the Division (letter dated March 25, 2010), the Applicant provided two year pregnancy data for Study 34530, which was ongoing at the time of the request. As of the data lock point date of March 12, 2010, a total of 58 subjects had been exposed to the implant for less than 1 year (exposure of 365 days at most), 58 subjects received treatment at the beginning of year 2 (exposure between 366 and 730 days), and 185 subjects received treatment beyond 2 years (exposure greater than 730 days). The Applicant calculated that there were 3,610 (28-day) cycles of exposure in year 1 and 2,758 (28-day) cycles in year 2 (see Table 21).***

***Per the information submitted, no in-treatment pregnancies occurred, and no pregnancies occurred within 14 days of implant removal. The following table presents the tabulation of the annual (Year 1 and Year 2) and the cumulative (Years 1 & 2) Pearl indices together with the 95% confidence intervals.***

**Table 21 Year One and Year Two Pearl Indices and Two-Sided 95% Confidence Intervals in Study 34530, All-Subjects-Treated Group**

Parameter	Nexplanon® All-Subjects-Treated Group		
	Annual Year 1 (Day 1-365)	Annual Year 2 (Day 266-730)	Cumulative (Day 1-730)
Number of subjects	301	243	301
In-treatment pregnancies	0	0	0
Women Years	276.753	211.431	488.183
28-day cycles equivalents	3610.143	2758.036	6368.179
<b>Pearl Index (PI) estimates</b>	<b>0</b>	<b>0</b>	<b>0</b>
Lower limit95% CI	0	0	0
Upper limit95% CI	1.333	1.745	0.756

Source: Adapted from sNDA 21-529/SES-007; Information submitted April 8, 2010, Table-2 Year One and Two Pearl Indices and Two-Sided 95% CIs (Study 34530) All-Subjects-Treated (AST) Group.

In the Statistical Review, dated April 9, 2010, the FDA Statistical Reviewer also calculated year 1 and year 2 Pearl Index values for all subjects in ongoing Study 34530. See Table 22.

**Table 22 Pearl Index Calculations of Treatment Failure Rates for On-Treatment Pregnancies Occurring During the First Two Years of 3-Year Study 34530: All Cycles for ITT Population – Subjects 18-35 Years of Age AND Subjects Over 35 Years of Age**

Treatment	N (Subjects)	Number of Reported Pregnancies	Number of 28-day Cycle Equivalents	Pearl Index	95% Confidence Interval
Subjects 18 – 35 Year of Age					
NEXPLANON®					
Year 1 (Day 1-365)	240	0	2856.57	0	(0, 1.68)
Year 2 (Day 366-730)	190	0	2129.04	0	(0, 2.26)
Cumulative 2-Year (Day 1-730)	240	0	4985.61	0	(0, 0.96)
Subjects Over 35 Year of Age					
NEXPLANON®					
Year 1 (Day 1-365)	61	0	753.57	0	(0, 6.39)
Year 2 (Day 366-730)	53	0	629	0	(0, 7.65)
Cumulative 2-Year (Day 1-730)	61	0	1382.57	0	(0, 3.48)

Source: Adapted from the Statistical Review of sNDA 21-529/SES-007 dated April 9, 2010; Table A.4.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***Study 34530 was not intended to assess contraceptive efficacy. The Applicant has provided this information at the request of the Division. No pregnancies are reported for the first two years of Study 34530 for the radiopaque NEXPLANON® implant.***

**6.1.7 Subpopulations**

The Applicant did not provide specific subpopulation information in completed 3-year Study 34528 and ongoing 3-year Study 34530.

See Section 4.4 Clinical Pharmacology, Subsection 4.4.3 Pharmacokinetics for information on BMI and serum etonogestrel concentrations.

**6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

No analyses were performed regarding dosing as all study implants used in Study 34528 and Study 34530 contained 68 mg of etonogestrel.

**6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects**

No pregnancies occurred in 3-year Study 34528 between implant insertion and implant removal. One pregnancy occurred within 14 days of implant removal (conception estimated on day 7).

No pregnancies occurred in the first two years of Study 34530

**6.1.10 Additional Efficacy Issues/Analyses**

No additional efficacy issues/analyses have been identified.

## 7 Review of Safety

### Safety Summary

The serious and common adverse events reported in clinical trials conducted to support the approval of radiopaque NEXPLANON® and the redesigned applicator are consistent with approved non-radiopaque IMPLANON®, other non-implantable progestin-only contraceptives, and with combination progestin plus estrogen contraceptives except for events related to the insertion and removal of the radiopaque etonogestrel implant. These serious and common adverse events do not raise any new safety concerns for NEXPLANON® and the redesigned applicator.

### 7.1 Methods

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

##### Study 34528:

The applicant conducted a 3-year bioequivalence study (Study 34528) in support of *in vivo* bioequivalence. Study 34528 involved two treatment groups: (1) the current approved non-radiopaque IMPLANON® (etonogestrel implant), and (2) the radiopaque NEXPLANON® implant. Both implants contain 68 mg of etonogestrel. The composition of the proposed radiopaque implant core differs from the current approved IMPLANON® core by the addition of 15 mg of barium sulfate which can be detected by two-dimensional x-ray imaging [REDACTED] <sup>(b) (4)</sup>. In Study 34528, both single rod implants were inserted using the currently approved IMPLANON® applicator at insertion.

A total of 108 women of reproductive age, 18 to 40 years of age, were treated in Study 34528 (56 subjects in the IMPLANON® treatment group and 52 subjects in the NEXPLANON® treatment group). Study 34528 was conducted in Switzerland, France, and The Netherlands. The full Clinical Trial Report (CTR) is included in the submission.

On June 21, 2010, the Applicant was requested to provide an additional safety analysis for Study 34528: “For Study 34528, provide a listing by treatment group and subject of all adverse events, other than insertion related, with a start date within the first 60 days after implant insertion for the non-radiopaque Implanon® group and the radiopaque etonogestrel implant group to include onset and ending dates based on study day, severity, relationship to study drug, and outcome.” The Applicant provided the requested information on July 9, 2010.

**Study 34530:**

The Applicant conducted a 3-year clinical trial with the radiopaque implant and the redesigned applicator. Per the Applicant, “Postmarketing surveillance has realized that localization of the Implanon® implant *in situ* is sometimes difficult. This especially occurs when insertion has not been performed as instructed in the product physician’s labeling and includes errors such as wrong insertion site, too deep insertion and non-insertion.”

The primary objective of Study 34530 was to evaluate the redesigned applicator and the newly developed instructions for proper insertions. Study 34530 was ongoing at the time of the sNDA application; therefore, the original sNDA application included an interim safety analysis consisting of insertion characteristics and implant site status.

A total of 301 women of reproductive age, 18 to 40 years of age, have been treated in Study 34530 (insertions performed by 23 investigators [both experienced and non-experienced]). Study 34530 was conducted in Australia, Germany, France, United Kingdom, Norway, and Sweden.

**Safety Update Report:**

On March 25, 2010, the Division requested that the Applicant submit the required (see 21CFR314.50) 4-month Safety Update to sNDA 21-529/SES-007. The following information for all ongoing studies or studies not previously reported was requested:

- “1. A listing of all serious adverse events to include onset and ending dates based on study day, severity, relationship to study drug, and outcome. We also request narratives for each of these events.
2. A listing of all premature terminations for any reason to include the reason for, and the date of, the premature termination.
3. A listing of all adverse events related to insertion and removal of the implant not previously reported.
4. All reports not previously submitted regarding malfunction of the new applicator.”

The Applicant responded on April 8, 2010. The Safety Update Report included results from Study 34530 (which was on-going at the time) with a data lock cut-off date of March 12, 2010. Per the Safety Update Report, “The tables and listings include unverified data as this study is ongoing.”

On June 21, 2010, the Applicant was requested to provide additional safety data for Study 34530:

- “1. For Study 34530, provide “verified” safety data through at least one year of treatment to include:
  - a. A summary listing of adverse events by MedDRA system-organ class, preferred term, and relationship to study drug (All-Subjects-Treated Group) for all adverse events with an incidence of > 1.0% using a format similar to Table 8 in your Safety Update Report of April 8, 2010.
  - b. A summary listing of serious adverse events by MedDRA system-organ class, preferred term, and relationship to study drug for all serious adverse events.
  - c. A summary listing of all premature terminations for adverse events by MedDRA system-organ class, preferred term, and relationship to study.
  - d. A summary listing of all adverse events related to implant insertion by preferred term.
  - e. A listing by subject of all adverse events (other than insertion-related) to include onset and ending dates based on study day, severity, relationship to study drug, and outcome using a format similar to Table 6 in your Safety Update Report of April 8, 2010.
  - f. A listing by subject of all adverse events (other than insertion-related) with an onset date within 60 days of implant insertion to include onset and ending dates based on study day, severity, relationship to study drug, and outcome.
  - g. A listing by subject of all serious adverse events (other than insertion-related) to include onset and ending dates based on study day, severity, relationship to study drug, and outcome.
  - h. A listing by subject of all premature terminations for any reason using a format similar to that of Table 9 in your Safety Update Report of April 8, 2010.
  - i. A listing by subject of all adverse events related to implant insertion.
2. Revise, as needed, all narratives provided in your Safety Update Report of April 8, 2010, based on changes to the “verified” adverse event safety date. In addition, provide new narratives for cases of serious adverse events not previously reported through at least one year of treatment.”
3. For Study 34528, provide a listing by treatment group and subject of all adverse events, other than insertion-related, with a start date within the first 60 days after implant insertion for the non-radiopaque IMPLANON® group and the radiopaque NEXPLANON® group to include onset and ending dates based on study day, severity, relationship to study drug, and outcome.

The Applicant provided the requested information for requested item number 3 on July 9, 2010 and requested items numbers 1 and 2 on July 26, 2010.

Implant Removal Information:

On October 13, 2010, the Applicant was requested to provide implant removal data for Study 34530 (request that all information be based on fully verified data):

1. Provide a complete listing for all removals from all subjects. The listing (by center and subject) should include insertion date, removal date, number of days that the implant was in place, and any significant insertion and/or removal problems identified by the Investigator:

Insertion Problem: Yes/No – If yes, describe the problem.

Removal Problem: Yes/No – If yes, describe the problem (i.e., provide comments made by the Investigator).

2. Provide a separate listing of removals for subjects for whom adverse events/difficulty related to implant removal was reported. The list will be a subset of Listing No. 1 above and will include all of the information requested for Listing No. 1.
3. Provide copies of all primary case report forms (CRFs) that pertain to implant removal. This should include, at a minimum, your implant removal form “Form 34530-IR.”
4. Provide a summary/frequency table of complications associated with implant removal.
5. Provide a listing and summary statistics for implant removal times.
6. Provide any other information that you believe will be of value in our assessment of the acceptability of your new insertion device.

The Applicant provided the requested information on November 30, 2010.

Updated Safety Update Report:

On April 19, 2011, the Applicant was requested to provide an updated Safety Update, primarily for Study 34530, to include all serious AEs and premature terminations through the completion of the study. The requested information was received on April 25, 2011.

### **7.1.2 Categorization of Adverse Events**

In Studies 34528 and 34530, all adverse events as described by the investigator were coded using the dictionary terms from the Medical Dictionary for Regulatory Activities

(MedDRA) (version 11.1 for Study 34528 and version 10.0 for Study 34530). A “drug-related” adverse event (AE) was defined as an adverse event that was definitely, probably, or possibly related to the drug product according to the investigator. A “non drug-related” AE was defined as unlikely or not related.

Subjects with any serious adverse event (SAE) (including SAEs leading to death) are listed by treatment group and the following variables: SAE description (by investigator), MedDRA preferred term, MedDRA primary path system-organ class (SOC), start/stop days relative to the first treatment day, intensity, relationship to the drug product according to the investigator, action taken and outcome. An SAE was defined as any untoward medical occurrence that:

- resulted in death
- was life-threatening (at risk of death at the time of the event)
- required in-patient hospitalization or prolongation of existing hospitalization
- resulted in persistent or significant disability/incapacity, or
- was a congenital anomaly/birth defect

The assessment of safety in these two clinical trials required special attention since non-radiopaque IMPLANON® and the currently used applicator and the radiopaque etonogestrel implant and its redesigned applicator have both drug and device properties. Etonogestrel is regulated as a drug, but the product (single rod including etonogestrel and the disposable applicator) must be viewed as a whole (drug and its applicator). Therefore, the investigator could specify if the adverse event was related to the single rod implant containing etonogestrel, to the applicator, or to both the drug and the applicator.

### **7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence**

The safety data submitted in sNDA 21-529/SES-007 is not pooled, either between the two studies submitted (completed Study 34528 and ongoing Study 34530) in support of the radiopaque NEXPLANON® implant with its redesigned applicator or with the safety data submitted in 2006 when the non-radiopaque IMPLANON® was approved.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Participants in Study 34528 and Study 34530 were exposed to a single dose (i.e., single implant) of etonogestrel (68 mg). Labeling for approved IMPLANON® indicates that the etonogestrel dose released by the single rod implant amounts to 60-70 mcg/day in week 5-6 following insertion which decreases to approximately 35-45 mcg/day at the end of the first year, and to approximately 30-40 mcg/day at the end of the second year, and then to approximately 25-30 mg/day at the end of the third year. See the last approved IMPLANON® (etonogestrel implant) 68 mg labeling dated February 19, 2009.

#### **Study 34528 Overall Exposure at Appropriate Doses/Durations and Demographics of Target populations:**

In Study 34528, the total extent of exposure was similar between the two treatment groups: 120.7 women-years for approved IMPLANON® and 121.5 women-years for the radiopaque NEXPLANON® implant (see Table 23).

**Table 23 Extent of Exposure: Summary of Total Exposure in Study 34528, All-Subjects-Treated Group**

Parameter Statistic	Treatment Group		
	Implanon® (N = 56)	Nexplanon® (N = 52)	Combined <sup>a</sup> (N = 108)
Number of women years Total	120.7	121.5	242.2
Number of 28-day cycle equivalents Total	1574.3	1585.1	3159.4

<sup>a</sup> Both study treatment groups combined.

Source: Adapted from sNDA 21-529/S-007, Clinical Trial Report, Section 14.3.5 Extent of exposure, Table 14.3.5-2.1 Extent of exposure: summary of total exposure, page 539.

The mean (SD) treatment duration in Study 34528 was 787.1 (402.0) days in the IMPLANON® treatment group and 853.5 (359.8) days in the radiopaque etonogestrel implant treatment group. See Table 24.

**Table 24 Extent of Exposure: Summary of Treatment Duration in Study 34528, All-Subjects-Treated Group**

Treatment Duration	Treatment Group		
	Implanon® (N = 56)	Nexplanon® (N = 52)	Combined <sup>a</sup> (N = 108)
Summary statistics			
Mean (SD) (days)	787.1 (402.0)	835.5 (359.8)	819.1 (382.9)
Median (Min-Max) (days)	1085.5 (15 - 1120)	1087.0 (21 - 1127)	1086.0 (12 - 1127)
Frequency distribution n (%)			
<= 3 months	4 (7.10)	2 (3.8)	6 (5.6)
3 - 6 months	2 (3.6)	2 (3.8)	4 (3.7)
6 - 9 months	4 (7.1)	4 (7.7)	8 (7.4)
9 - 12 months	2 (3.6)	1 (1.9)	3 (7.4)
12 - 15 months	4 (7.1)	1 (1.9)	5 (4.6)
15 - 18 months	2 (3.6)	1 (1.9)	3 (4.6)
18 - 21 months	3 (5.4)	2 (3.8)	5 (4.6)
21 - 24 months	1 (1.8)	2 (3.8)	3 (2.8)
24 - 27 months	-	2 (3.8)	2 (1.9)
27 - 30 months	-	2 (3.8)	2 (1.9)
30 - 33 months	2 (3.6)	1 (1.9)	3 (2.8)
33 - 36 months	10 (17.9)	17 (32.7)	27 (25.0)
> 36 months	22 (39.3)	15 (28.8)	37 (34.3)

<sup>a</sup> Both study treatment groups combined.

Source: Adapted from sNDA 21-529/S-007, Clinical Trial Report, Section 14.3.5 Extent of exposure, Table 14.3.5-1.1 Extent of exposure: summary of treatment duration, page 537.

**Medical Officer's Comments:**

*The median number of days of exposure is similar between the two treatment groups in Study 34528.*

**Study 34530 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations:**

For the safety analysis of Study 34530 included in the original sNDA submission, safety data from screening up to and including the day of the insertion of the radiopaque etonogestrel implant was used. The interim report included in the sNDA application provides only short-term information, and the extent of exposure was not determined or tabulated.

Safety Update:

Drug exposure in Study 34530 was presented in the Safety Update Report submitted April 8, 2010. As of the cut-off date of the report (March 12, 2010), the All-Subjects-Treated (AST) group had an estimated median 999 days of exposure to the radiopaque etonogestrel implant.

Summary of exposure (days) to the radiopaque etonogestrel implant (based on March 12, 2010 data cut-off date):

N	=	301
Mean (SD)	=	765.2 (334.7)
Median	=	999
Min – Max	=	15 – 1050
Total women years	=	630.6

Updated Safety Update Report:

In the updated Safety Update Report received on April 25, 2011, drug exposure in completed Study 34530 for the AST group is as follows:

N	=	301
Mean (SD)	=	794.8 (365.1)
Median	=	1068.0
Min – Max	=	15 – 1207
Total women years	=	655.0

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***The median number of days of exposure is similar between the 3-year completed Study 34528 (1086) and the 3-year completed Study 34530 (1068).***

### 7.2.2 Explorations for Dose Response

No dose response information is presented in the application as both the approved IMPLANON® implant and the radiopaque NEXPLANON® implant contain 68 mg of etonogestrel.

### 7.2.3 Special Animal and/or In Vitro Testing

Per the Pharmacology/Toxicology Review and Evaluation dated December 14, 2009, all preclinical studies have been submitted previously under the original NDA 21-529/S-000. No new toxicology information is required.

In this sNDA application, in vitro release testing of barium sulfate was conducted in accelerated release medium (ethanol/water 90/10, 45 °C) and after 3 years in water at 37 °C which mimics the in vivo conditions. Barium sulfate is present in the core of the radiopaque implant but not in the skin layer of the implant

#### Accelerated in-vitro release test:

In this test, the whole 3-years in vivo release is mimicked in an 18 days in-vitro test. Each day the release amount of etonogestrel is measured and the dissolution medium is refreshed. Six days release in this accelerated release test corresponds with one year in the real time release test.

#### Real time in-vitro release test:

In this test, the release of etonogestrel from the implant is measured for a period of up to 3 years in water at 37 °C. Each day the release amount of etonogestrel is measured and the dissolution medium is refreshed. The daily released amount of etonogestrel in water is comparable to the in-vivo release. This 3-year test is used for development and stability purposes. For batch release purposes, this test is used to measure the etonogestrel release in the first three days only, in order to control for dose dumping.

#### Medical Officer's/Cross Discipline Team Leader's Comments:

***The cumulative release of barium ions in water over a period of 1 year of implant batches containing 0, 2, 3 and 4 vol% of barium sulfate, and of broken and damaged implants demonstrated that even with severely damaged implants (for example, with the skin layer [EVA copolymer layer] cut in the longitudinal direction), the average daily release of Ba<sup>2+</sup> ions was extremely low*** (b) (4)

***Based on the risk assessment information provided in the application, the Pharmacology/Toxicology reviewer states that "the proposed use of Radiopaque Etonogestrel Implant is acceptable." See the Pharmacology/Toxicology Review of sNDA 21-529/SES-007, dated December 14, 2009, for additional information regarding barium sulfate.***

***This reviewer concurs with the Pharmacology/Toxicology reviewer's risk assessment that the use of the radiopaque etonogestrel implant is acceptable.***

#### **7.2.4 Routine Clinical Testing**

The clinical testing observed for 3-year Study 34528 and Study 34530 met recommended routine clinical standards for testing healthy women of reproductive age who seek contraceptive health services.

#### **7.2.5 Metabolic, Clearance, and Interaction Workup**

No outstanding biopharmaceutical issues have been identified.

#### **7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

IMPLANON® (etonogestrel implant) 68 mg is the only implant contraceptive currently marketed in the U.S.

### **7.3 Major Safety Results**

#### **7.3.1 Deaths**

No deaths were reported in Study 34528 or in Study 34530.

Additionally, no deaths were reported in the 19 completed Phase 1 and Phase 3 studies in the original NDA application (approximately 1,803 subjects treated with IMPLANON® (etonogestrel implant) for up to 2 to 5 years in 16 different countries (Southeast Asia, North America, and South America).

#### **7.3.2 Nonfatal Serious Adverse Events**

##### **Study 34528 Nonfatal Serious Adverse Events:**

Ten (10) subjects reported a total of 12 serious adverse events (SAEs) in Study 34528 (6 subjects in the IMPLANON® treatment group and 4 subjects in the NEXPLANON® treatment group). These reported SAEs are shown below by treatment group:

IMPLANON® treatment group:

Subject (b) (6) - vertebral injury  
Subject (b) (6) - mammoplasty and scar excision  
Subject (b) (6) - intervertebral disc protrusion  
Subject (b) (6) - ligament rupture  
Subject (b) (6) - eating disorder  
Subject (b) (6) - deep vein thrombosis

NEXPLANON® treatment group:

Subject (b) (6) - tibia fracture  
Subject (b) (6) - peripheral arterial occlusive disease (arterial thrombosis)  
Subject (b) (6) - deep vein thrombosis  
Subject (b) (6) - tendon injury and peripheral nerve injury

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***Four of the subjects listed above had SAE events that were considered not related to study medication by the investigator and the Applicant (Subjects (b) (6), (b) (6), (b) (6) and (b) (6)). This reviewer concurs. All four subjects experienced traumatic adverse events.***

***Three subjects experienced adverse events that were either considered as unlikely related or unlikely/not related by the investigator and the Applicant (Subjects (b) (6), (b) (6) and (b) (6)). This reviewer concurs that these reported events are unlikely to be related to etonogestrel use.***

***Three subjects experienced adverse events of concern to this reviewer:***

- 1. Subject (b) (6) (deep vein thrombosis [DVT]) is a 29 year old woman who was diagnosed with a DVT of her left leg on (b) (6). Study implant (IMPLANON®) was inserted on (b) (6). She received anti-coagulation treatment and continued study medication until her early termination on (b) (6). She received study drug for a total of 489 days. The subject was a one pack of cigarettes per day smoker for many years. Both the investigator and the Applicant considered this adverse event as being unlikely related to study medication.***
- 2. Subject (b) (6) (peripheral artery occlusive disease) was a 34 year old woman who initially reported pain in her left calf on (b) (6). Study implant (radiopaque etonogestrel implant) was inserted on (b) (6). She was diagnosed with an arterial embolism (left common iliac artery and left profunda femoris artery) on (b) (6) (entrapment syndrome was excluded) after which she was hospitalized and underwent a surgical***

**embolectomy. She required a second embolectomy following a re-occlusion of the superficial femoral artery with a patent profunda and patent iliac shaft). Her implant was removed on [REDACTED] at discontinuation. She received study drug for a total of 447 days. Subject [REDACTED] was overweight (75.4 kg), smoked approximately 20 cigarettes per day, and had a past history of a pulmonary embolism in [REDACTED]. The investigator considered this adverse event as being possible related to study medication. The Applicant considered this adverse event as being unlikely related to study medication.**

- 3. Subject [REDACTED] (DVT) was a 28 year old woman who experienced pain in her left leg on [REDACTED] and was diagnosed with a DVT by ultrasound. Study implant (radiopaque etonogestrel implant) was inserted [REDACTED]. She received fluidione and tinzaparin and recovered. Her implant was removed on [REDACTED] after 124 days of study medication. Subject [REDACTED] was reported to be protein C deficient and had a family history of thrombosis. The investigator considered this adverse event as being not related to study medication. The Applicant considered this adverse event as being unlikely related to study medication.**

**The use of etonogestrel as causality of these three reported serious adverse events cannot be definitely ruled-out even though all three subjects had pre-existing risk factors.**

**In NDA 21-529/S-000, one case of DVT was reported after 4 months of therapy in the clinical trial safety data for 942 women treated for up to 3 years prior to the 2006 approval of IMPLANON®. Therefore, three cases of vascular disease (two DVTs and one arterial thrombosis) reported in 108 women treated for up to 3 years in Study 34528 is unexpected. See Section 8 Postmarketing Experience in this review for postmarketing information for approved IMPLANON®.**

#### **Study 34530 Nonfatal Serious Adverse Events:**

No SAEs were reported in the interim report for Study 34530 included in the sNDA application.

#### **Safety Update:**

As of the cut-off date of March 12, 2010 for the Safety Update Report, 17 serious adverse events were reported for 14 subjects in ongoing Study 34530 (4.6%, 14 of 301 treated subjects). Table 25 lists the subjects and reported adverse events.

**Table 25 Listing of Subjects With Serious Adverse Events in Study 34530**

Subject number	Event (Preferred Term)	Start day/Stop day	Relationship to study drug <sup>a</sup>	Outcome
(b) (6)	Lethargy	Day 638/Day 639	None	Not recovered
	Recurrent thyroid cancer Gastrointestinal carcinoma	Day 715/Ongoing	None	Not recovered
	Leiomyoma	Day 905/Ongoing	Unlikely	Not recovered
	Migraine	Day 110.Ongoing	Unlikely	Not recovered
	Intervertebral disc protrusion	Day 283/Day 538	None	Recovered with sequelae
	Hypoglycemia	Day 210/Day 205	None	Recovered
	Suicide attempt	Day 94/Day 95	None	Recovered
	Sciatica	Day 115/Day 123	None	Recovered
	Appendicitis	Day 851/ Day 852	None	Recovered
	Depression	Day 138/Day 159	Unlikely	Recovered
	Urinary calculus Campylobacter gastroenteritis	Day 91/Day 92	None	Recovered
	Salpingo-oophoritis Ovarian cyst	Day 432/Day 440	Unlikely	Recovered
	Abdominal pain	Day 387/Day 389	None	Recovered
	Appendicitis	Day 320/Day 323	None	Recovered

Note: Table includes unverified data.

<sup>a</sup> As judged by the investigator.

Source: Adapted from sNDA 21-529/SES-007, Safety Update Report, Table 6 Listing of subjects with serious adverse events in Study 34530; page 11 of 66 (Based on MedDRA version 12.0 and 12.1).

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***As shown in Table 25, there were no reports of vascular events (DVTs or arterial thrombosis) in Study 34530 as of the cut-off date of March 12, 2010. The Safety Update Report presents information on 185 subjects receiving treatment up to and beyond 2 years. The absence of reports of DVTs or arterial thrombosis in completed Study 34530 is reassuring.***

***Four reports of interest appear, however, including one report each of ovarian cysts, worsening of depression, suicide attempt, and thyroid-gastrointestinal cancer:***

- ***Per the narratives included in the safety report, Subject (b) (6) developed abdominal pains on (b) (6) and was diagnosed with bilateral ovarian cysts and salpingo-oophoritis. Her implant was inserted (b) (6). She was hospitalized and treated with antibiotics. Subject outcome was reported as recovered and she continued participation in Study 34530. The “in-house”***

***evaluation of ovarian cyst was judged as being possible related to study medication, and salpingo-oophoritis as unlikely related to study medications.***

- ***Subject (b) (6) had a history of bipolar condition and was admitted to a psychiatric hospital on (b) (6) due to worsening of her previous depression. Her implant was inserted on (b) (6). Upon release from the hospital, she continued study participation. The “in-house” evaluation judged the event as being possible related to study medication.***
- ***Subject (b) (6) was hospitalized on (b) (6) due to voluntary intake of 24 Valium tablets following a pregnancy termination in (b) (6) and a break-up with her boy friend. Her implant was inserted on (b) (6). She recovered with psychiatric follow-up, and continued participation in Study 34530. The “in-house” evaluation judged the event as being not related to study medication.***
- ***Subject (b) (6) had her implant inserted on (b) (6). On (b) (6) she was diagnosed with recurrent thyroid cancer and gastrointestinal cancer (subsequently not confirmed). No further information is available for this subject.***

***Ovarian cysts, acute exacerbation of depression, and suicide attempt were similarly reported in the data submitted prior to the 2006 approval of IMPLANON®.***

***These reported adverse events do not raise any new safety concerns for the radiopaque NEXPLANON® implant.***

One-Year “Verified” Safety Information for Study 34530:

The safety information in the 1-year Study 34530 report reflects the status of the database as per July 13, 2010. Per the Applicant, full data cleaning according to Organon SOPs was performed between the safety update, dated April 8, 2010, and the 1-year safety information received on July 26, 2010. “Therefore, the data presented in this document are considered verified safety data.”

The subjects with at least one-in-treatment serious adverse event starting within year 1 of implant insertion are shown in Table 26.

**Table 26 Number of Subjects With at Least One In-Treatment Serious Adverse Events Starting Within 365 Days of Implant Insertion in Study 34530, All-Subjects-Treated Group**

Subject number	Event (Preferred Term)	Start day/Stop day	Relationship to study drug	Outcome
(b) (6)	Migraine	Day 110/Day 126	Unlikely	Not recovered
	Intervertebral disc protrusion	Day 284/Day 538	None	Recovered
	Hypoglycemia	Day 201/Day 205	None	Recovered
	Suicide attempt	Day 94/Day 95	None	Recovered
	Sciatica	Day 115/123	None	Recovered with sequelae
	Depression	Day 138/159	Unlikely	Recovered
	Urinary calculus	Day 91/Day 92	None	Recovered
	Appendicitis	Day 320/Day 323	None	Recovered
	Bipolar disorder	Day 282/-	None	Drug withdrawn

Source: Adapted from sNDA 21-529/SES-007. One-Year ‘Verified’ Safety Information in Study 34530, Listing 3 Serious adverse events other than insertion-related with an onset before and including Day 365 (Study 34530, All-Subjects-Treated Group).

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

**See the previous Medical Officer’s/Cross Discipline Team Leader’s Comments for information on Subject (b) (6) (suicide attempt) and Subject (b) (6) (depression). In the 1-year “verified” safety report, Subject (b) (6) (gastrointestinal cancer) was deleted from the safety report because the initial diagnosis was not confirmed. However, one new SAE was reported in the 1-year “verified” safety report. Subject (b) (6) (bipolar disorder) was reported:**

- **Subject (b) (6) had study medication inserted on (b) (6). On (b) (6), she was diagnosed with bipolar disorder and treated with diazepam (10 mg). Study implant was removed on (b) (6). The investigator reported the event as not related. During the in-house evaluation, the event was judged as being unlikely related to the study medication. No additional information is provided for this subject.**

**The “verified” SAEs reported within the first year of implant insertion do not raise any safety concerns for the radiopaque NEXPLANON® implant.**

**Updated Safety Update Report:**

The Applicant provided updated safety information for completed Study 34530 on April 25, 2011. In total, seventeen (17) subjects (5.6%, 17 of 301 treated subjects) in completed Study 34530 reported 19 SAEs (16 subjects reported 18 SAEs during the in-treatment period and 1 subject reported 1 SAE in the post-treatment period). The SAEs for 15 of these subjects have previously been presented and/or discussed above.

The remaining 2 subjects are discussed below:

- Subject (b) (6) had study medication inserted on (b) (6). On (b) (6) she experienced a sudden onset of jaundice and was hospitalized. She had previously received antibiotic treatment for 10 days for an upper respiratory infection. The study implant was removed on (b) (6). Subject (b) (6) was discharged on medication and recovered. The investigator reported the event as unlikely related. During the in-house evaluation, the event was judged as being unlikely related to study medication.
- Subject (b) (6) had study medication inserted on (b) (6). The study implant was removed (b) (6) at study completion. A mammogram was performed on (b) (6) for a palpable right breast nodule. A breast biopsy was performed on (b) (6). Histology showed high grade in situ ductal carcinoma with necrosis and microcalcifications. Her treatment continues. The investigator reported the event as not related. During the in-house evaluation, the event was judged as being unlikely related to study medication.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***These two additional SAEs reported on April 25, 2011 for completed Study 34530 do not raise and new safety concerns for NEXPLANON®.***

### 7.3.3 Dropouts and/or Discontinuations

**Study 34528 Dropouts and/or Discontinuations:**

A total of 44 subjects (40.7%) discontinued treatment in 3-year Study 34528 (24 subjects [42.9%] in the IMPLANON® treatment group and 20 subjects [38.5%] in the radiopaque etonogestrel implant treatment group). Of these 44 subjects, 32 subjects discontinued due to one or more AEs (17 subjects in the IMPLANON® treatment group and 15 subjects in the NEXPLANON® treatment group). Table 27 shows the primary reasons for discontinuation.

**Table 27 Primary Reason for Discontinuation in Study 34528, All-Subjects-Treated Group**

Primary reason for discontinuation	Treatment Group					
	Implanon®		Nexplanon®		Combined <sup>a</sup>	
	N=56		(N=52)		(n=108)	
	n	%	n	%	n	%
Bleeding irregularities	8	14.3	10	19.2	18	16.7
AEs	9	16.1	5	9.6	14	13.0
Other reasons	6	10.7	4	7.7	10	9.3
Lost to follow-up	1	1.8	1	1.9	2	1.9
<b>Total</b>	<b>24</b>	<b>42.9</b>	<b>20</b>	<b>38.5</b>	<b>44</b>	<b>40.7</b>

<sup>a</sup> Both study treatment groups combined.

Source: Adapted from sNDA 21-529/SES-007 Clinical Overview, Table 13 Primary reason for discontinuation All-Subject-Treated Group Study 34528, page 29 of 43.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***In total, 40.7% of subjects (44 of 108 treated subjects) discontinued from Study 34528. As shown in Table 27, the most frequently reported primary reason for discontinuation was "bleeding irregularities". These episodes of "bleeding irregularities" include metrorrhagia, menorrhagia, and spotting. The percentage of subjects discontinuing due to "bleeding irregularities" in Study 34528 is slightly higher than shown in the original data submitted for IMPLANON® (10.1% in non-U.S. studies; 62 of 612 subjects treated). This finding does not raise new safety concerns, however. See Subsection 6.1.3 Subject Disposition in this review for a full discussion of discontinuations.***

***"Other reasons" for discontinuation include "used other contraceptive, planning pregnancy, and other personal reasons".***

***The two subjects lost to follow-up (Subject (b) (6) in the IMPLANON® treatment group and Subject (b) (6) in the NEXPLANON® treatment group) were lost to follow-up with the study implant in situ. No further information is available for these two subjects.***

***The profile of adverse events leading to discontinuations in Study 34528 is similar to what is expected for a progestin-only contraceptive (for example, changes in bleeding patterns, weight gain, depressed mood and acne). See the October 28, 2004 Primary Medical Officer's review for detained information on bleeding patterns and their clinical significance in clinical trials with IMPLANON®.***

**Study 34530 Dropouts and/or Discontinuations:**

In the sNDA application, the interim report for Study 34530 includes the results of the in-treatment period defined as the insertion day and first 24 hours after implant insertion. No subjects discontinued due to an adverse event as the primary reason for discontinuation in this limited time period.

**Safety Update Report:**

In the Safety Update Report, discontinuations reported are based on information derived from end-of-trial forms (EoT). As of the March 12, 2010 cut-off date for the safety update, 40.9% of treated subjects, with a mean and median of 765 and 999 days of treatment, respectively, had discontinued Study 34530. See Table 28 for the reasons for discontinuation.

**Table 28 Number (%) of Subject Who Discontinued Study 34530 by Reason for Discontinuation, All-Subjects-Treated Group**

Reason for Discontinuation	Nexplanon® (N = 301)	
	n	%
AE	89	29.5
Withdrawal of consent	1	0.3
Other reason	20	6.6
Missing	13	4.3
<b>Total</b>	<b>123</b>	<b>40.9</b>

Note: "Table includes unverified data; AE = (Serious) adverse event.

Source: Adapted from sNDA 21-529/SES-007, Safety Update, Table 3 Number (%) of subjects who discontinued by reason for discontinuation in Study 34530 (All-Subjects-Treated Group), page 8 of 66.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***A review of the line listing of the reason for discontinuations submitted in the safety update demonstrates that menorrhagia and metrorrhagia accounted for the majority of the AEs reported in Table 28. Sixty-four (64, 21.2%) of subjects reported "bleeding irregularities" as the reason for discontinuation. The reported percentage of discontinuation due to "irregular bleeding" in Study 34530 is only slightly higher than the incidence reported in Study 34528 (16.7% for both study groups combined). Likewise, the reported percentage of discontinuations due to "irregular bleeding" in both Study 34528 and Study 34530 are higher than reported in the original NDA 21-529/S-000 application (13.0% of U.S. subjects and 10.1 % of non-U.S. subjects). Cultural differences may contribute to this finding.***

***Irregular bleeding is a common complaint with progestin contraceptives. Therefore, labeling (both physician and patient) of progestin-only contraceptives fully describe the types of bleeding patterns that a woman might expect to help her decide if a progestin-only contraceptive is an acceptable method of contraception for her.***

One-Year “Verified” Safety Information for Study 34530:

The number and percent of subjects who discontinued Study 34530 within the first year after implant insertion are shown by system-organ class/preferred term in Table 29.

**Table 29 Number (%) of Subjects Who Discontinued from Study 34530 Due to In-Treatment Adverse Events Within 365 Day of Implant Insertion by MedDRA System-Organ Class, Preferred Term and Relationship to Study Product, All-Subjects-Treated Group**

System Organ Class <sup>a</sup> Preferred term	Relationship to Nexplanon®	
	Related <sup>b</sup> (N = 301) n (%)	Total (N = 301) n (%)
<b>Reproductive System and Breast Disorders</b>	<b>46 (15.3)</b>	<b>46 (15.3)</b>
Metrorrhagia	27 (9.0)	27 (9.0)
Vaginal hemorrhage	9 (3.0)	9 (3.0)
Menorrhagia	7 (2.3)	7 (2.3)
Dysmenorrhea	2 (0.7)	2 (0.7)
Atrophic vulvovaginitis	1 (0.3)	1 (0.3)
Breast pain	1 (0.3)	1 (0.3)
Breast tenderness	1 (0.3)	1 (0.3)
Dyspareunia	1 (0.3)	1 (0.3)
Irregular menstruation	1 (0.3)	1 (0.3)
Pelvic pain	1 (0.3)	1 (0.3)
Uterine spasm	1 (0.3)	1 (0.3)
Vaginal odor	1 (0.3)	1 (0.3)
<b>General Disorders and Administrative Site Conditions</b>	<b>3 (1.0)</b>	<b>4 (1.30)</b>
Irritability	3 (1.0)	3 (1.0)
Device expulsion	0 (0.0)	1 (0.3)
Implant site pain	0 (0.0)	1 (0.3)
<b>Investigations</b>	<b>11 (3.70)</b>	<b>12 (4.0)</b>
Weight increased	11 (3.7)	11 (3.7)
Weight decreased	0 (0.0)	1 (0.3)
<b>Injury, Poisoning and Procedural Pain</b>	<b>0 (0.0)</b>	<b>1 (0.3)</b>
Procedural complication	0 (0.0)	1 (0.3)

<sup>a</sup> Based on MedDRA version 13.0. A subject can have adverse events in more than one class/term.

<sup>b</sup> Related: relationship specified as ‘Definite’, ‘Probable’, ‘Possible’.

Source: Adapted from sNDA 21-529/SES-007 One-Year ‘Verified’ Safety Information of Trial 34530, Table 3, page 11.

***Medical Officer's/Cross Discipline Team Leader's Comments:***

***As demonstrated in Table 29, the system-organ class that accounted for the highest number of discontinuations is Reproductive System and Breast Disorders. See the Medical Officer's/Cross Discipline team Leader's Comments under Safety Update Report for a discussion regarding discontinuations due to metrorrhagia, menorrhagia, and vaginal bleeding. No new safety concerns have been raised in the "verified" 1-year safety data.***

Updated Safety Update Report:

As previously discussed on page 83 of this review, bleeding irregularities (metrorrhagia, menorrhagia, and vaginal hemorrhage) accounted for the highest number of discontinuation in completed Study 34530.

***Medical Officer's/Cross Discipline Team Leader's Comments:***

***No new safety concerns have been raised in the updated safety information received on April 25, 2011.***

### **7.3.4 Significant Adverse Events**

See Subsection 7.3.2 Nonfatal Serious Adverse Events in this review for information on the 2 DVTs and the one arterial occlusion reported in Study 34528.

### **7.3.5 Submission Specific Primary Safety Concerns**

**Study 34528 Submission Specific Primary Safety Concerns:**

Implant Site, Insertion and Removal:

Per protocol, complications during implant insertion or removal were reported as AEs. Subject (b) (6) developed an adverse event at implant insertion (allergic cutaneous reaction). For the remaining 107 subjects in Study 34528 (99.1%), no complications were reported at insertion. Additionally, no complications were reported during removal of the implant in Study 34528.

Table 32 shows, however, that 32 subjects (29.6%, 32 of 108 subjects) experienced in-treatment implant site hematoma, and 10 subjects (9.3%, 10 of 108 subjects) experience in-treatment implant site pain. Study 34528 was conducted using the currently approved applicator not the redesigned applicator that is the subject of this sNDA application.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***Implant site hematoma and pain are not unexpected adverse events following implant insertion.***

**Adverse Events (other than insertion-related) within 60 Days of Implant Insertion:**

On June 21, 2010, the Applicant was requested to provide additional safety data for Study 34528: "For Study 34528, provide a listing by treatment group and subject of all adverse events, other than insertion related, with a start date within the first 60 days after implant insertion for the non-radiopaque Implanon® group and the radiopaque etonogestrel implant group to include onset and ending dates based on study day, severity, relationship to study drug, and outcome." This additional safety data was requested to determine if any adverse events occurred within this time period that could be attributed to the slightly higher upper limit of the 90% CI for  $C_{max}$  for the radiopaque etonogestrel implant. The Applicant provided the requested information on July 9, 2010.

Seventy-two (72) subjects (67%, 72 of 108 treated subjects) participating in Study 34528 reported 185 adverse events with a start date within the first 60 days of implant insertion (excluding insertion-related adverse events). Thirty-eight (38) subjects were in the IMPLANON® treatment group (35.2%, 38 of 108 treated subjects) and 34 subjects were in the NEXPLANON® treatment group (31.5%, 34 of 108 treated subjects).

The following adverse events were reported by subjects in the IMPLANON® treatment group (decreasing order of frequency) within the first 60 days of implant insertion: vaginal spotting, vaginal bleeding, acne, headache, metrorrhagia, common cold/flu, dizziness, weight gain, back pain, rash, tiredness, and other adverse reaction singularly reported. In the NEXPLANON® treatment group, the following adverse events were reported by subjects (decreasing order of frequency) within the first 60 days of implant insertion: vaginal spotting, vaginal bleeding, headache, weight gain, dizziness, diarrhea, metrorrhagia, acne, nausea, decreased libido, pruritis at insertion site, and other adverse reaction singularly reported.

A total of 11 subjects (7 in the IMPLANON® group and 4 in the NEXPLANON® group) discontinued Study 34528 due an adverse event with a start date within the first 60 days of implant insertion (10.1%, 11 of 108 treated subjects) :

IMPLANON® treatment group:

- Subject (b) (6) = vaginal pain, Day 41 start date; Day 445 stop date; implant removed; probable relationship to study drug; outcome: recovered.
- Subject (b) (6) = weight increased, Day 23 start date; Day 653 stop date; implant removed; probable relationship to study drug; outcome: recovered.
- Subject (b) (6) = metrorrhagia, Day 21 start date; Day 119 stop date; implant removed; definite relationship to study drug; outcome: recovered.
- Subject (b) (6) = vaginal bleeding, Day 23 start date; Day 54 stop date; implant removed; possible relationship to study drug; outcome: recovered.
- Subject (b) (6) = pruritis, redness, and swelling at insertion site, Day 12 start date; Day 19 stop date; implant removed; probable relationship to study drug; outcome: recovered.
- Subject (b) (6) = vaginal bleeding, Day 26 start date; Day 53 stop date; implant removed; possible relationship to study drug; outcome: recovered.
- Subject (b) (6) = vaginal spotting, Day 14 start date; Day 79 stop date; implant removed; possible relationship to study drug; outcome: recovered.

NEXPLANON® treatment group:

- Subject (b) (6) = vaginal spotting, Day 1 start date; Day 66 stop date; implant removed; definite relationship to study drug; outcome: recovered.
- Subject (b) (6) = decreased libido and mood change, Day 1 start date; Day 108 stop date; implant removed; possible relationship to study drug; outcome: recovered.
- Subject (b) (6) = skin irritation, Day 1 start date; Day 373 stop date; implant removed; probable relationship to study drug; outcome: recovered.
- Subject (b) (6) = vaginal bleeding, Day 46 start date; Day 246 stop date; implant removed; possible relationship to study drug; outcome: recovered.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***The adverse events reported within 60 days of implant insertion for the two treatment groups in Study 34528 are known and expected adverse events reported for a progestin-only contraceptive product. The occurrence of these commonly reported adverse events, such as vaginal spotting, vaginal bleeding, acne, headaches, weight gain, and mood change, are similar between the two treatment groups. No apparent difference between the two treatment groups is demonstrated in this safety data that could be attributed to the slightly higher upper limit of the 90% CI for  $C_{max}$  for the radiopaque NEXPLANON® implant.***

**Study 34530 Submission Specific Primary Safety Concerns:**

**Implant Site and Insertion:**

Of the 301 subjects treated in Study 34530, a total of 27 subjects (9.0%, 27 of 301 treated subjects) had one or more AEs within 24-hours after implant insertion. Study investigators classified the reported adverse events as either “drug-related” or “applicator-related” events. See Table 30.

**Table 30 Number (%) of Subjects with at Least One Adverse Event at Insertion within 24-Hours after Implant Insertion**

System Organ Class <sup>a</sup> /Preferred Term		Nexplanon® (N – 301)		
		Drug-Related <sup>b</sup> n (%)	Applicator-Related n (%)	Total <sup>c</sup> n (%)
General Disorders and Administration Site Conditions	Total	14 (4.7)	12 (4.0)	26 (8.6)
	Implant site bruising	2 (0.7)	6 (2.0)	6 (2.0)
	Implant site erythema	5 (1.7)	5 (1.7)	10 (3.3)
	Implant site hematoma	4 (1.3)	2 (0.7)	9 (3.0)
	Implant site hemorrhage	0 (0.0)	1 (0.3)	1 (0.3)
	Implant site pain	3 (1.0)	0 (0.0)	3 (1.0)
	Implant site swelling	1 (0.3)	1 (0.3)	2 (0.7)
Injury, Poisoning and Procedural Complications	Total	0 (0.0)	0 (0.0)	1 (0.3)
	Post procedural complication	0 (0.0)	0 (0.0)	1 (0.3)

a. A subject can have adverse events in more than one class. Per subject the highest related adverse event within class is taken.

b. Drug-Related: relationship specified as “Definite”, “Probable”, “Possible”.

c. Total includes the drug- and applicator-related and not-related AEs.

Source: Adapted from sNDA 21-529, Study 34530 Clinical Trial Report, Table 12 Number (%) of subjects with at least one in-treatment adverse event at insertion day, All-subject-Treated Group, page 63 of 298.

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***As shown in the table above, the reported adverse events within 24-hours post insertion in decreasing order were: implant site erythema (3.3%), implant site hematoma (3.0%), implant site bruising (2.0%), implant site pain (1.0%), implant site swelling (0.7%), and implant site hemorrhage (0.3%). While the table shows a determination of relationship to drug or applicator, there is no evidence of***

**consistency in the reported relationship. It appears that the reported relationship was based on the individual investigator's judgment.**

**Subject (b) (6) reported left forearm numbness as the insertion post-procedural complication which lasted for one day. This adverse event was not considered to be study drug- or applicator-related according to the investigator's judgment.**

**The overall 8.6% (26 of 301 treated subjects) of "insertion events" for the radiopaque implant and the redesigned applicator is significantly higher than insertion-related events reported in the original NDA 21-529 application (a total of 3% for 942 insertions in all original studies). This difference, however, is more likely related to the objective of Study 34530 and the concentrated efforts undertaken to evaluate the redesigned applicator and its instructions for proper insertion rather than the drug product as a whole (drug plus the applicator).**

Adverse Events Within 60 Days of Implant Insertion:

On June 21, 2010, the Applicant was requested to provide additional safety data for Study 34530 including, but not limited to, the following:

"A listing by subject of all adverse events (other than insertion-related) with an onset date within 60 days of implant insertion to include onset and ending dates based on study day, severity, relationship to study drug, and outcome."

The Applicant provided the requested information on July 26, 2010.

One hundred forty-one (141) subjects (47%, 141 of 301 treated subjects) participating in Study 34530 reported 267 adverse events with a start date within the first 60 days of implant insertion (excluding insertion-related adverse events).

The following adverse events were reported by subjects who received the radiopaque NEXPLANON® implant (decreasing order of frequency) within the first 60 days of implant insertion: vaginal spotting, vaginal bleeding, headache, acne, metrorrhagia, menorrhagia, amenorrhea, weight gain, upper respiratory tract infection, decreased libido, dysmenorrhea, urinary tract infection, mood altered, sinusitis, mood swings, abdominal pain, vaginitis, irritability, abdominal bloating, back pain, and other adverse reaction doubly or singularly reported.

A total of 29 subjects discontinued Study 34530 due an adverse event with a start date within the first 60 days of implant insertion (9.6%, 29 of 301 treated subjects):

- Subject (b) (6) = menorrhagia; Day 8 start date, Day 20 stop date; endometriosis pain, Day 20 start date, unknown stop date; implant removed Day 50; possible relationship to study drug; outcome: not recovered.

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

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- Subject (b) (6) = menorrhagia; Day 15 start date, implant removed Day 168; probable relationship to study drug; outcome: recovered.
- Subject (b) (6) = affect liability; Day 12 start date, implant removed Day 121; possible relationship to study drug; outcome: recovered.
- Subject (b) (6) = irritability (Day 11 start date)/acne (Day 13 start date), implant removed Day 259; possible relationship to study drug; outcome: recovered.
- Subject (b) (6) = metrorrhagia; Day 37 start date, Day 507 stop date; implant removed Day unknown; possible relationship to study drug; outcome: recovered.
- Subject (b) (6) = mood altered (Day 1 start date)/vaginal spotting and bleeding (Day 10 start date), implant removed Day 181; probable relationship to study drug; outcome: recovered.
- Subject (b) (6) = metrorrhagia; Day 1 start date, implant removed Day 141; probable relationship to study drug; outcome: recovered.
- Subject (b) (6) = metrorrhagia; Day 1 start date, implant removed Day 204; probable relationship to study drug; outcome: recovered.
- Subject (b) (6) = metrorrhagia; Day 1 start date, implant removed Day 172; probable relationship to study drug; outcome: recovered.
- Subject (b) (6) = weight gain (Day 15 start date)/migraine (Day 58 start date); implant removed Day 211; probable/possible relationship to study drug; outcome: unknown.
- Subject (b) (6) = metrorrhagia/mood altered; Day 31 start date, implant removed Day 74; definite relationship to study drug; outcome: recovered.
- Subject (b) (6) = night sweats; Day 15 start date, Day 339 stop date: implant removed Day 242; possible relationship to study drug; outcome unknown.
- Subject (b) (6) = metrorrhagia; Day 1 start date: implant removed Day 215; probable relationship to study drug; outcome: recovered.
- Subject (b) (6) = vaginal spotting; Day 1 start date; implant removed Day 624; probable relationship to study drug; outcome: recovered.
- Subject (b) (6) = acne (Day 7 start date)/hot flushes (Day 10 start date)/reduced libido (Day 10 start date)/mood altered (Day 11 start date); implant removed Day 16; probable relationship to study drug; outcome recovered.
- Subject (b) (6) = weight increase; Day 32 start date; implant removed Day 182; probable relationship to study drug; outcome: unknown.
- Subject (b) (6) = weight increase; Day 28 start date; implant removed Day 327; probable relationship to study drug; outcome: unknown.
- Subject (b) (6) = metrorrhagia; Day 1 start date; implant removed Day 258; definite relationship to study drug; outcome: recovered.
- Subject (b) (6) = decreased libido; Day 1 start date, implant removed Day 551; possible relationship to study drug; outcome recovered.

- Subject (b) (6) = affect lability; Day 1 start date; implant removed Day 124; probable relationship to study drug; outcome: recovered.
- Subject (b) (6) = metrorrhagia; Day 1 start date; implant removed Day 135; definite relationship to study drug; outcome: recovered.
- Subject (b) (6) = metrorrhagia/dysmenorrhea; Day 1 start date; implant removed Day 175; definite relationship to study drug; outcome: recovered.
- Subject (b) (6) = weight loss; Day 1 start date; implant removed Day 186; no relationship to study drug; outcome: recovered.
- Subject (b) (6) = acne/metrorrhagia; Day 1 start date; implant removed Day 118; possible relationship to study drug; outcome: unknown.
- Subject (b) (6) = weight increase; Day 1 start date; implant removed Day unknown; possible relationship to study drug; outcome: unknown.
- Subject (b) (6) = decreased libido/irritability; Day 16 start date; implant removed Day 43; possible relationship to study drug; outcome: recovered.
- Subject (b) (6) = mood altered/metrorrhagia; Day 8 start date; implant removed Day 84; probable relationship to study drug; outcome: recovered.
- Subject (b) (6) = menorrhagia/metrorrhagia; Day 1 start date, implant removed Day 116; definite relationship to study drug; outcome: recovered.
- Subject (b) (6) = menorrhagia; Day 1 start date; implant removed Day 89; definite relationship to study drug; outcome: recovered.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***The adverse events reported within 60 days of implant insertion of the radiopaque NEXPLANON® implant in Study 34530 are known and expected adverse events for a progestin-only contraceptive product. The occurrence of these commonly reported adverse events, such as vaginal spotting, vaginal bleeding, menorrhagia/metrorrhagia, acne, headaches, weight gain, and mood change do not raise new safety concerns. This data does not demonstrate any specific adverse events that could be directly attributed to the slightly higher upper limit of the 90% CI for C<sub>max</sub> for the radiopaque NEXPLANON® implant.***

See Subsection 7.4.1 Common Adverse Events in this review for a detailed discussion of implant site adverse events reported for Study 34530 for common adverse events reported in the one-year “verified” safety information received on July 26, 2010, and for “verified” implant removal safety information received on November 30, 2010.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

#### **Study 34528 Common Adverse Events:**

Of the 108 subjects treated in Study 34528, 106 subjects (98.1%) had one or more treatment-emergent adverse events (TEAEs) (see Table 31). Per the Applicant, 96 subjects (88.9%) with TEAEs had “drug-related” TEAEs defined as a TEAE related to the single rod implant containing 68 mg of etonogestrel plus the redesigned applicator. Per the application, “Although Implanon® as a whole (i.e., including its applicator) is regulated as a drug, the applicator itself has solely device properties.”

**Table 31 Overview of Subjects With at Least One Adverse Event in Study 34528, All-Subject-Treated Group**

Event type	Treatment Group as Treated		
	Implanon®  N=56 n (%)	Nexplanon®  N=52 n (%)	Combined <sup>a</sup>  N=108 n (%)
Subjects with AEs	54 (96.4)	52 (100.0)	106 (98.1)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with SAEs	6 (10.7)	4 (7.7)	10 (9.3)
Subject who discontinued due to AE	17 (30.4)	15 (28.8)	32 (29.6)
Subjects with drug-related AEs <sup>b</sup>	49 (87.5)	47 (90.4)	96 (88.9)

<sup>a</sup> Both study treatment groups combined.

<sup>b</sup> Relationship defined as “Definite”, “Probable”, or “Possible.”

Source: Adapted from sNDA 21-529, Final Study Report for Study 34528, Table 14.3.2-1 and Clinical Overview, Table 11, Overview of subjects with at least one adverse event, All-Subject-Treated Group (Study 34528), page 26 of 43.

#### **Medical Officer’s Comments:**

*The two treatment groups were similar with regard to occurrence of SAEs and TEAEs. The currently approved IMPLANON® applicator was used for both treatment groups in Study 34528.*

Adverse events in Study 34528 that occurred with an incidence rate of  $\geq 5\%$  starting during the in-treatment period are shown in Table 32.

**Table 32 Number (%) of Subjects Reporting Treatment-Emergent Adverse Events ≥ 5% in Any Treatment Group in Study 34528, All-Subjects-Treated Group**

System Organ Class/Preferred Term <sup>b</sup>	Treatment Group as Treated		
	Implanon® N=56 n (%)	Nexplanon® N=52 n (%)	Combined <sup>a</sup> N=108 n (%)
<b>Infections and Infestations</b>			
Cystitis	4 (7.1)	8 (15.4)	12 (11.1)
Gastroenteritis	4 (7.1)	6 (11.5)	10 (9.3)
Influenza	14 (25.0)	12 (23.1)	26 (24.1)
Nasopharyngitis	14 (25.0)	18 (34.6)	32 (29.6)
Sinusitis	3 (5.4)	2 (3.8)	5 (4.6)
Vulvovaginal candidiasis	2 (3.6)	4 (7.7)	6 (5.6)
Vulvovaginal mycotic infection	7 (12.5)	3 (5.8)	10 (9.3)
<b>Immune System Disorders</b>			
Seasonal allergy	3 (5.4)	2 (3.8)	6 (5.6)
<b>Nervous System Disorders</b>			
Dizziness	5 (8.9)	5 (9.6)	10 (9.3)
Headache	15 (26.8)	14 (26.9)	29 (26.9)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>			
Cough	3 (5.4)	3 (5.8)	6 (5.6)
Oropharyngeal pain	4 (7.1)	5 (9.6)	9 (8.3)
<b>Gastrointestinal Disorders</b>			
Abdominal pain	2 (3.6)	6 (11.5)	8 (7.4)
Diarrhea	3 (5.4)	5 (9.6)	8 (7.4)
Nausea	8 (14.3)	6 (11.5)	14 (13.0)
Toothache	3 (5.4)	1 (1.9)	4 (3.7)
<b>Skin and Subcutaneous Tissue Disorders</b>			
Acne	18 (32.1)	11 (21.2)	29 (26.9)
Rash	3 (5.4)	0 (0.0)	3 (2.8)
<b>Musculoskeletal and Connective Tissue Disorders</b>			
Arthralgia	4 (7.1)	4 (7.7)	8 (7.4)
Back pain	6 (10.7)	11 (21.2)	17 (15.7)
Myalgia	1 (1.8)	3 (5.8)	4 (3.7)
Neck pain	0 (0.0)	3 (5.8)	3 (2.8)
Pain in extremity	1 (1.8)	4 (7.7)	5 (4.6)

Continued on next page.

System Organ Class/Preferred Term <sup>b</sup>	Treatment Group as Treated		
	Implanon®  N=56 n (%)	Nexplanon®  N=52 n (%)	Combined <sup>a</sup>  N=108 n (%)
<b>Reproductive System and Breast Disorders</b>			
Amenorrhea	6 (10.7)	3 (5.8)	9 (8.3)
Breast pain	4 (7.1)	4 (7.7)	8 (7.4)
Breast tenderness	1 (1.8)	4 (7.7)	5 (4.6)
Dysmenorrhea	4 (7.1)	6 (11.5)	10 (9.3)
Genital hemorrhage	23 (41.1)	24 (46.2)	47 (43.5)
Metrorrhagia	9 (16.1)	9 (17.3)	18 (16.7)
Oligomenorrhea	3 (5.4)	0 (0.0)	3 (2.8)
Pelvic pain	5 (8.9)	3 (5.8)	8 (7.4)
Polymenorrhea	0 (0.0)	3 (5.8)	3 (2.8)
Vaginal discharge	3 (5.4)	3 (5.8)	6 (5.6)
Vaginal hemorrhage	18 (32.1)	21 (40.4)	39 (36.1)
<b>General Disorders and Administration Site Conditions</b>			
Fatigue	3 (5.4)	2 (3.8)	5 (4.6)
Hangover	2 (3.6)	3 (5.8)	5 (4.6)
Implant site hematoma	16 (28.6)	16 (30.8)	32 (29.6)
Implant site pain	16 (10.7)	4 (7.7)	10 (9.3)
<b>Investigations</b>			
Weight decreased	4 (7.1)	1 (1.9)	5 (4.6)
Weight increased	8 (14.3)	4 (7.7)	12 (11.1)
<b>Injury, Poisoning and Procedural Complications</b>			
Procedural pain	3 (5.4)	5 (9.6)	8 (7.4)

<sup>a</sup> Both study treatment groups combined.

<sup>b</sup> A subject can have adverse events in more than one class/term.

Source: Adapted from sNDA 21-529/SES-007, Clinical Trial Report, Table 18 Number (%) of subjects with at least one adverse event starting during the in-treatment period, All-Subject-Treated Group, page 79 of 590.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***In Study 34528, a total of 90 subjects (83.3%) reported AEs from the System Organ Class "Reproductive System and Breast Disorders". As shown in Table 32, the most commonly reported AEs in this System Organ Class and in decreasing order were: genital hemorrhage (47 subjects, 43.5%), vaginal hemorrhage (39 subjects, 36.1%) and metrorrhagia (18 subjects, 16.7%). The term "hemorrhage" in this context does not necessarily imply excessively heavy bleeding but rather any genital or vaginal bleeding.***

***Bleeding irregularities are known to occur with the use of approved IMPLANON® as with all low dose progestin-only contraceptive products. In the original NDA 21-529/S-000 application, the most common adverse events were vaginal***

***hemorrhage and metrorrhagia (10 to 13% of 942 treated subjects in all studies submitted). Approved IMPLANON® labeling (both the Physician Insert and the Patient Information insert) fully describes the types of bleeding patterns that a woman might expect to assist her in decision making regarding the acceptability of a progestin-only contraceptive method.***

**Study 34530 Common Adverse Events:**

**Safety Update Report:**

In the safety update received on April 8, 2010, which included safety data beyond 2-years of treatment, the four System Organ Classes in which adverse events were most frequently reported were: “Reproductive System and Breast Disorders”, “Infections and Infestations”, “Nervous System Disorders”, and “General Disorders and Administrative Site Conditions”. See Table 33.

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**Table 33 Number (%) of Subjects by System Organ Class (SOC) with at least One Adverse Event in Study 34530, All-Subjects-Treated Group (Based on Interim Data through March 12, 2010)**

System Organ Class <sup>a</sup>	Nexplanon®	
	Related <sup>b</sup> (N = 301) n (%)	Total (N = 301) n (%)
Infections and infestations	2 (0.7)	123 (40.9)
Neoplasm benign, malignant and unspecified	1 (0.3)	7 (2.3)
Blood and lymphatic system disorders	0 (0.0)	1 (0.3)
Immune system disorders	0 (0.0)	10 (3.30)
Metabolism and nutrition disorders	2 (0.7)	5 (1.7)
Psychiatric disorders	33 (11.0)	56 (18.6)
Nervous system disorders	30 (10.0)	76 (25.2)
Eye disorders	1 (0.3)	3 (1.0)
Ear and labyrinth disorders	0 (0.0)	4 (1.3)
Cardiac disorders	0 (0.0)	3 (1.0)
Vascular disorders	3 (1.0)	7 (2.3)
Respiratory, thoracic, and mediastinal disorders	0 (0.0)	9 (3.0)
Gastrointestinal disorders	7 (2.3)	57 (18.9)
Skin and subcutaneous tissue disorders	5 (1.7)	36 (12.0)
Musculoskeletal and connective tissue disorders	5 (1.7)	36 (12.0)
Renal and urinary disorders	0 (0.0)	5 (1.7)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	1 (0.3)
Reproductive system and breast disorders	146 (48.5)	153 (50.8)
General disorders and administration site conditions	35 (11.6)	67 (22.3)
Investigations	25 (8.3)	33 (11.0)
Injury, poisoning and procedure complications	0 (0.0)	18 (6.0)
Surgical and medical procedures	0 (0.0)	9 (3.0)
Not coded	17 (5.6)	29 (9.6)

<sup>a</sup>. A subject can have adverse events in more than one class or for more than one preferred term within a system-organ class.

<sup>b</sup>. Considered to be possible, probably or definitely related to trial drug (i.e., drug-related) by the investigator.

Applicant's Note: "Table includes unverified data."

Source: Adapted from sNDA 21-529/SES-007, Safety Update Report, Table 7 Number (%) of subjects with at least one adverse event, by MedDRA system-organ class and relationship to trial drug Trial 34530. All-Subjects-Treated Group, page 12.

Individually reported treatment-emergent adverse events  $\geq 5\%$  within a System Organ Class in Study 34530 are shown in Table 34.

**Table 34 Number (%) of Subjects with Treatment-Emergent Adverse Events  $\geq$  5% in Study 34530, All-Subjects-Treated Group (Based on Interim Data through March 12, 2010)**

System Organ Class <sup>a</sup> Preferred term	Relationship to Nexplanon®	
	Related <sup>b</sup> (N = 301) n (%)	Total (N = 301) n (%)
<b>Infections and Infestations</b>		
Nasopharyngitis	0 (0.0)	30 (10.0)
Upper respiratory tract infection	0 (0.0)	19 (6.3)
Vulvovaginal candidiasis	0 (0.0)	17 (5.6)
Influenza	0 (0.0)	16 (5.3)
Urinary tract infection	0 (0.0)	16 (5.3)
<b>Nervous System Disorders</b>		
Headache	25 (8.3)	58 (19.3)
<b>Skin and Subcutaneous Tissue Disorders</b>		
Acne	37 (12.3)	39 (13.0)
<b>Reproductive System and Breast Disorders</b>		
Vaginal hemorrhage	80 (26.6)	82 (27.2)
Metrorrhagia	36 (12.0)	36 (12.0)
Menorrhagia	19 (6.3)	20 (6.6)
Amenorrhea	18 (6.0)	18 (6.0)
Dysmenorrhea	10 (3.3)	16 (5.3)
<b>General Disorders and Administration Site Conditions</b>		
Implant site pain	12 (4.0)	19 (6.3)
Implant site hematoma	7 (2.3)	17 (5.6)
<b>Investigations</b>		
Weight increased	25 (8.3)	26 (8.6)
<b>Not coded</b>	17 (5.6)	29 (9.6)

<sup>a</sup> A subject can have adverse events in more than one class or for more than one preferred term within a system-organ class.

<sup>b</sup> Considered to be possible, probably or definitely related to trial drug (i.e., drug-related) by the investigator.

Applicant's Note: "Table includes unverified data."

Source: Adapted from sNDA 21-529/SES-007, Safety Update Report, Table 8 Number (%) of subjects with at least one adverse event (AE incidence of > 1.0%, by MedDRA system-organ class, preferred term and relationship to trial drug Trial 34530. All-Subjects-Treated Group, page 14.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***The "unverified" treatment-emergent adverse events (TEAEs) reported in Study 34530 are similar to the TEAEs reported in Study 34528 and to the TEAEs reported in the original clinical trials conducted prior to the approval of IMPLANON® in the U.S. in 2006. These reported TEAEs do not raise new safety concerns.***

***Almost all of the “bleeding irregularities” reported in the System Organ Class “Reproductive System and Breast Disorders” were considered to be drug related by the investigator.***

One-Year “Verified” Safety Information in Ongoing 3-Year Study 34530:

As previously noted in Subsection 7.1.1 Studies/Clinical Trials Used to Evaluate Safety in this review, the Applicant was requested to provide 1-year “verified” safety data for Study 34530. The Safety Update Report received on April 8, 2010 provided only “unverified” safety data.

The “verified” safety data, received on July 26, 2010, reflects the status of the database as per July 13, 2010. Per the Applicant, full data cleaning according to Organon’s standard operating procedures, had been performed. Summary tables for Study 34530 demonstrate safety data with an onset within 365 days of implant insertion. The in-treatment period is defined as the time-period from the day of insertion up to and including the 5<sup>th</sup> day after implant removal.

Individually reported treatment-emergent adverse events > 1% within a System Organ Class in the first year of Study 34530 are shown in Table 35.

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**Table 35 Number (%) of Subjects with Treatment-Emergent Adverse Events > 1% in Study 34530, All-Subjects-Treated Group (One-year Verified Data)**

System Organ Class <sup>a</sup> Preferred term	Relationship to Nexplanon®	
	Related <sup>b</sup> (N = 301) n (%)	Total (N = 301) n (%)
<b>Infections and Infestations</b>		
Nasopharyngitis	0 (0.0)	24 (8.0)
Upper respiratory tract infection	0 (0.0)	16 (5.3)
Urinary tract infection	0 (0.0)	13 (4.3)
Vulvovaginal candidiasis	0 (0.0)	13 (4.3)
Influenza	0 (0.0)	12 (4.0)
Sinusitis	0 (0.0)	8 (2.7)
Tonsillitis	0 (0.0)	7 (2.3)
Vaginitis bacterial	2 (0.7)	6 (2.0)
Gastroenteritis	0 (0.0)	5 (1.7)
Viral upper respiratory tract infection	0 (0.0)	5 (1.7)
Vulvovaginal mycotic infection	1 (0.3)	4 (1.3)
Lower respiratory tract infection	0 (0.0)	4 (1.3)
<b>Psychiatric Disorders</b>		
Libido decreased	11 (3.7)	12 (4.0)
Mood altered	9 (3.0)	10 (3.3)
Depression	0 (0.0)	7 (2.3)
Depressed mood	4 (1.3)	5 (1.7)
Insomnia	0 (0.0)	5 (1.7)
Loss of libido	4 (1.3)	4 (1.3)
Mood swings	4 (1.3)	4 (1.3)
Anxiety	0 (0.0)	4 (1.3)
<b>Nervous System Disorders</b>		
Headache	25 (8.3)	52 (17.3)
Dizziness	2 (0.7)	5 (1.7)
Migraine	1 (0.3)	5 (1.7)
<b>Gastrointestinal Disorders</b>		
Gastritis	0 (0.0)	6 (2.0)
Abdominal pain	0 (0.0)	5 (1.7)
Constipation	0 (0.0)	5 (1.7)
Toothache	0 (0.0)	5 (1.7)
Abdominal pain lower	0 (0.0)	4 (1.3)
Diarrhea	0 (0.0)	4 (1.3)
<b>Skin and Subcutaneous Tissue Disorders</b>		
Acne	35 (11.6)	37 (12.3)
Alopecia	3 (1.0)	4 (1.3)
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Back pain	0 (0.0)	9 (3.0)
Arthralgia	1 (0.3)	5 (1.7)

Continued on next page

System Organ Class <sup>a</sup> Preferred term	Relationship to Nexplanon®	
	Related <sup>b</sup> (N = 301) n (%)	Total (N = 301) n (%)
<b>Reproductive System and Breast Disorders</b>		
Vaginal hemorrhage	64 (21.3)	66 (21.9)
Metrorrhagia	32 (10.6)	32 (10.6)
Menorrhagia	18 (6.0)	19 (6.3)
Amenorrhea	15 (5.0)	15 (5.0)
Dysmenorrhea	9 (3.0)	13 (4.3)
Pelvic discomfort	5 (1.7)	5 (1.7)
Breast tenderness	4 (1.3)	5 (1.7)
Menstrual irregular	4 (1.3)	4 (1.3)
Polymenorrhea	4 (1.3)	4 (1.3)
Pelvic pain	2 (0.7)	4 (1.3)
<b>General Disorders and Administration Site Conditions</b>		
Implant site pain	11 (3.7)	18 (6.0)
Implant site hematoma	7 (2.3)	16 (5.3)
Implant site erythema	6 (2.0)	12 (4.0)
Irritability	6 (2.0)	6 (2.0)
Fatigue	3 (1.0)	4 (1.3)
Implant site pruritis	3 (1.0)	4 (1.3)
<b>Investigations</b>		
Weight increased	24 (8.0)	25 (8.3)

<sup>a</sup> A subjects can have AEs in more than one system-organ class.

<sup>b</sup> Related: relationship specified as Definite, Probable, Possible.

Source: Adapted from sNDA 21-529/SES-007, One-year “verified” safety information in Study 34530, Table 1 Number (%) of subjects with at least one in-treatment adverse event starting within 365 days of implant insertion by MedDRA system-organ class, preferred term and relationship to investigational product. Adverse events with incidence >1% (Study 34530, All-Subjects-Treated Group), page 6.

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***The treatment-emergent adverse events (TEAEs) reported in year one of Study 34530 are similar to the TEAEs reported in Study 34528 and to the TEAEs reported in the original clinical trials conducted prior to the approval of IMPLANON®. These reported TEAEs do not raise new safety concerns. This data does not demonstrate any specific adverse events that could be directly attributed to the slightly higher upper limit of the 90% CI for C<sub>max</sub> for the radiopaque NEXPLANON® implant.***

Updated Safety Update Report:

The updated safety information for completed Study 34530 received on April 25, 2011 demonstrates similar numbers and percentages of subject with at least one adverse event for the AST group as shown in Table 34 and Table 35 above.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***The TEAEs reported in completed Study 34530 are similar to the TEAEs reported in Study 34528 and in the original clinical trials conducted prior to the approval of IMPLANON® in 2006. These reported TEAEs do not raise new safety concerns for the radiopaque NEXPLANON® implant.***

**3- and 6-Month Evaluation of Implant Palpability and Implant Site Status in Study 34530:**

Included in the sNDA application is an evaluation of implant palpability and implant site status at 3- and 6-months in ongoing Study 34530. Per the application, all of the 3-month data have been validated; the 6-month data have not been validated. Ten (10) of the 301 treated subjects in Study 34530 had no data at month 3 (9 subjects discontinued during the first 3 months and 1 subject did not attend the 3-month and 6-month assessments).

**Palpability:**

Three hundred (300) implants were palpable following insertion. One implant was not palpable at insertion or at the 3- and 6-month assessments (Subject (b) (6)). The implant in Subject (b) (6), however, was clearly visible on the two-dimensional x-ray. No removal complication was reported for this subject.

**Implant Site Status:**

The following table shows the implant site status following insertion and at the 3- and 6-month assessments in Study 34530.

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**Table 36 Status at Site of the Radiopaque Etonogestrel Implant, All-Subjects-Treated Group in Study 34530**

Assessment	Status at site of implant	Nexplanon®	
		n	%
Implant Insertion	TOTAL	301	100.0
	No abnormalities	275	91.4
	Swelling	4	1.3
	Redness	12	4.0
	Pain	2	0.7
	Hematoma	10	3.3
	Expulsion	0	0.0
Month 3 <sup>a</sup>	TOTAL	291	100.0
	No abnormalities	287	98.6
	Swelling	0	0.0
	Redness	2	0.7
	Pain	1	0.3
	Hematoma	0	0.0
	Expulsion	0	0.0
Month 6 <sup>b</sup>	TOTAL	242	100.00
	No abnormalities	242	100.0
	Swelling	0	0.0
	Redness	0	0.0
	Pain	0	0.0
	Hematoma	0	0.0
	Expulsion	0	0.0

<sup>a</sup>. At the 3-month assessment the implant site status was missing for Subject (b) (6). This subject was included in the Total for Month 3.

<sup>b</sup>. The data of the 6-month assessment were not validated.

Note: Subjects can have more than one condition at the implant site per assessment.

Source: Adapted from sNDA 21-529/SES-007, Clinical Trial Report, 3- and 6-month evaluation of implant palpability and implant site status, Table 2 Status at site of implant, All-subjects-Treated Group, page 5 of 7.

**Medical Officer's Comments:**

*As expected, over time fewer or no abnormalities are reported at the insertion site.*

**Implant Removal Safety Information in 3-Year Study 34530:**

As previously noted in Subsection 7.1.1 Studies/Clinical Trials Used to Evaluate Safety in this review, the Applicant was requested to provide implant removal information on all subjects. On November 30, 2010, the Applicant provided “fully verified” removal data. Per the protocol for Study 34530, complications during implant removal were reported as adverse events.

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.  
Supplemental NDA 21-529/SES-007  
Radiopaque Nexplanon® Implant

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A total of 16 subjects experienced complications (adverse events) at the time of removal (5.4%, 16 of 296 subjects):

- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (“slight resistance in skin” reported by Investigator); removal date (b) (6) (“fibrotic tissue around implant” reported by Investigator); days of exposure 168; removal time of 48 seconds.
- Subject (b) (6) (Center (b) (6)) = insertion date (b) (6) (no reported insertion problem); removal date (b) (6) (“fibrotic tissue around implant” reported by Investigator); days of exposure 597; removal time 1 minute and 10 seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (no reported insertion problem); removal date (b) (6) (“fibrotic tissue around implant, single removal attempt which took longer than usual” reported by Investigator); days of exposure 154; removal time 6 minutes and 10 seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (“wet gloves” reported by Investigator); removal date (b) (6) (“single removal attempt which took longer” reported by Investigator); days of exposure 141; removal time 5 minutes and 9 seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (no reported insertion problem); removal date (b) (6) (“fibrotic tissue around implant, larger incision required; multiple removal attempts” reported by Investigator); days of exposure 1073; removal time 7 minutes and no seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (no reported insertion problem); removal date (b) (6) (“second incision required at proximal end” reported by Investigator); days of exposure 391; removal time 8 minutes and no seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (“slightly stiff” reported by Investigator); removal date (b) (6) (“fibrotic tissue around implant” reported by Investigator); days of exposure 1072; removal time 4 minutes and 10 seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (no reported insertion problem); removal date (b) (6) (“fibrotic tissue around implant” reported by Investigator); days of exposure 552; removal time 10 minutes and no seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (no reported insertion problem); removal date (b) (6) (“fibrotic tissue around implant” reported by Investigator); days of exposure 918; removal time 7 minutes and 20 seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (no reported insertion problem); removal date (b) (6) (“fibrotic tissue around implant” reported by Investigator); days of exposure 1076; removal time 8 minutes and 15 seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (no reported insertion problem); removal date (b) (6) (“fibrotic tissue around implant” reported by Investigator); days of exposure 1106; removal time 6 minutes and 10 seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (“harder than usual” reported by Investigator); removal date (b) (6) (“fibrotic tissue around implant”

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.  
Supplemental NDA 21-529/SES-007  
Radiopaque Nexplanon® Implant

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reported by Investigator); days of exposure 1123; removal time 1 minute and 40 seconds.

- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (no reported insertion problem); removal date (b) (6) ("fibrotic tissue around implant" reported by Investigator); days of exposure 793; removal time 2 minutes and 30 seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (no reported insertion problem); removal date (b) (6) ("fibrotic tissue around implant" reported by Investigator) days of exposure 775; removal time 5 minutes and 20 seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (no reported insertion problem); removal date (b) (6) ("fibrotic tissue around implant" reported by Investigator); days of exposure 611; removal time 2 minutes and 45 seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (no reported insertion problem); removal date (b) (6) ("fibrotic tissue around implant" reported by Investigator); days of exposure 329; removal time 8 minutes and 33 seconds.

Two (2) additional subjects in Study 34530 experienced adverse events which resulted in implant removal without complication at the time of implant removal:

- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (no reported insertion problem); removal date (b) (6) ("worsening implant site pain" reported by subject); days of exposure 422; removal time 35 seconds.
- Subject (b) (6) (Center (b) (6)) = Insertion date (b) (6) (no reported insertion problem); removal date (b) (6) ("implant site pain and expulsion of implant" reported by subject); days of exposure 15; removal time 2 minutes and 10 seconds.

### **Medical Officer's/Cross Discipline Team Leader's Comments:**

***Fourteen (14) of the 16 subjects (87.5%) who experience an adverse event at the time of implant removal were reported to have developed fibrotic tissue around the implant. Thirteen of these 14 subjects had the implant removed in a single removal attempt with removal times that ranged from 48 seconds to 8 minutes/22 seconds. Subject (b) (6) required a larger incision at implant removal and multiple removal attempts (removal time of 7 minutes).***

***For the remaining two subjects without reported fibrotic tissue around the implant, Subject (b) (6) had her implant removed in a single attempt which took 5 minutes and 9 seconds, and Subject (b) (6) required a second incision at the proximal end of the implant (reported removal time of 8 minutes). These reported complications at implant removal are not unexpected and do not raise safety concerns for the radiopaque NEXPLANON® implant and the redesigned applicator.***

***The two additional adverse events reported at the time of implant removal (Subject (b) (6) and Subject (b) (6)) also do not raise safety concerns.***

## **7.4.2 Laboratory Findings**

### **Study 34528 Laboratory Findings:**

Blood samples for etonogestrel concentrations were collected in Study 34528. See Section 4.4 Clinical Pharmacology for reported findings. No other clinical laboratory evaluations were collected in Study 34528.

### **Study 34530 Laboratory Findings:**

No clinical laboratory evaluations were collected in Study 34530.

## **7.4.3 Vital Signs**

### **Study 34528 Vital Signs:**

In Study 34528, vital signs (blood pressure and weight) were assessed at screening, at each 2 or 3-monthly assessments and at implant removal. Height was assessed only at screening.

In Study 34528, no apparent overall effect of treatment was apparent for blood pressure. Seven (7) subjects (3 in the IMPLANON® treatment group and 4 in the NEXPLANON® treatment group) occasionally had blood pressure values above the upper safety limit.

Body weight showed an overall slight increase from baseline during treatment (mean [SD] increase of 1.34 [4.53] kg in the IMPLANON® treatment group and 1.54 [4.64] in the NEXPLANON® treatment group) after 36 months of treatment. Table 32 shows that a total of 12 subjects (11.1%, 12 of 108 treated subjects) reported weight increase in Study 34528.

### **Study 34530 Vital Signs:**

Only the screening assessments of blood pressure, body weight and body height were reported in the interim report included in the application.

#### Safety Update Report:

As of the March 12, 2010 data lock point for the Safety Update Report, weight increase was reported in 26 subjects (8.6%, 26 of 301 treated subjects). No other specifics were provided regarding weight increase.

#### **7.4.4 Electrocardiograms (ECGs)**

Electrocardiograms were not obtained in Studies 34528 and 34530.

#### **7.4.5 Special Safety Studies/Clinical Trials**

Study 34530 conducted to evaluate the use of the redesigned applicator (Next Generation Applicator) and its instructions for proper insertion of the radiopaque NEXPLANON® implant are discussed elsewhere in this review.

#### **7.4.6 Immunogenicity**

No human immunogenicity studies, data, or published literature regarding same were submitted in the sNDA.

### **7.5 Other Safety Explorations**

#### **7.5.1 Dose Dependency for Adverse Events**

No dose dependency analyses are presented. All of the study implants used in Study 34528 and Study 34530 contained 68 mg of etonogestrel.

#### **7.5.2 Time Dependency for Adverse Events**

There were no significant time dependent safety findings. None of the 3 vascular events previously described in Study 34528 (see Subsection 7.3.2 Nonfatal Serious Adverse Events) appear to be time dependent: Subject (b) (6) = DVT diagnosed approximately 4 months after implant insertion, Subject (b) (6) = DVT diagnosed approximately 8½ months after implant insertion, and Subject (b) (6) = arterial occlusion diagnosed approximately 14 months after implant insertion.

### **7.5.3 Drug-Demographic Interactions**

No drug-demographic interactions were studied in Studies 34528 and 34530.

### **7.5.4 Drug-Disease Interactions**

No drug-disease interactions were studied in Studies 34528 and 34530.

### **7.5.5 Drug-Drug Interactions**

No drug-drug interactions were studied during the radiopaque etonogestrel implant development program. The potential for agents that induce liver enzymes to lower exposure to etonogestrel, and increase the risk for pregnancy, has been reviewed in previous review cycles for NDA 21-529.

## **7.6 Additional Safety Evaluations**

### **7.6.1 Human Carcinogenicity**

All preclinical studies were submitted during the first review cycle of NDA 21-529/S-000. No new preclinical data is required.

### **7.6.2 Human Reproduction and Pregnancy Data**

See the pregnancy data reported in Study 34528 and Study 34530 presented elsewhere in this review. See Subsection 6.1.4 Analysis of Primary Endpoint(s).

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

The safety and efficacy of approved IMPLANON® has been established in women of reproductive age. The safety and efficacy of the radiopaque NEXPLANON® implant are expected to be the same for postpubertal adolescents. However, no clinical trials have been conducted in women less than 18 years of age. Use of approved IMPLANON® before menarche is not indicated.

#### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

No cases of overdose with the radiopaque NEXPLANON® implant have been reported. The labeling for approved IMPLANON® states, "Insertion of multiple rods has been reported. Overdosage may result if more than one IMPLANON® is inserted. In case of suspected overdose, IMPLANON® should be removed. It is important to remove the IMPLANON® rod or other contraceptive implant(s) before inserting a new IMPLANON® rod."

#### **7.7 Additional Submissions / Safety Issues**

##### **Barium Sulfate Release:**

Per the sNDA application, approved x-ray visible products containing barium sulfate such as stents and IUDs are in widespread use without barium sulfate-related problems. "It has been shown by Beck Scatter Electron (BSE) detector photographs that barium sulfate particles are mainly encapsulated in the EVA28 material of the etonogestrel radiopaque implant." The BSE detector photographs have also shown that after the release of etonogestrel from the implant the barium sulfate is still present in the EVA28 material of the core. Barium sulfate is not leached out of the implant to migrate into skin layers. This has been demonstrated by barium sulfate content analysis of implants before and after in-vitro release testing in both the accelerated release medium (ethanol/water 90/10, 45 °C) and after 3 years in water at 37 °C which mimics the in vivo conditions. In tests of broken or damaged implant containing 0, 2, 3 and 4 vol% of barium sulfate, the average daily release of barium ions was extremely low (b) (4)

##### **Medical Officer's/Cross Discipline Team Leader's Comments:**

***Barium ions are natural constituents of the human body. Daily dietary and inhalatory exposure of the general population is > 1 mg. Normal body content is about 22 mg. A normal blood value is 1.2 mcg/L.***

***See the Pharmacology/Toxicology Review and Evaluation, dated December 14, 2009, for additional information.***

##### **Clinical Training Program (CTP) and Controlled Distribution of the Radiopaque NEXPLANON® Implant and the Redesigned Applicator:**

In the sNDA 21-529/SES-007 submission, the Applicant states, "Upon careful review of the most currently available study results and data, since the meeting held with FDA on 20 August 2007, Schering-Plough (now Merck & Co., Inc.) is proposing that (b) (4)

However, controlled distribution as previously committed to the Division will continue.

(b) (4)

proposed in the sNDA application.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***This reviewer believes that it is advisable that all healthcare providers who will be inserting the radiopaque etonogestrel implant with the redesigned applicator, including those previously trained for insertion of IMPLANON® with the currently approved applicator, should undergo Applicant-sponsored training with the redesigned applicator. However, I do not believe that this should be a condition of approval of NEXPLANON®.***

The Applicant stated in a communication dated August 17, 2010, that the training program for NEXPLANON® and the redesigned applicator training will adhere to the basic principles of the CTP program established in 2006 for approved IMPLANON®:

- Recommended company-sponsored training before a healthcare provider may order the product.

“i.e. All healthcare providers (HCPs) who will be inserting the radiopaque etonogestrel implant (b) (4), including those who were previously trained for insertion of Implanon, will undergo company-sponsored training with the redesigned applicator.”

- Training program to primarily focus on proper technique for insertion/removal and localization of the radiopaque etonogestrel implant.
- Distribution of product only to healthcare providers who have been trained in the company-sponsored training program.

The August 17, 2010 submission contained detailed information regarding faculty training and healthcare provider training.

**Faculty Development Program (FDP):**

The purpose of the FDP is to train clinicians who will serve as faculty trainers for the NEXPLANON® implant CTP. Faculty trainers will be comprised of practicing academicians and other healthcare professionals who have: 1) participated in and completed the Applicant-sponsored CTP, and 2) participated in and completed the Applicant-sponsored in person FDP training session. The following controls will be in place to assure the overall effectiveness of the radiopaque etonogestrel implant and the redesigned applicator FDP:

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

---

- “Merck’s Global Pharmacovigilance Department (GPV) will continue to monitor trained clinician’s IRREs and address any issues per current procedure.”
- “CTPs will be randomly audited/reviewed by Merck’s Global Medical Affairs Department (GMA).”

### HCP Training/Re-Training Program:

The CTP for NEXPLANON® and the redesigned applicator will utilize two training venues:

1. **In Person Session:** HCPs who have not previously attended an Applicant-sponsored CTP for approved IMPLANON® will be recommended to attend an in-person training session for NEXPLANON® and the redesigned applicator.
2. **Web-Based Training:** Web-based training will be available for HCPs who have previously attended an IMPLANON® CTP. The Applicant believes that for experienced (previously trained) IMPLANON® using clinicians, a through, web-based training program is an appropriate vehicle of training for NEXPLANON® and the redesigned applicator.

The web-based CTP will include the following components:

- Module 1: Introducing the radiopaque NEXPLANON® implant and the redesigned applicator
- Module 2: Counseling candidates for the radiopaque NEXPLANON® implant and the redesigned applicator
- Module 3: Inserting the NEXPLANON® implant with the redesigned applicator
- Module 4: Removing NEXPLANON®
- Module 5: Reinserting the NEXPLANON® with the redesigned applicator
- Module 6: Localizing the radiopaque NEXPLANON® implant

Per the Applicant, previously trained HCPs who wish to use NEXPLANON® and the redesigned applicator will register for the web-based program. A “Training Kit” and “Training Binder” will then be sent to them. “The Web-Based Program software will be designed to ensure that all six modules are completed, with knowledge checks throughout.” Upon completion of the “Web-Based Training”, the clinician’s name will be added to the NEXPLANON® database for trained clinicians.

The “Training Binder” provided during the “In Person Session” and the “Web-Based Training” will contain:

- CTP slide booklet

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

---

- NEXPLANON® Patient Labeling (PPI) and Consent Form
- Summary of key points for insertion and removal
- Localization guidance for NEXPLANON®
- Patient User Card (and Patient Chart Label) instructions
- Support contact information
- Trained Clinician Acknowledgement Form \*
- 3-step ordering & billing information
- Drug Re-imburement Coding Sheet
- Curascript ordering instructions & form
- Curascript benefit verification form
- CVS Caremark direct service request form
- Physician prescribing information (PI)

The CTP “Training Kit” provided during the “In Person Session” and the “Web-Based Training” will contain:

- Prosthetic upper arm (the “Model Arm”)
- Redesigned applicators with placebo implants
- Straight hemostat
- Curved hemostat
- Disposable applicator with retractable blade
- Training video
- Desk top model (palpation simulator)
- Insertion site metric ruler
- Training Binder (as above)

### Post-Training Follow-Up for the Radiopaque Etonogestrel Implant and the Redesigned Applicator:

Merck’s Global Medical Information (GMI) Center will be available to provide assistance at any time with insertion/removal procedures post-training, or other questions and medical information related to NEXPLANON® and the redesigned applicator. During the CTP, HCPs will be provided Merck’s GMI contact information.

### **Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***This reviewer agrees with the Applicant’s recommended “In Person Session” training for all healthcare providers not previously trained to insert approved IMPLANON® or the radiopaque NEXPLANON® implant with the redesigned applicator. This reviewer agrees with the Applicant’s proposed “Web-Based Training” for healthcare providers previously trained to insert IMPLANON® with the currently approved applicator. This reviewer appreciates, however, that not all previously trained healthcare providers may wish to participate in “Web-Based Training”. Should this situation occur, the Applicant is encouraged to provide “In***

***Person Session” training upon request for HCPs previously trained to insert approved IMPLANON®.***

***This reviewer concurs with the Applicant’s “Controlled Distribution” process whereby healthcare providers trained for insertion of the radiopaque NEXPLANON® implant with the redesigned applicator will be placed on the NEXPLANON® implant “Trained Clinician Database”. Only trained healthcare providers will be able to order NEXPLANON® and the redesigned applicator.***

***The sample training materials provided on August 17, 2010 need to be revised with the drug product proprietary name NEXPLANON®.***

**Active Monitoring Program (AMP) and Pharmacovigilance Program:**

**Active Monitoring Program (AMP):**

In the original submission of sNDA 21-529/SES-007, the Applicant proposed to (b) (4) [REDACTED]. Per the Applicant, “Review of more than three years of safety data for Implanon has not given rise to concerns about safety of the product. The most medically significant issues that have been identified are related to the insertion and localization of the Implanon implant, and are reported at low rates. During the post-marketing period, the reports received from the Implanon AMP are of a similar nature to those received spontaneously. The (b) (4) [REDACTED] NGIA has the following functionalities that are expected to facilitate insertion:

1. Facilitate insertions:
  - The shape of the applicator and position of the handle relative to the needle should facilitate proper subdermal insertion of the needle.
2. Reduction of non-insertions:
  - The applicator is unusable if no implant is present in the applicator.
  - The applicator holds the implant in the needle after the needle protection cap is taken off until the lever of the applicator is pushed down during insertion.
  - The applicator is unusable after a complete insertion is performed.”

The Applicant was advised, however, of a Postmarketing Commitment (PMC) for the radiopaque NEXPLANON® implant and the redesigned applicator in a regulatory letter dated July 27, 2010, which stated:

“We are requiring that you conduct a postmarketing study to assess insertion and removal events. The design of the study should be similar to that of your ongoing “Active Monitoring Program” (AMP) for Implanon. We request that the study include at least 5,000 insertions and removals with the radiopaque etonogestrel implant and the redesigned applicator.”

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.  
Supplemental NDA 21-529/SES-007  
Radiopaque Nexplanon® Implant

---

On August 20, 2010, Organon USA, Inc. submitted a preliminary AMP protocol for a postmarketing study to assess insertion and removal events for the radiopaque implant and the redesigned applicator.

The proposed design of the AMP for the radiopaque NEXPLANON® implant and the redesigned applicator is similar to that of the Applicant's ongoing AMP for approved IMPLANON®. A total of 5,000 insertions of the radiopaque NEXPLANON® implant with the redesigned applicator and the subsequent removals will be monitored in the AMP. The AMP will involve healthcare providers (HCP) who complete the Clinical Training Program (CTP) and elect to register for the AMP. The AMP will monitor the effectiveness of the CTP for the radiopaque implant and the redesigned applicator. The Applicant estimates that up to 500 trained HCPs will need to participate. "These HCPs will be a subgroup assumed to be representative of the total group of trained clinicians across all practice types (clinics, groups, individuals)." These trained and registered HCPs will complete an Insertion Evaluation Form and a Removal Evaluation Form for each patient in whom they insert and/or remove NEXPLANON®. Per the Applicant, "A quarterly report on IRREs will be generated and submitted to the FDA for a period of 5 years after launch or until 5,000 insertion and removal forms have been received, at which time, a Final (or 5 Year) Report will be submitted."

The timetable that the Applicant submitted on August 20, 2010, states:

Study Start Date: March 2011

Study Completion Date: November 2016

Final Report Submission: Within 5 years after study launch

On January 19, 2011, the Applicant proposed changes to the design of the previously submitted AMP protocol for the radiopaque NEXPLANON® implant. "In addition to monitoring insertion and removals, the currently proposed study will follow at least 5,000 women from insertion up to 3 months after removal of the implant." Per the Applicant, in the time interval between insertion of the implant until implant removal, follow-up self-administered questionnaires will be sent to the subject at regular intervals. "This self-administered questionnaire contains questions on whether any actions have been taken to localize the implant, whether any attempts were made to remove the implant, whether removal has been successful, the occurrence of pregnancy and the occurrence of Serious Adverse Events (SAEs). When a subject reports that the implant was removed or attempts have been made to localize or remove the implant (successful or unsuccessful), she will be asked to fill in the name and address of the HCP involved in localization and/or removal of the implant. When a subject reports the occurrence of pregnancy or the occurrence of an SAE, she will be asked to fill in the name and address of the treating HCP." Per the revised postmarketing study protocol, conformation of pregnancy will be obtained from the subject's treating HCP, as well as additional information including data on the date pregnancy was diagnosed (and the

diagnostic method), the estimated gestational age, the estimated date of conception, the use of concomitant medication, pregnancy outcome (delivery, induced abortion, spontaneous abortion) and actions taken with respect to the implant (continuing or removed). In addition, the treating HCP will be sent a pregnancy monitoring form to complete after the expected date of delivery to obtain relevant details about the delivery and the health of the baby.

If the treating HCP is not registered to participate in the AMP, he/she, via a self-administered localization and/or removal questionnaire, will be asked to report on the (attempted) localization and/or (attempted) removal of the implant including localization and/or removal date, related adverse events, outcomes, and the reason for (premature) discontinuation of the implant.

The revised study protocol also indicates that the subject will be contacted 3 months after removal of the implant to ask whether pregnancy has been diagnosed since the removal of the implant.

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***The revised study design submitted on January 19, 2011 proposes to extend post-insertion monitoring to the patient herself in addition to the attending HCP. Per the Applicant, this proposed change to the study protocol is based on information learned from the approved IMPLANON® AMP. The number of Removal Evaluation Forms (REFs) received is lower than expected due to a high loss to follow-up.***

***Per the Applicant, due to the time span between insertion and removal (up to 3 years), many patients change address and/or change HCP. In addition, many HCPs also change their addresses. The Applicant feels that the high lost to follow-up could be due to the fact that the implant is removed by a different HCP than the one who did the implant insertion. "If at removal the patient is not identified as a patient participating in the AMP and/or the removal HCP is not enrolled in the program, it is likely that the REF will not be completed by the HCP and, therefore, not returned to the Sponsor." "Although different HCPs can be involved with the insertion and removal of the implant, the women are the constant factor and collecting data from the women will reduce the loss to follow-up." This reviewer concurs with this proposed change to the radiopaque NEXPLANON® implant AMP study design.***

***The January 19, 2011 submission, however, does not include a timetable for the study start date, study completion date, or the final report submission date. A preliminary timeline stating that the anticipated research will start within 6 months after the start of the NEXPLANON® Clinical Training Program in the U.S was provided in the study synopsis.***

On March 16, 2011, the Applicant provided an amended timeline for the radiopaque NEXPLANON® postmarketing study:

- |  |  |
|--|--|
| ● Submission date of final AMP protocol to FDA | July 2011  |
| ● Estimated start of subject recruitment       | September 2011                                       |
| ● Recruitment period                           | 28 months  |
| ● Last subject follow-up                       | Q3 2017  |
| ● Study update reports to be submitted to FDA  | At 6 month intervals during the conduct of the study |
| ● Final study report to be submitted to FDA    | Q1 2018  |

Per the Applicant, “All estimated timelines are dependent on the start date of the Clinical Training Program for Nexplanon as well as the actual market share of Nexplanon. In case the market share is lower than expected, this would lead to a reduction of monthly recruitment rates and thus an extension of the recruitment period, ultimately leading to a longer total study duration.”

A second amended timeline for the radiopaque NEXPLANON® postmarketing study was submitted by the Applicant on May 3, 2011:

Final Protocol Submission	July 2011
Study Completion Date	October 2017
Final Report Submission	March 2018

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***The AMP protocol submitted on August 20, 2010 and the amended AMP protocols submitted on January 19, 2011 and March 16, 2011 are all considered preliminary. The Applicant has indicated, however, that the final AMP protocol for the postmarketing commitment study (PMC) for the radiopaque NEXPLANON® implant and the redesigned applicator will be submitted in July 2011.***

***The timeline proposed in the May 3, 2011 submission is acceptable.***

**Pharmacovigilance Program:**

Organon USA, Inc. proposes to conduct the same pharmacovigilance activities for radiopaque NEXPLANON® as currently conducted for non-radiopaque IMPLANON®. The following Pharmacovigilance Program is proposed for NEXPLANON®:

- Postmarketing surveillance: Separate reporting for insertion and removal-related events (IRREs) related to insertion and removal of NEXPLANON® as is currently being done for approved IMPLANON®.
- Periodic adverse drug event reporting including preparation of Periodic Adverse Drug Evaluation Reports (PADER).
- Active follow-up (via questionnaires) of the following events to closely monitor the potential risks and to obtain as much information as possible about:
  - unintended pregnancy and pregnancy exposure
  - venous thromboembolism (VTE)
  - cerebrovascular accidents (CVA)
  - breast cancer
  - insertion and removal related events (IRREs).
- Healthcare provider (HCP) clinical training program (CTP) with availability of the Applicant's Global Medical Information (GMI) Center for follow-up calls.
- Controlled distribution of the product by authorized distributors who will verify that the order or prescription is from a healthcare provider who has completed the CTP.
- Appropriate product labeling that conveys important safety information including contraindications, warnings and precautions, and detailed instructions (including diagrams) on insertion and removal of the radiopaque etonogestrel implant.
- HCP Training Program with availability of Global Medical Information (GMI) for follow-up calls
- Follow-up self-administered questionnaires will be sent to the subject at regular intervals
- USER Card provided to the woman so that she will have a record of the location of the NEXPLANON® implant in the upper arm, and the date when it should be removed.
- Patient Consent Form.

## 8 Postmarket Experience

### **Active Monitoring Program (AMP):**

All safety data for approved IMPLANON® included in the original sNDA application are based on the time period from U.S. market introduction (July 16, 2006) to April 16, 2009. Analysis includes data from the approved IMPLANON® AMP as well as spontaneous reporting as of April 2009.

The following is a summary of the data from the U.S. approved IMPLANON® AMP submitted in the sNDA application:

- **IRREs:** The percentage of IRRE reported within the approved IMPLANON® AMP is (b) (4) %. The May 13, 2009 IRRE report includes a total of 210 IRRE cases reported

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

---

out of a total of (b) (4) AMP Insertion Evaluation forms (IEFs) received (b) (4)%. The 210 cases contain a total of 248 IRRE events (b) (4)%.

- Unintended pregnancy: The percentage of unintended pregnancies reported is (b) (4)% (n = 27). Per the original sNDA application, the percentage of confirmed contraceptive failure (b) (4)%; n = 2) and the percentage of pregnancies due to non-insertion (b) (4)%; n = 2) can be considered very small in relation to the total number of insertion forms received (b) (4).
- Other medically important IRRE events reported within the approved IMPLANON® AMP:
  - 1 report (b) (4)%) in which the implant was unable to be found and subsequently could not be removed.
  - 24 reports in which insertion or removal led to local sensory changes: 13 reports of arm paresthesia (b) (4)%, 10 reports of arm hypoesthesia (b) (4)%, and 1 report of injection site anesthesia (b) (4)%. None of these cases were reported as serious.
  - No cases in which insertion or removal led to vascular damage other than bruising or minor bleeding at the insertion site.

The following is a summary of the data from spontaneous reporting in the U.S. for approved IMPLANON® as of April 2009 and submitted in the sNDA application:

Of the (b) (4) IMPLANON® implants distributed in the U.S. and reported in the May 13, 2009 IMPLANON® Insertion and Removal Related Events (IRREs) report, there were 897 spontaneously reported IRREs (b) (4)% originating from 722 cases (for a reporting rate of (b) (4)%). Per the Applicant, the majority of these IRREs were not serious.

A U.S. Steering Committee, composed of four independent OB/GYN professors in the U.S. chosen as leaders in their field and with experience with the development of the IMPLANON® implant, reviews the data from the AMP and spontaneous reporting on a quarterly basis. Per the Applicant, the Steering Committee's review of the 11<sup>th</sup> IRRE quarterly report indicated that the "type of cases and reporting rate, is within acceptable limits and what is to be expected." "No labeling changes have resulted from the AMP and pharmacovigilance activity for IMPLANON®."

AMP data are collected by means of the Insertion Evaluation Form (IEF) and the Removal Evaluation Form (REF), which are completed by participating HCPs. An Insertion and/or Removal Related Event (IRRE) is defined as any untoward event that is related to the insertion, localization and/or removal of IMPLANON® that cannot be attributed to the exposure of active substance, but is related to the device-like properties of approved IMPLANON®.

16<sup>th</sup> Periodic Report on Insertion/Removal Related Events:

Per the 16<sup>th</sup> Periodic Report on Insertion/Removal Related Events, submitted during this sNDA review cycle, for approved IMPLANON® for the period from April 17, 2009 through July 16, 2010, a total of (b) (4) HCPs have been trained on IMPLANON® insertion since its 2006 launch ( (b) (4) HCPs trained during this reporting period). Of these (b) (4) HCPs trained, (b) (4) HCPs are now actively participating in the AMP (submitting IEF and REF forms during this reporting period).

A total of (b) (4) IMPLANON® implants were distributed during the 16<sup>th</sup> reporting period (a cumulative total of (b) (4) IMPLANON® implants have been distributed since U.S. launch in July 2006).

Per the 16<sup>th</sup> quarterly report, (b) (4) AMP forms were collected by the Applicant during the 16<sup>th</sup> quarter; (b) (4) AMP forms describe patients experiencing a total of 44 IRREs (a patient may experience more than one IRRE). Since U.S. launch in 2006, (b) (4) AMP forms have been submitted ( (b) (4) IEFs and (b) (4) REFs) until the data lock point for the 16<sup>th</sup> quarterly report (July 16, 2010).

*AMP Insertion-Related Events:*

A single insertion-related event was reported in the 16<sup>th</sup> AMP (IMPLANON® was inserted too deeply and was located in the muscle or deep in the fat tissue). In total, 165 insertion-related reports have been received since July 2006 as follows:

<u>IRRE</u>	Reporting Period	Total Period
Deep insertion	1	19
Difficult insertion	0	144
Multiple insert	0	1
No-rod (negative serum etonogestrel)	0	4
Wrong place	0	0
<u>TOTAL</u>	<u>1</u>	<u>168</u>

The most frequently reported insertion-related event is IRRE-difficult insertion (including, but not limited to, “implant stuck in the obturator”, “insertion took more time”, “multiple insertion attempts”, “difficulty withdrawing the cannula”, and “no rod” insertions).

*AMP Localization-Related Events:*

“Localization” refers to the process by which the HCP determines the location of approved IMPLANON® in situ. The localization process starts with palpation of the

insertion site. If palpation is unsuccessful, ultrasound followed by MRI is recommended. When these methods fail, a serum etonogestrel level is suggested (negative level = below 30 pg/mL). During this reporting period, 1 occasion describe the inability to localize the implant (the implant could not be palpated). Per the Applicant, a total of 24 IRRE reports were received in the AMP since U.S. launch that describe inability to localize the implant.

*AMP Removal-Related Events:*

During the 16<sup>th</sup> reporting period, 20 IRREs related to removal were reported to the AMP (a total of 247 IRREs related to removal problems have been reported in the IMPLANON® AMP since the 2006 launch of IMPLANON®). Examples of “removal problems” include: implant could not be found (including migration from the insertion site), a larger incision was needed (including one report of surgical removal under general anesthesia), and more time was needed for removal (difficulty dissecting the fibrous tissue surrounding the implant or difficulty grasping the implant). In this reporting period, a single report described the inability to locate IMPLANON® (by palpation, ultrasound, and MRI) although the serum etonogestrel level was positive.

*AMP Expulsion-Related Events:*

During the reporting period, no IRREs relating expulsion of approved IMPLANON® were reported in the AMP. A total of 9 expulsion-related events have been reported in the AMP since U.S. launch.

*AMP Broken or Cut Rod-Related Events:*

There were 2 reports describing broken or cut rods received during the reporting period. No reports described bent rods. In total since 2006, the AMP has received 17 reports of broken or cut rods, 15 reports of bent rods, and 11 reports describing “Other”.

See following summary presentation:

<u>IRRE</u>	Reporting Period	Total Period
Expulsion	0	9
Broken or cut	2	17
Rod bent	0	15
Other	1	11

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***The most commonly reported IRREs in the AMP is difficult insertion, both in this 16<sup>th</sup> reporting period and overall since product launch in July 2006. It appears, however, that difficult insertions (such as a failed insertion) are recognized and***

**reported immediately by trained HCPs (those actively participating in the AMP) and corrected and/or resolved on a second insertion. HCPs have reported that improper handling of the currently approved applicator has resulted in failed insertions. It is possible that the incidence of difficult insertions will be reduced with the introduction of the redesigned applicator.**

*AMP Cases Describing Possible Nerve or Vascular Injury:*

There were no AMP cases describing an event related to possible nerve injury in the 16<sup>th</sup> reporting period. There have been three nonserious possible nerve injury reports received since U.S. launch in 2006.

There were no AMP cases describing an event related to possible vascular injury, other than bruising or minor bleeding at the insertion site. Two nonserious AMP cases of possible vascular injury were reported in previous IRRE reports (Quarters 14 and 15).

**Spontaneous Case Reports:**

There were a total of 217 cases describing a total of 315 IRREs received by the Applicant via spontaneous reporting during the 16<sup>th</sup> reporting period (a total of 1,654 spontaneous U.S. cases describing 3,028 IRREs have been received since launch in July 2006).

*Spontaneously Reported Insertion-Related Events:*

One hundred and nine (109) insertion-related events were spontaneously reported in the 16<sup>th</sup> reporting period (978 total insertion-related events) as follows:

<u>IRRE</u>	<u>Reporting Period</u>	<u>Total Period</u>
Deep insertion	20	121
Difficult insertion	79	753
Multiple insert	2	39
No-rod (negative serum etonogestrel)	3	51
Wrong place	5	14
<u>TOTAL</u>	<u>109</u>	<u>978</u>

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***The nature and severity of insertion-related events identified from spontaneous reports are similar to those reported within the AMP. "Difficult insertion" continues to be the most frequently reported insertion-related event. A failed first insertion attempt continues to be the most common reason for "difficult***

***insertion”. While the 16<sup>th</sup> IRRE report identifies improper handling of the currently approved applicator as the cause of many failed first insertion attempts, unspecified difficulty with the applicator, “tough” skin, and scarring from previous implantable contraceptives are also listed.***

*Spontaneous Reported Localization-Related Events:*

During the 16<sup>th</sup> reporting period, there were 60 IRREs spontaneously reported for which IMPLANON® was not able to be localized (a total of 459 IRREs spontaneously reported where IMPLANON® was not able to be localized since product launch in July 2006).

*Spontaneously Reported Removal-Related Events:*

Thirty-four (34) IRREs related to removal were spontaneously reported in the 16<sup>th</sup> reporting period (a total of 340 reported since U.S. launch including 15 occasions with positive serum etonogestrel levels).

*Spontaneously Reported Expulsion-Related Events:*

During the reporting period, eight (8) IRREs relating expulsion were spontaneously reported. A total of 35 expulsion-related events have been spontaneously reported since U.S. launch.

*Spontaneously Reported Broken or Cut Rod-Related Events:*

There were 36 spontaneous reports describing broken or cut rods received during the reporting period, 17 reports described bent rods, and 10 describing “other”. In total, since IMPLANON® launch, a total of 249 broken or cut rods, 84 bent rods and 42 “other” IRREs have been spontaneously reported. See following summary presentation:

<u>IRRE</u>	Reporting Period	Total Period
Expulsion	8	35
Broken or cut	36	249
Rod bent	17	84
Other	10	42

The following two tables compare spontaneously reported IRRE cases in the U.S to four other countries (Australia, Germany, France, and the UK). Table 37 shows the IRRE cases reported in the 16<sup>th</sup> reporting period. Table 38 shows the IRRE cumulative cases.

**Table 37 Number of Cases and Insertion and/or Removal Related Events per Number of Implants Distributed in the United States versus Other Countries in the 16<sup>th</sup> Quarter**

Country	Number of Distributed IMPLANON Implants	Number of IRRE Cases	Cases per Distributed IMPLANON Implant
U.S.	(b) (4)	237	(b) (4) %
Australia	(b) (4)	12	%
Germany	(b) (4)	54	%
France	(b) (4)	81	%
UK	(b) (4)	42	%

Definition: IRRE = Insertion and Removal Related Event.

Source: Adapted from 15<sup>th</sup> Post-Marketing Monitoring Program for IMPLANON®, Insertion and Removal Related Events, 17 April 2010 through 16 July 21010; sNDA 21-529/SES-007, page 18 of 37.

**Table 38 Cumulative Number of Cases and Insertion and/or Removal Related Events Spontaneously Reported per Number of Implants Distributed in the United States versus Other Countries**

Country	Number of Distributed IMPLANON Implants	Number of IRRE Cases	Cases per Distributed IMPLANON Implant
U.S.	(b) (4)	2080	(b) (4) %
Australia	(b) (4)	276	%
Germany	(b) (4)	392	%
France	(b) (4)	720	%
UK	(b) (4)	550	%

Definition: IRRE = Insertion and Removal Related Event.

Source: Adapted from 16<sup>th</sup> Post-Marketing Monitoring Program for IMPLANON®, Insertion and Removal Related Events, 17 April 2010 through 16 July 21010; sNDA 21-529/SES-007, page 18 of 37.

Medical Officer's Comments:

Table 37 and Table 38 both demonstrate the frequency of spontaneously reported IRRE cases with approved IMPLANON®. This information is limited, however. The number of distributed IMPLANON® implants do not tell us the number of insertions performed (the desired denominator for calculating the incidence of insertion and/or removal-related adverse events). Nonetheless, the distribution number does provide a measure of the potential use of the product.

For the U.S., Table 37 and Table 38 show consistency in the IRRE cases spontaneously reported in the 16<sup>th</sup> reporting period and cumulatively since launch in July 2006 ((b) (4) % reporting rate or approximately (b) (4) IRRE cases per 1,000 distributed implants in Table 37 and (b) (4) % reporting rate or approximately (b) (4) IRRE cases per 1,000 distributed implants in Table 38). These findings are consistent with previous IRRE periodic reports.

Table 37 and Table 38 also show that the reporting rate of IRRE cases spontaneously reported is higher in the US than in the comparator countries listed. The CTP (which emphasizes reporting IRREs) and the AMP in the U.S. (soliciting IRRE reports) and unidentified differences in surveillance activities in Australia, Germany, France, and the UK may explain these reported results.

Overall, the IRRE reporting rate from both the AMP and spontaneous reporting are low in the U.S. ( (b) (4) % and (b) (4) %, respectively).

#### IRRE Cases Describing Possible Nerve Injury:

During the current reporting period (April 17, 2010 through July 16, 2010), there were 6 spontaneously reported cases describing an event related to possible nerve injury (cumulative total of 25 spontaneous reports of “possible nerve injury”).

These 6 spontaneously reported cases of “possible nerve injury” are discussed below:

1. Case (b) (6): 26 year old overweight patient, who had IMPLANON® inserted on (b) (6). The patient requested removal of IMPLANON® because of numbness in her arm. The patient had an MRI scan, which located the implant. A trained physician unsuccessfully tried to remove the implant twice ( (b) (6) and (b) (6) ). A CT scan was performed that visualized the implant. The patient decided to keep the IMPLANON® implant in place.
2. Case (b) (6): IMPLANON® trained physician removed the IMPLANON® implant inserted previously (unspecified date) by another clinician (unknown if CTP trained). The patient experienced tingling in her fingers. The outcome of the event was not reported.
3. Case (b) (6): 29 year old overweight patient, who had IMPLANON® inserted on (b) (6) by a trained physician. On (b) (6) she noticed that the IMPLANON® rod “felt like it was bent”. She reported that the bent rod caused irritation to her arm and numbness around the insertion site, and wanted the implant removed. The outcome of the event was not reported.
4. Case (b) (6): 28 year old overweight patient, who had IMPLANON® inserted on (b) (6). On (b) (6), she felt tingling and numbness in her arm and the rod “felt broken in the center”. A trained physician removed the implant on (b) (6). The implant was fractured on one side, not broken in half. The patient denied any trauma. The outcome of the event was not reported.
5. Case (b) (6): Unknown aged patient who had IMPLANON® inserted either (b) (6). It was reported that the physician could not locate the implant at removal and “touched several nerves after the incision was made.” The physician assumed that the IMPLANON® implant was now located deep in muscle tissue and scheduled the patient for an MRI. The patient stated that her arm had a “tingly sensation”. The outcome of the event was not reported.

6. Case (b) (6): 25 year old reported that the IMPLANON® implant was inserted too deep and the physician was not able to remove it. The patient experienced “electric shock through her arm when the clinician tried to remove the rod.” The IMPLANON® implant was surgically removed.

*IRRE Cases Describing Possible Vascular Injury:*

During the 16<sup>th</sup> reporting period, there were 2 spontaneous reports describing vascular conditions associated with an IRRE.

These 2 spontaneously reported cases of “possible vascular injury” are discussed below:

1. Case (b) (6): 18 year old patient reported to a trained nurse practitioner (NP) that the IMPLANON® implant was bent. The patient worked in a nursing home, and her arm had been grabbed. The patient described bruising, pain, and a pinching sensation at the implant site. The NP removed the implant without difficulty. The implant was intact, but in the middle there was a crack about halfway through. The patient left the office with another form of contraception (unspecified).
2. Case (b) (6): 20 year old; trained NP attempted to insert the IMPLANON® implant (date unknown). The rod did not release during insertion. A second device was used to successfully insert the IMPLANON® implant through the same insertion canal. The patient experienced some bruising and swelling at the insertion site. Placement of the IMPLANON® implant was confirmed with an ultrasound.

**Medical Officer Comments:**

***The IRRE Steering Committee reviewed the neurovascular injury cases listed above and noted that “the cases were not serious”. This reviewer concurs.***

***Overall, the IMPLANON® Steering Committee reported that the type of cases and rate of reporting in the 16<sup>th</sup> reporting period (RP) is within the “acceptable limit and what is to be expected. Consistent with previous RPs, there are no trends evident based on data from the current RP.” The Steering Committee did not recommend any modifications to the CTP or the AMP as a result of their analysis. This reviewer agrees.***

**Surgical Procedures Performed in the Operating Room Associated with IMPLANON® IRREs:**

The 16<sup>th</sup> Periodic Report on Insertion/Removal Related Events incorporates one added section at the request of the IMPLANON® Steering Committee. The IMPLANON® Steering Committee requested a separate analysis of the serious events of surgical procedures performed in ambulatory surgical centers and/or hospital operating rooms,

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.  
Supplemental NDA 21-529/SES-007  
Radiopaque Nexplanon® Implant

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as well as hospital admissions that were associated with the implant and related to an IRRE. The Steering Committee specifically requested that the focus be on events cause by complications of IRREs, and not on incidental events.

During the 16<sup>th</sup> reporting period there was 1 AMP report describing a surgical procedure performed in the operating room (either in a hospital or outpatient facility) associated with an IMPLANON® IRRE. This report is discussed below:

1. Case (b) (6): 40 year old who underwent an IMPLANON® insertion procedure on (b) (6) by a trained physician. On (b) (6), the patient returned for removal. Although the IMPLANON® implant was palpable before removal, the physician encountered difficulty removing it. The implant was removed in the operating room under general anesthesia.

One additional case of surgical removal under general anesthesia has been reported in the AMP since product launch in July 2006 (initially reported in the 14<sup>th</sup> reporting period).

There were 5 spontaneous reports describing a surgical procedure performed in the operating room associated with an IMPLANON® IRRE. Case (b) (6) is described above under “IRRE Cases Describing Possible Nerve Injury”. The additional 4 cases are summarized below:

1. Case (b) (6): 16 year old patient who had the IMPLANON® implant inserted on (b) (6) by a trained physician. On (b) (6), the physician was not able to palpate the implant prior to attempted removal. A second unsuccessful removal attempt by the physician using ultrasound guidance occurred on (b) (6). The “deep implant” was removed by a general surgeon on (b) (6).
2. Case (b) (6): 24 year old patient who had the IMPLANON® implant inserted on (b) (6) by a trained physician. Due to reported alopecia, the patient requested removal of the implant on (b) (6). The physician reported that the implant “kept moving during removal attempt”, and removal was unsuccessful. Follow-up information reported that this patient planned on seeing a surgeon for removal.
3. Case (b) (6): Patient reported “extreme pain” one week after insertion of the IMPLANON® implant. Ultrasound and MRI was performed and the IMPLANON® implant was located in the muscle. The IMPLANON® implant was surgically removed. The outcome of the extreme pain was not provided.
4. Case (b) (6): 21 year old patient who had the IMPLANON® implant inserted on (b) (6) by a trained NP. On (b) (6), the trained NP could not palpate the rod to remove it. The IMPLANON® implant was located via ultrasound. Follow-up information indicates that the implant was localized by an interventional radiologist and subsequently removed in (b) (6) by a surgeon.

There have been 7 spontaneous reports since U.S. launch in July 2006 describing a surgical removal of an IMPLANON® implant.

**Periodic Adverse Drug Evaluation Reports (PADER):**

In the application, the Applicant indicates that annual PADER reporting will continue to include the standard PADER form, comments on unintended pregnancy reports received and their follow-up, and on IRREs as well as information obtained from the radiopaque etonogestrel implant questionnaires. During the period when both IMPLANON® and the radiopaque etonogestrel implant are co-marketed, data will be presented separately for both in the PADER.

The PADER available during the review cycle for approved IMPLANON® reports on the period April 17, 2009 to July 16, 2009 (12<sup>th</sup> PADER). During this reporting interval, a total of 968 reports (924 initial and 44 follow-up) were received or submitted.

*Initial 15-Day Spontaneous Reports:*

Forty-eight (48) initial 15-day spontaneous reports were submitted during the reporting period (17 domestic and 31 foreign) involving 88 events with a total of 116 occurrences including:

- 7 occurrences of pregnancy
- 5 occurrences of spontaneous abortion
- 5 occurrences of metrorrhagia
- 4 occurrences of headache
- 2 occurrences each of nausea, implant site necrosis, implant site pain, weight increased, arthralgia, osteoporosis, convulsion, twin pregnancy, nephrolithiasis, amenorrhea, nerve injury, and alopecia

The remaining 73 events all had one occurrence each, including one occurrence of deep vein thrombosis.

*Initial Routine Periodic Experience Reports:*

A total of 876 initial routine periodic experience reports were received during this same reporting period (6 serious and 870 non-serious). The serious reports included:

- 3 reports of cerebrovascular accident
- 1 report of ectopic pregnancy
- 1 report of metrorrhagia and weight decreased
- 1 report of hypertension, metrorrhagia, back pain, dizziness, weight increased, alopecia, fatigue, and upper abdominal pain.

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

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The 870 non-serious reports included 190 events with a total of 1339 occurrences:

- 230 occurrences of irregular menses
- 118 occurrences of metrorrhagia
- 74 occurrences of weight increased
- 67 occurrences of menorrhagia
- 59 occurrences of headache
- 43 occurrences of pregnancy
- 42 occurrences of implant site pain
- 39 occurrences of mood swings
- 28 occurrences of acne
- 28 occurrences of nausea
- 24 occurrences of amenorrhea
- 23 occurrences of pain in extremity
- 21 occurrences of alopecia
- 20 occurrences of abdominal pain
- 18 occurrences of dizziness

The remaining 185 events were reported fewer than 18 times each including, but not limited to, 17 occurrences of depression, 11 occurrences of mood altered, 9 occurrences of spontaneous abortion, 3 occurrences of cerebrovascular accident, 1 occurrence of ovarian cyst, and 1 occurrence of ectopic pregnancy.

This reviewer also examined the 7<sup>th</sup> through 11<sup>th</sup> PADER reports for IMPLANON® covering the period January 17, 2008 through April 16, 2009. To summarize, the following 15-Day spontaneous reports were submitted:

- 11<sup>th</sup> PADER (January 17, 2009 – April 16, 2009) = 61 initial 15-day reports (25 domestic and 36 foreign) involving 111 events with a total of 163 occurrences
- 10<sup>th</sup> PADER (October 17, 2008 – January 16, 2009) = 36 initial 15-day reports (15 domestic and 21 foreign) involving 75 events with a total of 92 occurrences
- 9<sup>th</sup> PADER (July 17, 2008 – October 16, 2008) = 27 initial 15-day reports (10 domestic and 14 foreign) involving 54 events with a total of 64 occurrences
- 8<sup>th</sup> PADER (April 17, 2008 – July 16, 2008) = 17 initial 15-day reports (3 domestic and 14 foreign) involving 28 events with a total of 23 occurrences
- 7<sup>th</sup> PADER (January 17, 2008 – April 16, 2008) = 23 initial 15-day reports (8 domestic and 15 foreign) involving 30 events with a total of 36 occurrences

Across this time period, the most prominent occurrence in the 15-day reports received, in decreasing order, were headaches (16), pregnancy with implant contraceptive (15), weight increased (12), convulsion (10), irregular menstruation (8), breast cancer (8), mood swing (7), menorrhagia (6), depression (5), metrorrhagia (5), and spontaneous

## Clinical Review

Theresa H. van der Vlugt, MD, M.P.H.

Supplemental NDA 21-529/SES-007

Radiopaque Nexplanon® Implant

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abortion (5). Other occurrences reported were pulmonary embolism, acne, and cholelithiasis (3 occurrences each); myocardial infarction, deep vein thrombosis, and anemia (2 occurrences each); and cerebral artery occlusion, cerebral venous thrombosis, TIA, thrombophlebitis, anaphylactic shock, and ectopic pregnancy (1 occurrence each)

The following initial routine periodic reports were received between January 17, 2008 and July 16, 2009:

- 11<sup>th</sup> PADER (April 17, 2009 – July 16, 2009) = 770 initial routine periodic reports (6 serious and 770 non-serious):

6 serious reports = menorrhagia (2 cases), DVT (1), DVT and chest pain (1), ectopic pregnancy (1), and mood altered (1)

770 non-serious reports = 157 events with a total of 1172 occurrences = predominant occurrences, in decreasing order: irregular menstruation (239), metrorrhagia (100), weight increased (69), menorrhagia (61), headache (49), nausea (35), implant site pain (33), pregnancy with implant contraceptive (29), and mood swings (24). Other occurrences of interest include DVT (2), ovarian cyst (4), and ectopic pregnancy (1).

- 10<sup>th</sup> PADER (October 17, 2008 – January 16, 2009) = 531 initial routine periodic reports (1 serious and 530 non-serious):

1 serious report = menorrhagia

530 non-serious reports = 152 events with a total of 897 occurrences = predominant occurrences, in decreasing order: irregular menstruation (197), weight increased (53), headache (41), metrorrhagia (40), menorrhagia (29), nausea (28), implant site pain (28), and mood swings (26). Other occurrences of interest include: alopecia (28), acne (22), and ovarian cyst (1).

- 9<sup>th</sup> PADER (July 17, 2008 – October 16, 2008) = 786 initial routine periodic reports (6 serious and 780 non-serious):

6 serious reports = urinary tract infection

780 non-serious reports = 195 events with a total of 1391 occurrences = predominant occurrences, in decreasing order: irregular menstruation (246), metrorrhagia (131), headache (72), weight increased (69), menorrhagia (47), nausea (38), acne (31), pregnancy with implant contraceptive (30), implant site pain (30), mood swings (29), and alopecia (24). Other occurrences of interest include DVT (1), thrombosis (1), and ovarian cyst (6).

- 8<sup>th</sup> PADER (April 17, 2008 through July 16, 2008) = 666 initial routine periodic reports (2 serious and 664 non-serious):

2 serious reports = pulmonary embolism (1), and generalized rash and pyrexia (1)

664 non-serious reports = 149 events with a total of 1004 occurrences = predominant occurrences, in decreasing order: irregular menstruation (269), weight increased (74), headache (42), menorrhagia (31), vaginal hemorrhage (30), nausea (28), and acne (24). Other occurrences of interest include paresthesia (5), and implant site abscess (3).

- 7<sup>th</sup> PADER (January 17, 2008 through April 16, 2008) = 608 initial routine periodic reports (5 serious and 603 non-serious):

5 serious reports = DVT (4), and thrombosis (1)

604 non-serious reports = 146 events with a total of 963 occurrences = predominant occurrences, in decreasing order: irregular menstruation (216), weight increased (50), vaginal hemorrhage (42), headache (35), menorrhagia (28), alopecia (28), pregnancy with implant contraceptive (27), and implant site pain (26). Other occurrences of interest include mood swings (21), depression (18), paresthesia (8), DVT (4), and ovarian cyst (2).

**Medical Officer's/Cross Discipline Team Leader's Comments:**

***It is evident in the periodic adverse drug evaluation reports for approved IMPLANON® that irregular menstruation (including amenorrhea, menorrhagia, metrorrhagia, and vaginal hemorrhage [bleeding]) is the most frequently reported adverse event with IMPLANON®.***

Two reviews were received from the Division of Pharmacovigilance II (DPV II), Office of Surveillance and Epidemiology (OSE), both dated May 19, 2010, regarding approved IMPLANON® (etonogestrel implant) 68 mg. One review addresses the postmarketing review of IMPLANON® and the associated insertion and removal-related events (IRREs), thromboembolic events, strokes, myocardial infarctions, and deaths. The second review addresses the postmarketing review of seizure-related activity with IMPLANON®.

The DPV II assessments are based on a review of FDA's Adverse Event Reporting System (AERS) and the Applicant's approved IMPLANON® labeling and labeling submitted with sNDA 21-529/SES-007.

A March 9, 2010 AERS search for all adverse events of interest retrieved 82 reports of 59 cases for this analysis. A total of 23 reports were excluded for unrelated adverse events (6), duplicate reports (10), unassessable reports (5), and drug interaction reports (2). Specifically discussed in the DPV II review are 3 fatalities, 14 cases of arterial and venous thromboembolism, 11 stroke related events, 4 myocardial infarctions, and 27 cases of IRRs possibly associated with IMPLANON® use.

A March 31, 2010 AERS search for all adverse events associated with IMPLANON® retrieved 393 reports. The most commonly reported preferred term with a count of  $\geq 8$  are: pregnancy with implant contraceptive (70), spontaneous abortion (48), drug interaction (46), vaginal hemorrhage (28), headache (24), convulsion (23), ectopic pregnancy (23), weight increased (23), nausea (18), induced abortion (15), amenorrhea (15), condition aggravated (15), depression (15), menorrhagia (15), mood swings (14), hemorrhage (13), syncope (13), pregnancy (13), hypoesthesia (12), pain in extremity (11), unintended pregnancy (11), cerebrovascular accident (10), device migration (10), dizziness (10), irregular menstruation (10), suicidal ideation (10), deep vein thrombosis (9), paresthesia (9), alopecia (8), back pain (8), and weight decreased (8).

Per the DPV II review, the reviewer did not find any new safety signals following an evaluation of the postmarketing data relating to thromboembolism, stroke, and myocardial infarction. These are labeled adverse events currently described in the Warnings section of IMPLANON® labeling, but not in the proposed labeling for the radiopaque NEXPLANON® implant (sNDA 21-529/SES-007) which states, “(b) (4)

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

**The DPV II reviewer believes** (b) (4)

***This reviewer concurs with the DPV II reviewer’s proposed strengthening of the radiopaque etonogestrel implant labeling under the subsection “Thrombotic and Other Vascular Events” to read. “There have been postmarketing reports of serious arterial and venous thromboembolic events, including cases of pulmonary emboli, deep vein thrombosis, myocardial infarction, and strokes in women using the etonogestrel implant.” This information appears in final agreed upon labeling for the radiopaque etonogestrel implant and the redesigned applicator.***

DPV II completed a separate postmarketing review investigating convulsion as a possible serious unlabeled adverse event with approved IMPLANON®. DPV II found 28 AERS cases (21 domestic and 7 foreign) of seizure activity in association with

IMPLANON® use. The DPV II reviewer believes that the AERS case series suggest a causal relationship between IMPLANON® and seizure-related activity in some cases. Eight (8) cases suggest the possibility of a drug interaction between IMPLANON® and anticonvulsant medications resulting in increase seizure activity. DPV II recommends that the Applicant update labeling (both the currently approved IMPLANON® labeling and the proposed radiopaque NEXPLANON® implant labeling) to include “convulsions” in the postmarketing experience section.

**Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***This reviewer concurs with the DPV II recommendation. The final agreed upon labeling for NEXPLANON® and the redesigned applicator contain this information regarding convulsions under the subsection “Postmarketing Experience”.***

## **9 Appendices**

### **9.1 Literature Review/References**

Per the application, the Applicant thoroughly searched the scientific literature for English and non-English literature relating to IMPLANON for use by women to prevent pregnancy (see attachment I in the sNDA application4). No additional review of the published literature was conducted by this reviewer.

### **9.2 Labeling Recommendations**

The proposed proprietary name NEXPLANON® is acceptable to the FDA and appears in labeling.

Physician Insert:


#### **Highlights**

The most important recommended clinical changes to the Highlights include:

- Expanding CONTRAINDICATIONS to include: “Known or suspected pregnancy”, and “Undiagnosed abnormal genital bleeding”
- Reformatting and expanding WARNINGS AND PRECAUTIONS to include: “Thrombotic and other vascular events”, “Liver disease”, “Elevated blood pressure”, and “Carbohydrate and lipid metabolic effects”

### Full Prescribing Information

The most important recommended clinical changes to the Full Prescribing Information include:

- Modified CONTRAINDICATIONS to match Highlights
- Expanded WARNINGS AND PRECAUTIONS to include subsections on “Depressed Mood” (5.12), “Return to Ovulation” (5.13), “Fluid Retention” (5.14), and “Contact Lenses” (5.15).
- Included cases of “convulsions” in Subsection 6.2 Postmarketing Experience
- Added Subsection 8.8 Overweight Women under Section 8 Use in Specific Populations
- Updated Subsection 12.3 Pharmacokinetics under Section 12 Clinical Pharmacology to include text and Figure 20.
- Deleted proposed (b) (4)  


Patient Information leaflet:

- Modified “What are the most common side effects I can expect while using NEXPLANON?” to include the same adverse reactions identified in Highlights.
- Relocated “Serious Blood Clots” to a more prominent position under “What are the possible risks of using NEXPLANON?”

### **Medical Officer’s/Cross Discipline Team Leader’s Comments:**

***The NEXPLANON® label was submitted in the format prescribed by the Physician Labeling Rule (PLR). Individual consultative reviews were provided by the Division of Drug Marketing, Advertising, and Communications (DDMAC), Office of New Drugs (OND) Study Endpoints and Labeling Development (SEALD), and the Office of Surveillance and Epidemiology (OSE) Division of Risk Management (DRISK). Their comments were incorporated into the label as appropriate.***

***This reviewer recommends approval of the final agreed upon labeling submitted by the Applicant on May 9, 2011.***

### **9.3 Advisory Committee Meeting**

No advisory committee meeting was conducted or needed.

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/s/  
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THERESA H VAN DER VLUGT  
05/12/2011

SCOTT E MONROE  
05/12/2011

I concur with Dr. van der Vlugt's overall assessment and her recommendation that this Application be approved.

## Human Factors Review (Amended)

**Name of the Device:** Implanon® (etonogestrel implant)  
**Device Premarket Path:** NDA 21529  
**ODE Coordinator:** Alan Stevens (ODE)  
**Applicant:** NDA 21529  
**Kind of Device:** Combination product: Insertion device for subcutaneous delivery of contraceptive drug  
**Date sent:** 07/22/2010, **Amended** 08/03/2010  
**Reviewer:** Ron Kaye

### Conclusion (amended)

Based on subsequent review of a later clinical trial that focused on the insertion characteristics of the “next generation applicator” (Study 34530, July 2008) it appears that good performance was obtained for multiple users and actual insertions. It is, however, not clear in that study whether the modifications to the training video and the design of the applicator were made prior to the 2008 study, and whether improvements in terms of use-error reduction can be demonstrated from the results of that study. Please provide a summary of the modifications to the device and the training video that were made prior to the 2008 clinical trial and a clarification of their effectiveness based on the results of that study.

### **End of Amended Review**

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### Conclusions

The response to May 11, 2010 FDA Information Request included: APPENDIX-6 INTERNATIONAL USE TEST PROTOCOL & REPORT”

The report contained a description of use testing done in 2005. The test methodology was acceptable and well-done overall. The Agency is concerned, however, with the following:

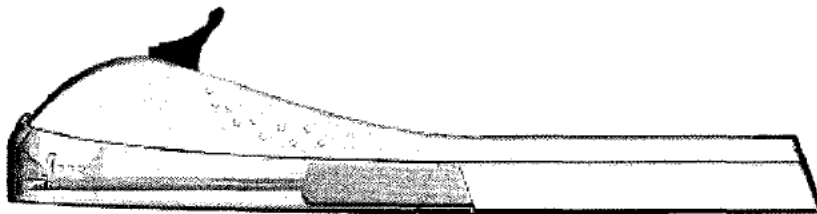
1. Although performance criteria were met, a few failures occurred. Discussion of the failures appeared to indicate that there was little clinical impact from the failures that did occur, however the cause of the performance failures led to suggestions to modifying the design of the applicator, and several specific components in the instruction video training as it existed at the time of testing. Whether modifications were made is not stated, nor are the specific modifications described or reevaluated for effectiveness.
2. The clinical impact of the residual risk associated with performance failures is not discussed in terms of the likely performance of practitioners using the device in the field.

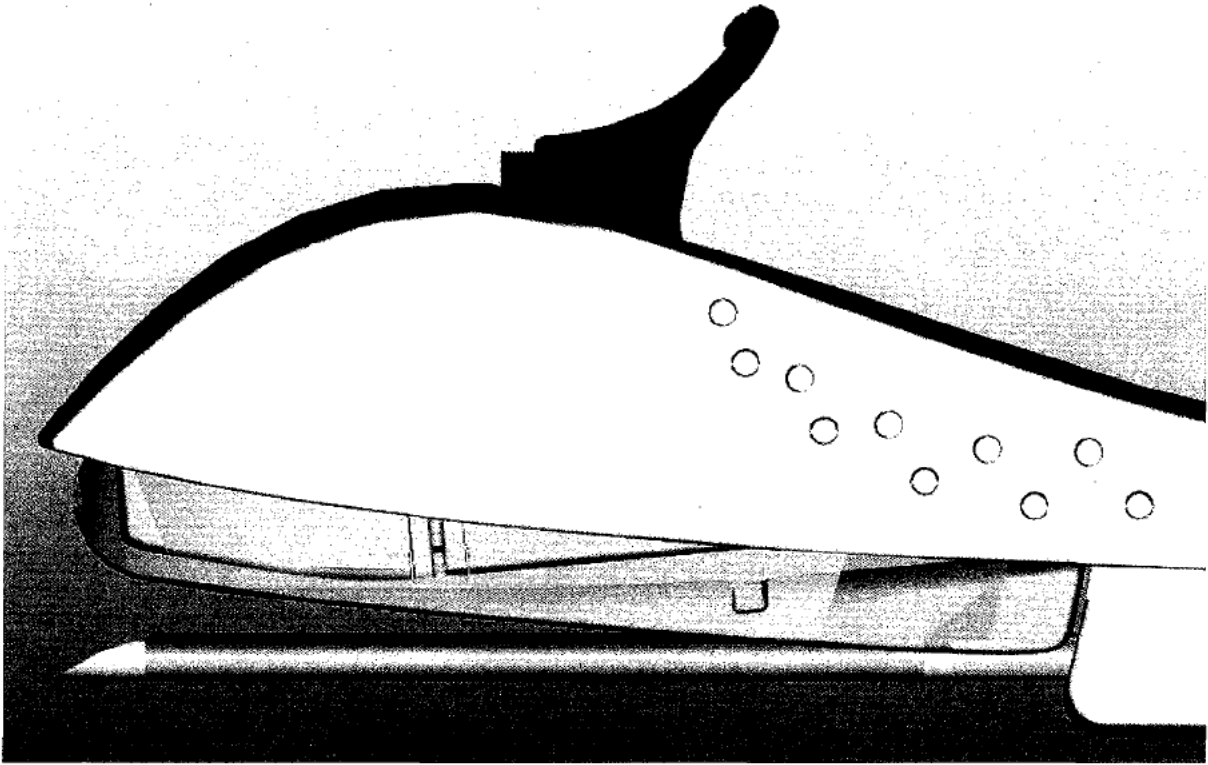
## **Recommendations**

Please describe any modifications made subsequent to your use testing. Also describe any evaluations that were done to evaluate improvements in the design of the device and/or training if such were implemented. If reevaluation of the modifications has not been done, it should be. Based on the results of the reevaluation, please also discuss the failure rates you found in terms of what can be reasonably expected for practitioners using the applicator and associated training video as they are currently designed. Note that for the purposes of the Agency, the reevaluation can be a smaller, more focused study involving a minimum of 15 representative users performing simulated insertion. For the purposes of the Agency, the users should be drawn from practitioners in the United States.

## **Device Description**

The implant is placed inside a stainless steel needle which is fitted to an applicator. The loaded applicator is placed in a (b) (4) tray which is subsequently sealed with lidding foil.






The implant is meant to be inserted subdermally. It should be palpable after insertion. In order to facilitate the manual handling of the applicator by healthcare providers the Next Generation Implanon Applicator (NGIA, new applicator) has been developed. As is the case for the current applicator, the new applicator is a ready-for-use disposable applicator where the implant is pre-filled in the stainless steel needle of the applicator.

**Materials Reviewed**

NDA 2159 Use testing materials (Response to May 11, 2010 FDA Information Request); prior review Alan Stevens (4/29/2010)

Subsequent review of Study 34530, Clinical Trial Report (as per this amended review)

**End of Review**

 8/04/2010

  
TEAM LEADER, COMB PROD Aug 4, 2010

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/s/

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ZETA-MAE C WILLIAMSON  
09/17/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021529Orig1s007**

**CHEMISTRY REVIEW(S)**

**MEMO – FINAL DRAFT LABELING REVIEW – ONDQA CMC**

APPLICATION NUMBER	NDA 21-529 / SES-007
APPLICANT	Organon USA, Inc.
PRODUCT NAME	Nexplanon (etonogestrel implant), 68mg / Radiopaque
SUBMISSION DATE	09-MAY-2011
SUPPORTING DOCUMENT NUMBER	309
REVIEWER	Joel S. Hathaway, Ph.D.

The final draft version of the physician's labeling (package insert) for NDA 21-527 / SES-007, submitted 09-MAY-2011 (SDN 309, CTD# 0150) was reviewed with respect to the chemistry and manufacturing sections of the SPL-formatted label.

The [REDACTED] <sup>(b) (4)</sup> has been removed from the Title section of the PI label, as recommended in the SEALD review dated 29-APR-2011.

No other changes were made by the applicant to any of the CMC-related sections (Title, Sections 3, 11 and 16) since the most recent formal CMC review (review #2, dated 26-APR-2011).

This draft label is acceptable for these CMC-related sections.

Joel Hathaway, Ph.D.  
Reviewer,  
ONDQA / DNDQA II / Branch VI  
joel.hathaway@fda.hhs.gov

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/s/  
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JOEL S HATHAWAY  
05/11/2011

THOMAS F OLIVER  
05/11/2011

**OFFICE ON NEW DRUG QUALITY ASSESSMENT**  
**DIVISION OF NEW DRUG QUALITY ASSESSMENT II, BRANCH VI**  
Review of Chemistry, Manufacturing, and Controls  
for the Office of New Drugs,  
Division of Reproductive and Urology Products

**NDA #:** 21-529      **CHEM.REVIEW #:** 2    **REVIEW DATE:** 25-APR-2010  
**TYPE:** SES-007

<b><u>SUPPORTING DOC. NO.</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
283	18-AUG-2010	19-AUG-2010	19-AUG-2010
284	20-AUG-2010	20-AUG-2010	20-AUG-2010
289	06-OCT-2011	06-OCT-2011	06-OCT-2011
293	30-NOV-2011	30-NOV-2011	30-NOV-2011
302	17-MAR-2011	17-MAR-2011	17-MAR-2011
304	05-APR-2011	05-APR-2011	05-APR-2011

**NAME & ADDRESS OF APPLICANT:** Oragnon USA, Inc.  
56 Livingston Avenue  
Roseland, New Jersey 07068

Ed Nellis,  
Senior Manager, Regulatory Affairs

(b) (6)

**DRUG PRODUCT NAME**

<u>Proprietary:</u>	Implanon®
<u>Nonproprietary/USAN:</u>	etonogestrel implant
<u>Code Names/#s:</u>	ORG 32222
<u>Chemical Type/</u>	1, New Chemical Entity
<u>Therapeutic Class:</u>	S, Standard Review

**ANDA Suitability Petition/DESI/Patent Status:**

N/A

**PHARMACOLOGICAL**

**CATEGORY/INDICATION:** Indicated for contraception.

<b><u>DOSAGE FORM:</u></b>	Subdermal Implant
<b><u>STRENGTHS:</u></b>	68mg
<b><u>ROUTE OF ADMINISTRATION:</u></b>	Subdermal
<b><u>DISPENSED:</u></b>	<input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC

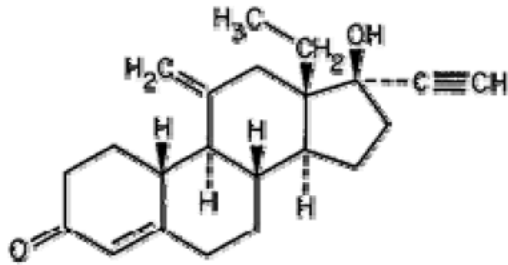
**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,**

**MOL.WT:**

Etonogestrel: 13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one

Molecular Formula:	C <sub>22</sub> H <sub>28</sub> O <sub>2</sub>
Molecular Weight:	324.46
CAS No.:	[54048-10-1]

**IMPLANON® (etonogestrel implant), 68mg  
Organon USA, Inc.**



**SUPPORTING DOCUMENTS:**

DMF [REDACTED] (b) (4) held by [REDACTED] (b) (4); Letter of Authorization dated [REDACTED] (b) (4). Not reviewed; facility is currently approved for sterilization operations for NDA 21-529.

**REMARKS/COMMENTS:**

Refer to CMC Review #1, dated 19-APR-2010 for CMC recommendations. The current amendments to this Prior Approval Supplement provided revised labeling (physician's package insert and patient's package insert) employing a new proprietary name for the new formulation [REDACTED] (b) (4) was rejected by OSE) as well as a revised established (non-proprietary) name (Nexplanon®). Nexplanon® and the proposed labeling were found acceptable by OSE/DMEPA in their reviews dated 31-JAN-2011 and 31-MAR-2011.

Consult reviews were requested from the CMC Microbiologist (18-AUG-2009) and from CDRH (18-FEB-2010) for the insertion device. The CMC Microbiology review was completed by Dr. Steven E. Fong on 09-OCT-2009, and recommended approval. The CDRH consult has been completed; in the review dated 17-SEP-2010, the information and data regarding the design, human factors and operation of the implantation device have been found to be acceptable.

**CONCLUSIONS & RECOMMENDATIONS:**

**APPROVAL**

The chemistry, manufacturing, control and labeling information submitted in this supplement, as amended, is adequate for the proposed changes. Approval is recommended.

*(see attached electronic signature page)*

---

Joel S. Hathaway, Ph.D.  
Reviewing Chemist

cc: Orig. NDA 21-529  
OND/DRUP/Division File  
ONDQA/DNDQA2/Chem/JSHathaway  
ONDQA/DNDQA2/CMCLead/DLewis  
ONDQA/DNDQA2/CMCBranchChf/HPatel

**NDA 21-529 / SES-007**  
**IMPLANON® (etonogestrel implant), 68mg**  
**Organon USA, Inc.**

**Page 3 of 11**

ONDQA/DNDQA2/DivDir/TOcheltree  
ONDQA/DNDQA2/ProjMgr/CTranZwanetz

**filename:** C:\Documents and Settings\hathaways\My Documents\MSWordDocs\NDA  
Reviews\SuppNDAs\21529 Implanon Implant\N21529r2.ses.007.doc

**Approval**

**IMPLANON® (etonogestrel implant), 68mg  
Organon USA, Inc.****CHEMISTRY REVIEW NOTES AND ASSESSMENTS**

The approved Implanon® product consists of a non-biodegradable single-rod implant, pre-filled in the stainless steel needle of a sterilized, ready-for use disposable applicator. The implant has a length of 4cm and a diameter of 2 mm and contains a synthetic progestagen, etonogestrel (3-ketodesogestrel, Org 3236). After subdermal insertion of the implant in the upper-arm, a continuous, slowly decreasing release of etonogestrel occurs, providing contraceptive protection for three years.

To improve the clinical safety performance of the product, a revised formulation of the implant was developed to make the implant opaque to X-ray, through addition of 15mg of barium sulfate to the core matrix of the implant, corresponding to (b) (4)% by volume and (b) (4).

A new applicator device for inserting the implant was also developed, referred to in the Application as the Next Generation Implanon Applicator (NGIA). The main goal of the NGIA development is to facilitate the manual handling of the applicator for implant insertion by the healthcare providers. The shape of the blister tray was modified to accommodate the dimensions of the new applicator. The currently approved (b) (4) blister lidding material was replaced by (b) (4), which is said to have better mechanical properties.

**II. Review of Common Technical Document-Quality (CTD-Q) Module 1****A. Label**

**Reviewer Evaluation:** The various labels, depicted and reviewed individually below, all display the common elements of proprietary name, established name, etc. on structures analogous to those already approved (patient chart adhesive label, patient chart, carton, blister package). Revisions were submitted for the suite of labeling in response to FDA requests for revised labeling. As a result of the denial of the proposed (b) (4) to "NEXPLANON" or "Nexplanon". In addition, the established name has been changed back to the original "etonogestrel implant", as is preferred by FDA, (b) (4).

All references to applicant/manufacturer were changed to reflect the change of ownership filed on 04-NOV-2009.

**Label for Patient Chart:**



LABEL DIMENSIONS: 166mm x 55mm

**User Card:**



CARD DIMENSIONS: 3-3/8" x 2-1/8"

**Commercial Blister Label:**



BLISTER DIMENSIONS: 127mm x 45mm

**Commercial Carton:**



**CARTON DIMENSIONS: 67mm x 31mm x 179.5mm**

**Professional Sample Carton:**



**CARTON DIMENSIONS: 67mm x 31mm x 179.5mm**

**Professional Sample Blister Label:**



BLISTER DIMENSIONS: 127mm x 45mm

**Reviewer Evaluation:** The remaining elements of the carton, blister, chart and user card labeling are acceptable. The labeling provides the manufacturer identification, ingredients, declared strength, 'Rx only' and 'Subdermal Use Only' warnings and storage conditions. The storage conditions are identical to those in the approved labeling.

**Package Insert Label:**

Revised package insert labeling was provided; the CMC-related sections are excerpted below.

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

NEXPLANON (etonogestrel implant) Radiopaque

(b) (4)

Subdermal Use Only

Initial U.S. Approval: 2006

**Reviewer Evaluation:** The tradename, established name (b) (4) have been revised in accordance with FDA recommendations. Acceptable.

**FULL PRESCRIBING INFORMATION**

**3. DOSAGE FORMS AND STRENGTHS**

Single, white/off-white, soft, radiopaque, flexible, ethylene vinylacetate (EVA) implant, 4 cm in length and 2 mm in diameter containing 68 mg etonogestrel and 15mg of barium sulfate.

**Reviewer Evaluation:** The "Dosage Forms and Strengths" section has been revised to include a more detailed physical description, as well as the inclusion of the barium sulfate ingredient. The (b) (4) has been moved to the "Description" section, #11. Acceptable.

## 11. DESCRIPTION

NEXPLANON is a radiopaque, progestin-only, soft, flexible implant preloaded in a sterile, disposable applicator for subdermal use. The implant is white/off-white, non-biodegradable and 4 cm in length with a diameter of 2 mm (see Figure 18). Each implant consists of an ethylene vinylacetate (EVA) copolymer core, containing 68 mg of the synthetic progestin etonogestrel and barium sulfate (radiopaque ingredient), surrounded by an EVA copolymer skin. Once inserted subdermally, the release rate is 60-70 mcg/day in week 5-6 and decreases to approximately 35-45 mcg/day at the end of the first year, to approximately 30-40 mcg/day at the end of the second year, and then to approximately 25-30 mcg/day at the end of the third year. NEXPLANON is a progestin-only contraceptive and does not contain estrogen. NEXPLANON does not contain latex.

**Reviewer Evaluation:** The "Description" section adds the "radiopaque" information of the proposed formulation, and includes the barium sulfate ingredient. The chemical name and structure are unchanged from the previously approved label. Acceptable.

## 16. HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

One NEXPLANON package consists of a single implant containing 68 mg etonogestrel that is 4 cm in length and 2 mm in diameter, which is pre-loaded in the needle of a disposable applicator. The sterile applicator containing the implant is packed in a blister pack.

NDC 0052-0274-01

### 16.2 Storage and Handling

Store NEXPLANON (etonogestrel implant) Radiopaque at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Avoid storing NEXPLANON at temperatures above 30°C (86°F).

**Reviewer Evaluation:** Acceptable.

## FACILITIES INSPECTIONS

Establishment inspection requests were submitted on 03-SEP-2010 for the facilities utilized in production of the drug product (manufacturing, testing and sterilization sites). The Office of Compliance issued an "Acceptable" recommendation on 10-FEB-2011, based in part on on-site inspection of the drug product manufacturing facility:

(b) (4)



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JOEL S HATHAWAY  
04/26/2011

THOMAS F OLIVER  
04/26/2011

**OFFICE ON NEW DRUG QUALITY ASSESSMENT  
DIVISION OF POST-MARKETING EVALUATION, BRANCH VIII**

Review of Chemistry, Manufacturing, and Controls  
for the Division of Reproductive and Urology Products

**NDA #:** 21-529      **CHEM.REVIEW #:** 1      **REVIEW DATE:** 19-APR-2009  
**TYPE:** SES-007

<b><u>SUPPORTING DOC. NO.</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
190	29-JUL-2009	30-JUL-2009	18-AUG-2009
223	18-SEP-2009	21-SEP-2009	21-SEP-2009
227	24-SEP-2009	24-SEP-2009	24-SEP-2009
238	09-OCT-2009	09-OCT-2009	09-OCT-2009

**NAME & ADDRESS OF APPLICANT:** Oragnon USA, Inc.  
56 Livingston Avenue  
Roseland, New Jersey 07068

Ed Nellis,  
Senior Manager, Regulatory Affairs

(b) (6)

**DRUG PRODUCT NAME**

<u>Proprietary:</u>	Implanon®
<u>Nonproprietary/USAN:</u>	etonogestrel implant
<u>Code Names/#s:</u>	ORG 32222
<u>Chemical Type/</u>	1, New Chemical Entity
<u>Therapeutic Class:</u>	S, Standard Review

**ANDA Suitability Petition/DESI/Patent Status:**

N/A

**PHARMACOLOGICAL**

**CATEGORY/INDICATION:** Indicated for contraception.

<b><u>DOSAGE FORM:</u></b>	Subdermal Implant
<b><u>STRENGTHS:</u></b>	68mg
<b><u>ROUTE OF ADMINISTRATION:</u></b>	Subdermal
<b><u>DISPENSED:</u></b>	<u> X </u> Rx <u>  </u> OTC

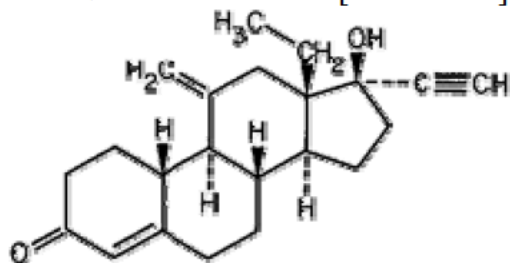
**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,  
MOL.WT:**

Etonogestrel: 13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one

Molecular Formula: C<sub>22</sub>H<sub>28</sub>O<sub>2</sub>  
Molecular Weight: 324.46

**IMPLANON® (etonogestrel implant), 68mg  
Organon USA, Inc.**

CAS No.: [54048-10-1]



**SUPPORTING DOCUMENTS:**

DMF [REDACTED] (b) (4), held by [REDACTED] (b) (4); Letter of Authorization dated [REDACTED] (b) (4). Not reviewed; facility is currently approved for sterilization operations for NDA 21-529.

**REMARKS/COMMENTS:**

The current "Supplement for Prior Approval" application provides for a new, radiopaque version of the implant rod and a "Next Generation Implanon Applicator"(NGIA). Implanon® consists of a non-biodegradable, single-rod implant, pre-filled in the stainless steel needle of a ready-for use disposable applicator. The implant has a length of 4cm and a diameter of 2mm and contains a synthetic progestagen, etonogestrel. After subdermal insertion of the implant in the upper-arm, a continuous, slowly decreasing release of etonogestrel occurs, providing contraception for three years.

The presence of the current marketed Implanon® implant *in situ* can be verified by palpation, ultrasonography and/or Magnetic Resonance Imaging (MRI). In cases where the implant cannot be located by any of these techniques, serum etonogestrel measurements can be performed to assure presence of the implant. However, etonogestrel assays are very specialized, time consuming, can only be performed in a limited number of (Organon) laboratories and cannot reveal the location of the implant. Therefore, an X-ray visible implant was developed to add an additional mechanism for localization. In order to make the implant X-ray visible, 15mg of barium sulfate, corresponding to [REDACTED] (b) (4) (w/v), was added to the core matrix of the implant, [REDACTED] (b) (4).

Additionally, a new applicator for subdermally inserting the implant has been developed, referred to as the Next Generation Implanon Applicator (NGIA). The main goal of the NGIA development was to improve the handling of the applicator for insertion of the implant by the healthcare provider. The shape of the blister pack has been adapted to accommodate the dimensions of the new applicator. The current paper blister lidding material was replaced by a

**IMPLANON® (etonogestrel implant), 68mg  
Organon USA, Inc.**

material with better mechanical properties. This material does not contact the implanted drug product.

In addition to these changes, the drug product specification has been harmonized with the international product's specification. This results in [REDACTED] <sup>(b) (4)</sup> **of the acceptance range for unspecified degradation products.**

A large number of the Quality Module 3 documents are affected by these changes, and a new, complete CTD Module 3 for drug product part was submitted, replacing the currently approved drug product part of the CTD.

During a transition period post-approval, the Applicant expects that both the current (not radiopaque) Implanon® product and the revised-formulation product will be concurrently in distribution for a period of time. The Applicant has proposed a new proprietary name for the new formulation, [REDACTED] <sup>(b) (4)</sup>, as well as a new established (non-proprietary) name.

Consult reviews were requested from the CMC Microbiologist (18-AUG-2009) and from CDRH (18-FEB-2010) for the insertion device. The CMC Microbiology review was completed by Dr. Steven E. Fong on 09-OCT-2009, and recommended approval. The CDRH consult is still pending as of the date of this review.

**CONCLUSIONS & RECOMMENDATIONS:****APPROVAL**

The data and information submitted in the supplement are adequate to support the new formulation of Implanon® Implant. However, a number of labeling elements require revision. The following comments have been revised in the draft labeling and have been communicated to the OND reviewers:

- The proposed established name, "[REDACTED] <sup>(b) (4)</sup>", is not acceptable. The Applicant may continue to use the currently approved established name, 'etonogestrel implant', [REDACTED] <sup>(b) (4)</sup>
- In Section 11 of the Physician's Package Insert, the description of the applicator is incorrect. Change from [REDACTED] <sup>(b) (4)</sup> to [REDACTED] <sup>(b) (4)</sup>.

The patient chart label, user card, blister label, carton label and package inserts should be revised to incorporate the above recommendations.

*(see attached electronic signature page)*

**NDA 21-529 / SES-007**  
**IMPLANON® (etonogestrel implant), 68mg**  
**Organon USA, Inc.**

**Page 4 of 52**

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Joel S. Hathaway, Ph.D.  
Reviewing Chemist

cc: Orig. NDA 21-529  
OND/DRUP/Division File  
ONDQA/DPE/Chem/JSHathaway  
ONDQA/DPE/ChemPAL/SDe  
ONDQA/DPE/ChemBranchChf/HPatel  
ONDQA/DPE/ProjMgr/ACuff

**filename:** C:\Documents and Settings\hathaways\My Documents\MSWordDocs\NDA  
Reviews\SuppNDAs\21529 Implanon Implant\N21529r.ses.007.doc

**Approval**

## CHEMISTRY REVIEW NOTES AND ASSESSMENTS

Implanon® consists of a non-biodegradable single-rod implant, pre-filled in the stainless steel needle of a ready-for use disposable applicator. The implant has a length of 4cm and a diameter of 2 mm and contains a synthetic progestagen, etonogestrel (3-ketodesogestrel, Org 3236). After subdermal insertion of the implant in the upper-arm, a continuous, slowly decreasing release of etonogestrel occurs, providing contraceptive protection for three years.

An X-ray visible implant was developed to make the implant opaque to X-ray, through addition of 15mg of barium sulfate to the core matrix of the implant, corresponding to  $\frac{(b)}{(4)}\%$  by volume and  $\frac{(b)}{(4)}$ .

A new applicator for inserting the implant was also developed, referred to in the Application as the Next Generation Implanon Applicator (NGIA). The main goal of the NGIA development is to facilitate the manual handling of the applicator for implant insertion by the healthcare providers. The shape of the blister pack was modified to accommodate the dimensions of the new applicator. The currently approved  $\frac{(b)}{(4)}$  paper blister lidding material was replaced by  $\frac{(b)}{(4)}$  film, which has better mechanical properties.

### **I. Review of Common Technical Document-Quality (CTD-Q) Module 3.2: Body of Data** **P DRUG PRODUCT** **P.1 Description and Composition of the Drug Product**

Implanon® (etonogestrel) Implant, 68mg, (XR-NGIA) is a subdermal contraceptive implant consisting of a implant and an applicator. The proposed revised formulation for the implant consists of a core containing a mixture of the drug substance, etonogestrel (Org 3236), barium sulfate and ethylene vinylacetate copolymer (vinylacetate content 28%), and a skin composed of ethylene vinylacetate copolymer (vinylacetate content 14%). Each implant contains 68mg etonogestrel. The implant has a length of 4.0cm and a diameter of 2.0mm (nominal).

### **P.2 Pharmaceutical Development** **P.2.1 Components of the Drug Product**

The complete composition of the barium sulfate-containing Org 3236 Implants 68mg (XR-NGIA) is listed below:

(b) (4)



## II. Review of Common Technical Document-Quality (CTD-Q) Module 1

### A. Label

**Reviewer Evaluation:** The various labels depicted below all display the common elements of proprietary name, established name, etc. on structures analogous to those already approved (patient chart adhesive label, patient chart, carton, blister package).

The proposed trade name, "[REDACTED] (b) (4)", is not acceptable. In general, [REDACTED] (b) (4)

(b) (4) is considered to be confusing and a potential source of medication errors (see OSE/DMEPA review of 23-DEC-2009). A recommendation will be made to the Applicant to (b) (4) and to utilize instead the tradename "IMPLANON®".

The proposed established name, "(b) (4)", is also not acceptable. It is current policy that FDA "will not routinely designate official names under subsection 508 of the Act. As a result, the established name under subsection 502(e) of the Act will ordinarily be either the compendial name of the drug or, if there is no compendial name, the common and usual name of the drug." The proposed established name is inappropriate for two reasons. First, it would establish a (b) (4) which is judged to be unacceptable. (b) (4)

The Applicant may continue to use the currently approved established name, 'etonogestrel implant', (b) (4).

(b) (4)

**Label for Patient Chart:**

(b) (4)

LABEL DIMENSIONS: 166mm x 55mm

**NDA 21-529 / SES-007**  
**IMPLANON® (etonogestrel implant), 68mg**  
**Organon USA, Inc.**

**Page 47 of 52**

**User Card:**

(b) (4)



CARD DIMENSIONS: 3-3/8" x 2-1/8"

**Commercial Carton:**



(b) (4)

**CARTON DIMENSIONS: 67mm x 31mm x 179.5mm**

**Commercial Blister Label:**



(b) (4)

**NDA 21-529 / SES-007**  
**IMPLANON® (etonogestrel implant), 68mg**  
**Organon USA, Inc.**

**Page 49 of 52**

BLISTER DIMENSIONS: 127mm x 45mm

**Professional Sample Carton:**



CARTON DIMENSIONS: 67mm x 31mm x 179.5mm

**Professional Sample Blister Label:**



(b) (4)

BLISTER DIMENSIONS: 127mm x 45mm

**Reviewer Evaluation:** The remaining elements of the carton, blister, chart and user card labeling are acceptable, except where noted above. The labeling provides the manufacturer identification, ingredients, declared strength, 'Rx only' warning and storage conditions. The storage conditions are identical to those in the approved labeling.

**Package Insert Label:**

A revised package insert was provided; the CMC-related sections are excerpted below. Note that the **proposed** trade and established names are used throughout the package insert and patient package insert; these should be revised to the **recommended** nomenclature.

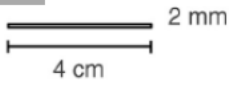
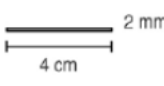
The proposed sections are on the left, and the approved labeling on the right:

<p>3. <b>DOSAGE FORMS AND STRENGTHS</b> Single, white/off-white, soft, radiopaque, flexible, ethylene vinylacetate (EVA) implant, 4 cm in length and 2 mm in diameter containing 68 mg etonogestrel (b) (4) (b) (4)</p>	<p><b>DOSAGE FORM AND STRENGTHS</b> One IMPLANON™ (etonogestrel implant) package consists of a single rod implant containing 68 mg etonogestrel that is 4 cm in length and 2 mm in diameter. IMPLANON™ is pre-loaded in the needle of a disposable applicator. The applicator consists of acrylonitrile-butadiene-styrene body with a stainless steel needle and a polypropylene shield. The sterile applicator containing IMPLANON™ is packed in a blister pack.</p>
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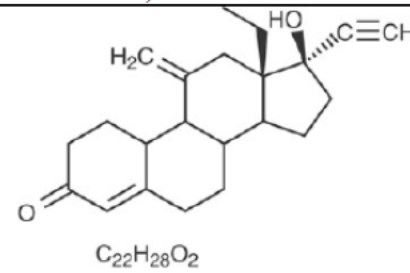
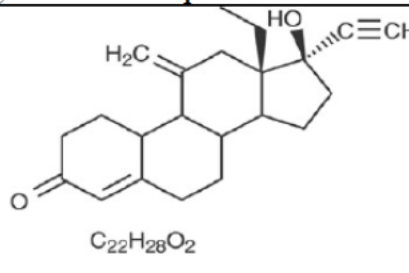
**Reviewer Evaluation:** The "Dosage Forms and Strengths" section has been revised to include a more detailed physical description. (b) (4)

Acceptable.

**IMPLANON® (etonogestrel implant), 68mg  
Organon USA, Inc.**

<p><b>11. DESCRIPTION</b>                  IMPLANON NXT is a radiopaque, progestin-only, soft, flexible implant preloaded in a sterile, disposable applicator. The implant is white/off-white, non-biodegradable and 4 cm in length with a diameter of 2 mm (see Figure 18). Each (b) (4) implant consists of an ethylene vinylacetate (EVA) copolymer core, containing 68 mg of the synthetic progestin etonogestrel and barium sulfate (radiopaque ingredient), surrounded by an EVA copolymer skin. Once inserted subdermally, the release rate is 60-70 µg/day in week 5-6 and decreases to approximately 35-45 µg/day at the end of the first year, to approximately 30-40 µg/day at the end of the second year, and then to approximately 25-30 µg/day at the end of the third year. (b) (4) is a progestin-only contraceptive and does not contain estrogen. (b) (4) does not contain latex.</p>  <p>Figure 18 (Not to scale)</p> <p>Etonogestrel [13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one], structurally derived from 19-nortestosterone, is the synthetic biologically active metabolite of the synthetic progestin desogestrel. It has a molecular weight of 324.46 and the following structural formula (Figure 19)</p>	<p><b>DESCRIPTION</b>                  IMPLANON™ (etonogestrel implant) is an off-white, non biodegradable, etonogestrel-containing single sterile rod implant for subdermal use. The implant is 4 cm in length with a diameter of 2 mm (see Figure 1). Each IMPLANON™ rod consists of an ethylene vinyl acetate (EVA) copolymer core, containing 68 mg of the synthetic progestin etonogestrel (ENG), surrounded by an EVA copolymer skin. The release rate is 60-70 µg/day in week 5-6 and decreases to approximately 35-45 µg/day at the end of the first year, to approximately 30-40 µg/day at the end of the second year, and then to approximately 25-30 µg/day at the end of the third year. IMPLANON™ is a progestin-only contraceptive and does not contain estrogen. IMPLANON™ does not contain latex and is not radio-opaque.</p>  <p>Figure 1 (Not to scale)</p> <p>ENG [13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one], structurally derived from 19-nortestosterone, is the synthetic biologically active metabolite of the synthetic progestin desogestrel. It has a molecular weight of 324.46 and the following structural formula:</p>
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**Reviewer Evaluation:** The "Description" section adds the "radiopaque" information of the proposed formulation, and includes the barium sulfate ingredient. Acceptable.

 <p>Figure 19</p>	 <p>Figure 19</p>
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**Reviewer Evaluation:** The structure is unchanged; Acceptable.

<p><b>16. HOW SUPPLIED/STORAGE AND HANDLING</b>                  One (b) (4) package consists of a single implant containing 68 mg etonogestrel that is 4 cm in length and 2 mm in diameter, which is pre-loaded in the needle of a disposable applicator. (b) (4)                  (b) (4) The sterile applicator containing the implant is packed in a blister pack.</p> <p>NDC 0052-0274-01</p> <p><b>Storage</b>                  Store (b) (4) at 25°C (77° F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. (b) (4) Avoid storing (b) (4) at temperatures above 30°C (86° F).</p>	<p><b>HOW SUPPLIED/STORAGE AND HANDLING</b></p> <p><b>How supplied</b>                  One IMPLANON™ (etonogestrel implant) package consists of a single rod implant containing 68 mg etonogestrel that is 4 cm in length and 2 mm in diameter. IMPLANON™ is pre-loaded in the needle of a disposable applicator. The applicator consists of acrylonitrile-butadiene-styrene body with a stainless steel needle and a polypropylene shield. The sterile applicator containing IMPLANON™ is packed in a blister pack.</p> <p>NDC 0052-0272-01</p> <p><b>Storage</b>                  Store IMPLANON™ (etonogestrel implant) at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light. Avoid storing IMPLANON™ in direct sunlight or at temperatures above 30°C (86°F).</p>
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**Reviewer Evaluation:** The description of the applicator is incorrect. Change from (b) (4) to " (b) (4)

(b) (4) "

**B. Environmental Assessment or Claim of Categorical Exclusion**

No EA or EA waiver request was provided in the supplement. In the original NDA, the Applicant asked for categorical exclusion, and subsequently provided an EIC value of (b) (4) ppb. Since the barium sulfate-containing formulation is intended to replace the currently approved formulation (despite the intent to co-market them during a transitional period), and considering the low EIC value, no EA would be required. This supplemental application may be categorically excluded from the requirement for an EA.

APPEARS THIS WAY ON  
ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	SUPPL-7	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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

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/s/

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JOEL S HATHAWAY  
04/21/2010

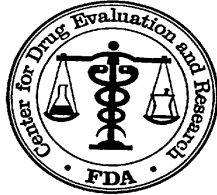
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021529Orig1s007**

**PHARMACOLOGY REVIEW(S)**



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

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-529
SERIAL NUMBER:	S007
DATE RECEIVED BY CENTER:	7/29/09
PRODUCT:	Implanon (etonogestrel implants), formulation: radio -opaque rods
INTENDED CLINICAL POPULATION:	Pregnancy prevention
SPONSOR:	Organon, Inc
DOCUMENTS REVIEWED:	New sNDA- Electronic submission
REVIEW DIVISION:	Division of Reproductive & Urologic Products (HFD-580)
PHARM/TOX REVIEWER:	Krishan L. Raheja, D.V.M., Ph.D.
PHARM/TOX SUPERVISOR:	Alex Jordan, Ph.D.
DIVISION DIRECTOR:	Scott Monroe, M.D.
PROJECT MANAGER:	Charlene Williamson

Date of review submission to Division File System (DFS): 12-14-09

## ***EXECUTIVE SUMMARY***

### **I. Recommendations**

- A. Recommendation on approvability: Pharmacology/toxicology recommends approval of sNDA 21-259 for contraception.
- B. Recommendation for the nonclinical studies: All preclinical studies have been previously submitted under the original NDA submission dated 9-30-03 and reviewed on 4-28-04. No new toxicology information is required.
- C. Recommendations on labeling: As required the draft labeling is in accordance with PLR and provided in SPL format. The Carcinogenesis, Mutagenesis, Impairment of fertility section is adequately described.

### **II. Summary of nonclinical findings**

- A. Brief overview of nonclinical findings: Nonclinical findings were primarily related to progestational effects of etonogestrel.
- B. Pharmacologic activity: The pharmacological activity of etonogestrel is attributed to suppression of gonadotropins and inhibition of ovulation. Etonogestrel affects cervical mucus, which makes sperm penetration difficult, and also affects endometrial lining which prevents embryo implantation.
- C. Nonclinical safety issues relevant to clinical use: None

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 21-529 S-007

**Review number:** 1

**Sequence number/date/type of submission:** 000/7-29-09/New sNDA

**Information to sponsor:** Yes ( ) No ( \* )

**Sponsor and/or agent:** Organon, Inc.

**Manufacturer for drug substance:** NV Organon

**Reviewer name:** Krishan L. Raheja, D.V.M., Ph.D.

**Division name:** Division of Reproductive & Urologic Drugs

**HFD #:** 580

**Review completion date:** 11-30-09

**Drug:**

Trade name: (b) (4)

Generic name: (b) (4)

Code name: Org 32222

Chemical name: (17  $\alpha$ )-13-ethyl-17-hydroxy-11-methylene-18, 19-dinopregn-4-en-20-yn-3-one

CAS registry number: [54048-10-1]

Molecular formula/molecular weight: C<sub>22</sub>H<sub>28</sub>O<sub>2</sub>/324.46

Structure:

**Relevant INDs/NDAs/DMFs:** IND 38,795 for combined contraceptive ring (etonogestrel & ethinyl estradiol)

IND 32,483 for oral contraception (desogestrel & ethinyl estradiol)

NDA 20-071 for Desogen tablets (desogestrel & ethinyl estradiol)

NDA 21-187 for NuvaRing (etonogestrel and ethinyl estradiol vaginal ring)

DMF 12293 for etonogestrel drug substance

**Drug class:** Progestin

**Intended clinical population:** Contraception

**Clinical formulation:** Implanon consists of a non-biodegradable single-rod implant, pre-filled in the stainless steel needle of a ready-for use disposable applicator. The implant has a length of 4 cm and a diameter of 2 mm and contains a synthetic progestogen, etonogestrel (3-ketodesogestrel, org 3236). After subdermal insertion of the implant in

the upper-arm, a continuous slowly decreasing release of etonogestrel occurs, providing contraceptive protection for three years.

Comparison of the current and new product is shown in table below:

	<b>Current product</b>	<b>New product</b>
Implant	Non X-ray visible (current implant)	X-ray visible by addition of (b) (4) 01% of barium sulfate to the implant core (new implant)
Applicator	Pre-filled in ABS applicator (current applicator)	Pre-filled in new next generation implanon applicator (NGLA) (new applicator)
Blister pack materials	(b) (4) blister and (b) (4) paper lidding material (current blister pack)	(b) (4) blister and (b) (4) lidding film (new blister pack)

Complete composition of the new implant and the current implant is given in table below:

Core of the implant				
Component	Reference to quality standard	Function(s)	Quantity per implant	
			New	current
Etonogestrel (org 3236)	In-house standard	Drug substance	68 mg	68 mg
Barium sulfate	Ph Eur/USP	Radio opacifier	15 mg	-
Ethylene vinylacetate copolymer (28% vinyl acetate)	In-house standard	Co-polymer	(b) (4)	(b) (4)
Core implant weight			(b) (4)	(b) (4)
Skin of the implant				
Ethylene vinylacetate copolymer (14% vinylacetate)	In-house standard	Skin polymer	(b) (4)	(b) (4)
Purified water	Ph. Eur./USP	Processing agent	-	-
Total implant weight			141 mg	129 mg

Comparison of old and new acceptance criteria for degradation products is given in table below:

	Old acceptance criteria		New acceptance criteria	
	Shelf-life and release		Shelf-life	Release
Degradation products:				
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total degradation products				

**Route of administration:** Subdermally implanted in woman's arm.

**Disclaimer:** Tabular and graphical information are constructed by the reviewer unless cited otherwise.

[For (b)(2) applications:

**Data reliance :** Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-529 are owned by Organon Inc. or are data for which Organon Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-529 that Organon Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Organon Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-529.

**Studies reviewed within this submission:** None. All P/T referred to original NDA 21-529 for Implanon approved for contraception on July 17,2006.

The only change made in the presently approved non-opaque Implanon is that the proposed contraceptive Radiopaque Etonogestrel implant has been made x-ray visible by incorporating 15 mg barium sulfate (b)(4)% v/v) per implant. Sponsor has evaluated the safety implications of this modification. Sponsor has provided the following facts and arguments for risk assessment of possible local and systemic toxicity due to release of barium ions and barium articles:

- Barium sulfate has very low solubility in water
- X-ray visible products containing barium sulfate such as stents and IUDs have been approved and are in widespread use without barium sulfate-related safety concerns
- Large oral doses (grams) of barium sulfate are used on a routine basis for the purpose of radiologic diagnosis of GI tract disease without causing significant health problems
- The daily release from the implant of barium ions is extremely low : (b)(4)
- Barium ions are natural constituents of the human body. Daily dietary and inhalatory exposure of the general population is > 1 mg. Normal body content is about 22 mg. A normal blood value is 1.2 ug/L
- The worst case estimation of total release of barium sulfate particles from the open ends of the implant is (b)(4). These minute amounts will be phagocytosed at the application site by macrophages.

Based on the above information, the proposed use of barium sulfate in Radiopaque Etonogestrel Implant is acceptable.

The extensive clinical experience with barium sulfate, the very low release of barium ions from barium sulfate containing rods, the pre-clinical studies with barium sulfate containing radiopaque IUD, as well as 6 month of safety data from clinical trial 34528 (including local tolerance), are sufficient to demonstrate the safety of barium sulfate.

#### **2.6.7 TOXICOLOGY TABULATED SUMMARY**

None providedd

#### **OVERALL CONCLUSIONS AND RECOMMENDATIONS**

Conclusions: The data provided supports the approval of (b) (4) for contraception.

Unresolved toxicology issues (if any): None

Recommendations: Pharmacology/toxicology recommends approval of NDA 21-529.

Suggested labeling: Draft labeling is accordance with PLR and presented in SPL format. The Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy sections are adequately described.

**APPENDIX/ATTACHMENTS: NONE**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	SUPPL-7	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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/s/

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KRISHAN L RAHEJA  
12/14/2009

ALEXANDER W JORDAN  
12/14/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021529Orig1s007**

**STATISTICAL REVIEW(S)**

## Memorandum of Statistical Review

**NDA Number:** 21-529 / Supplement 007 / Supporting Documents 190, 256, 257, 265  
**Drug Name:** (b) (4) (68 mg etonogestrel subdermal implant)  
**Indication(s):** Prevention of pregnancy  
**Applicant:** Organon USA Inc.  
**Date(s):** Letter Date: July 29, 2009 PDUFA Date: May 30, 2010  
**Review Priority:** 1 Standard  
**Biometrics Division:** Division of Biometrics 3  
**Biometrics Reviewer:** Sonia Castillo, Ph.D.  
**Biometrics Team Leader:** Mahboob Sobhan, Ph.D.  
**Medical Division:** Division of Reproductive and Urologic Drug Products  
**Clinical Team:** Theresa van der Vlugt, M.D., Medical Reviewer  
 Scott Monroe, M.D., Team Leader (Acting)  
**Project Manager:** Charlene Williamson  
**Key Words:** Clinical studies, NDA review

This submission contains information from a bioequivalence study and an applicator user study for a new radiopaque version of the already approved IMPLANON contraceptive implant to prevent pregnancy in healthy women (b) (4) of childbearing potential over three years of use. Although these studies were not specifically designed to evaluate efficacy, the Division requested that contraceptive efficacy be evaluated, which is the focus of this review. The radiopaque version of IMPLANON will be referred to as (b) (4) for the remainder of this review. Table 1 presents a brief summary of the two studies.

**Table 1**  
**Brief Summary of Clinical Study for (b) (4)**

Study Number (Study Type) (No. of Sites / Country) Dates of Study Conduct	Subject Population	Treatment	Number Randomized (ITT <sup>1</sup> )	Design <sup>2</sup>
34528 (Bioequivalence) (4 / Switzerland, 4 / France, 1 / The Netherlands) May 2005 to Feb. 2009	Healthy female subjects of childbearing potential, aged 18 to 40 years	(b) (4) IMPLANON	52	DB, R, PG, MC, 3 year
		<b>Total</b>	<b>108</b>	
34530 (Applicator User) (3 / Australia, 4 / Germany, 4 / France, 4 / Great Britain, 4 / Norway, 4 / Sweden) April 2007 to <i>ongoing</i>		(b) (4) <b>Total</b>	301 <b>301</b>	OL, MC, 3 year (ongoing)

Source: Statistical Reviewer's listing.

<sup>1</sup> ITT = Intent to Treat

<sup>2</sup> DB = Double-blind, OL = Open-label, R = Randomized, PC = Placebo Control, PG = Parallel Group, MC = Multicenter

### **Study 34528 Description, Subject Statistics, and Pearl Index Results**

Study 34528 is a multicenter, randomized, double-blind, parallel group Phase 3 trial designed to demonstrate the bioequivalence of (b) (4) to IMPLANON and to assess the X-ray visibility of (b) (4). A total of 90 healthy women of childbearing potential, aged 18 to 40 years, were treated at nine centers in three countries. Eligible subjects were equally randomized to either IMPLANON or (b) (4) which was inserted into the upper arm with the currently approved applicator. Although this study was designed as a bioequivalence study, the Division requested that contraceptive efficacy be evaluated for those pregnancies that occurred 1) while the implant was in place and 2) while the implant was in place and within 14 days after removal.

The annual and cumulative Pearl Indices were calculated for the on-treatment pregnancies together with 95% confidence intervals based on the Poisson distribution using the ITT population of women aged 18 to 35 years. The Pearl Index was defined as the number of pregnancies per 100 woman years of exposure. The total exposure was calculated in both woman-years (one woman-year = 365.25 days exposure) and total number of 28-day cycles. For

subjects who were lost to follow up, the date of the last assessment was used. Since this was designed as a bioequivalence study, the sample size of 45 subjects per group (90 total) was based on  $C_{max}$ .

A total of 108 subjects were randomized, 52 subjects received (b) (4) and 56 received IMPLANON. Discontinuation rates were similar in both groups (38.5% for (b) (4) and 42.9% for IMPLANON). The primary reasons for study discontinuation were bleeding irregularities (19.2% for (b) (4) and 14.3% for IMPLANON), other adverse events (9.6% for (b) (4) and 16.1% for IMPLANON), and lost to follow-up (7.7% for (b) (4) and 10.7% for IMPLANON).

Both groups were similar in baseline and demographic characteristics; the majority of subjects were Caucasian (>94%) and had a mean age of 27 years (range of 18 to 43 years) and mean BMI of 22.4 kg/m<sup>2</sup>. None of the women were breastfeeding at the time of randomization. Of the 108 subjects, 93 were less than 36 years of age and were used for the Pearl Index (PI) calculation. All referenced Pearl Index tables are listed in the Appendix and this Reviewer concurs with the Applicant's results.

Table A.1 presents yearly and 3-year cumulative Pearl Indices for subjects 18-35 years of age when no pregnancies occur before implant removal and when 1 pregnancy occurs in the (b) (4) group before and within 14 days after implant removal. When no pregnancies occur before implant removal, the cumulative 3-year PI for (b) (4) is 0 (95% C.I. from 0 to 3.74) and for IMPLANON is 0 (95% C.I. from 0 to 3.40). When one pregnancy occurs before and within 14 days after implant removal, the cumulative 3-year PI for (b) (4) is 1.01 (95% C.I. from 0.026 to 5.65).

Table A.2 presents yearly and 3-year cumulative Pearl Indices for subjects over 35 years of age. No pregnancies occurred in this group. When no pregnancies occur before and within 14 days after implant removal, the cumulative 3-year PI for (b) (4) is 0 (95% C.I. from 0 to 40.22) and for IMPLANON is 0 (95% C.I. from 0 to 14.78). These large PIs are the result of the small number of exposure cycles. Because no pregnancies occurred in subjects over 35 years of age, the Pearl Indices for pregnancies occurring before implant removal are the same.

Table A.3 presents yearly and 3-year cumulative Pearl Indices for all subjects when no pregnancies occur before implant removal and when 1 pregnancy occurs in the (b) (4) group before and within 14 days of implant removal. When no pregnancies occur before implant removal, the cumulative 3-year PI for (b) (4) is 0 (95% C.I. from 0 to 3.74) and for IMPLANON is 0 (95% C.I. from 0 to 3.40). When one pregnancy occurs before and within 14 days of implant removal, the cumulative 3-year PI for (b) (4) is 1.01 (95% C.I. from 0.026 to 5.56).

#### ***Study 34530 Description and Year 1 Pearl Index Results***

Study 34530 is an open-label, non-controlled multicenter, 3-year trial designed to evaluate the use characteristics of a new applicator and its instructions for proper insertion of (b) (4). A total of 300 healthy female subjects of childbearing potential, aged 18 to 40 years, were treated at 24 centers in 6 countries. (b) (4) was inserted into the upper arm with the new applicator. In each country two "experienced" (more than 10 IMPLANON insertions within the past year) and two "non-experienced" (10 or less IMPLANON insertions within the past year) investigators participated. The first subject entered the trial in April, 2007 and the last the last subject's insertion was performed in July of 2007. Completion of the last subject is expected in October of 2010.

The Division requested that the Year 1, Year 2, and cumulative 2-Year Pearl Indices be reported but they have not been verified by this Statistical Reviewer because no datasets have been submitted for this ongoing study. As presented in Table A.4, since there were no pregnancies during the first two years, the Applicant reports that the cumulative 2-Year PI for (b) (4) is 0 (95% C.I. from 0 to 0.96) for subjects aged 18 to 35 years and is 0 (95% C.I. from 0 to 3.48) for subjects aged over 35 years.

#### ***Conclusions***

From a statistical perspective, both studies were not designed to demonstrate contraceptive efficacy. The Pearl Index is calculated to check that there are no excess pregnancies for radiopaque IMPLANON compared to the non-radiopaque version. Both studies did not report any pregnancies while any version of IMPLANON was in place and one pregnancy was reported after its removal in the radiopaque group. The upper bound of the 95% confidence interval for all Pearl Indices is larger than what is acceptable, but the number of pregnancies and the PIs are useful descriptive measures. Except for the one pregnancy that occurred after implant removal in the radiopaque IMPLANON group, no pregnancies occurred while either version of the IMPLANON implant was in place.

APPENDIX

**Table A.1**  
**Study 34528: Pearl Index Calculation of Treatment Failure Rates for On-Treatment Pregnancies Occurring Before Implant Removal AND Occurring Before and Within 14 Days After Implant Removal:**  
**All Cycles for ITT Population – Subjects 18-35 Years of Age**

Treatment Period	N	Number of Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval*
<b><i>Year 1 to Year 3 and Cumulative 3-Year Results <u>not</u> including pregnancy that occurred within 14 days after implant removal</i></b>					
<b>Year 1 (Day 1 – 365)</b>					
IMPLANON	51	0	593.8	0	(0, 8.10)
(b) (4)	42	0	497.8	0	(0, 9.67)
<b>Year 2 (Day 366 – 730)</b>					
IMPLANON	39	0	442.0	0	(0,10.89)
(b) (4)	36	0	433.5	0	(0, 11.10)
<b>Year 3 (Day 731 – 1095)</b>					
IMPLANON	30	0	379.7	0	(0, 12.67)
(b) (4)	31	0	355.0	0	(0, 13.55)
<b><i>Cumulative 3-Year (Day 1 – 1095)</i></b>					
IMPLANON	51	0	1415.5	0	(0, 3.40)
(b) (4)	42	0	1286.4	0	(0, 3.74)
<b><i>Year 3 and Cumulative 3-Year Results including pregnancy that occurred within 14 days after implant removal</i></b>					
<b>Year 3 (Day 731 – 1095)</b>					
IMPLANON	30	0	379.7	0	(0, 12.67)
(b) (4)	31	1	355.0	3.67	(0.093, 20.47)
<b><i>Cumulative 3-Year (Day 1 – 1095)</i></b>					
IMPLANON	51	0	1415.5	0	(0, 3.40)
(b) (4)	42	1	1286.4	1.01	(0.026, 5.65)

Source: 1) Portion of table not including the one pregnancy within 14 days after removal: Tables 14.2.1-1.2.C and 14.2.1-1.4.C on pages 11 and 19 of Attachment A of January 13, 2010 submission. 2) Portion of table including the one pregnancy within 14 days after removal: Tables 14.2.1-1.2.D and 14.2.1-1.4.D on pages 12 and 20 of Attachment A of January 13, 2010 submission.

**Table A.2**  
**Study 34528: Pearl Index Calculation of Treatment Failure Rates for On-Treatment Pregnancies Occurring Before and Within 14 Days After Implant Removal: All Cycles for ITT Population – Subjects Over 35 Years of Age**

Treatment Period	N	Number of Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval*
<b>Year 1 (Day 1 – 365)</b>					
IMPLANON	5	0	41.5	0	(0, 116.05)
(b) (4)	10	0	126.0	0	(0, 38.18)
<b>Year 2 (Day 366 – 730)</b>					
IMPLANON	3	0	39.1	0	(0, 123.05)
(b) (4)	9	0	108.5	0	(0, 44.34)
<b>Year 3 (Day 731 – 1095)</b>					
IMPLANON	3	0	39.1	0	(0, 123.16)
(b) (4)	7	0	91.0	0	(0, 52.86)
<b><i>Cumulative 3 Year (Day 1 – 1095)</i></b>					
IMPLANON	5	0	119.6	0	(0, 40.22)
(b) (4)	10	0	325.6	0	(0, 14.78)

Source: Tables 14.2.1-1.2.E, 14.2.1-1.4.E, 14.2.1-1.2.F, and 14.2.1-1.4.F on pages 13, 14, 20, and 21 of Attachment A of January 13, 2010 submission.

**Table A.3**  
**Study 34528: Pearl Index Calculation of Treatment Failure Rates for On-Treatment Pregnancies Occurring Before**  
**Implant Removal AND Occurring Before and Within 14 Days After Implant Removal:**  
**All Cycles for ITT Population – All Subjects**

Treatment Period	N	Number of Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval*
<i>Year 1 to Year 3 and Cumulative 3-Year Results <u>not</u> including pregnancy that occurred within 14 days after implant removal</i>					
Year 1 (Day 1 – 365)					
IMPLANON	56	0	635.2	0	(0, 7.58)
(b) (4)	52	0	623.9	0	(0, 7.71)
Year 2 (Day 366 – 730)					
IMPLANON	42	0	481.1	0	(0,10.00)
(b) (4)	45	0	542.1	0	(0, 8.88)
Year 3 (Day 731 – 1095)					
IMPLANON	33	0	418.8	0	(0, 11.49)
(b) (4)	38	0	446.1	0	(0, 10.79)
<i>Cumulative 3-Year (Day 1 – 1095)</i>					
IMPLANON	56	0	1535.1	0	(0, 3.14)
(b) (4)	52	0	1612.0	0	(0, 2.98)
<i>Year 3 and Cumulative 3-Year Results including pregnancy that occurred within 14 days after implant removal</i>					
Year 3 (Day 731 – 1095)					
IMPLANON	33	0	418.8	0	(0, 11.49)
(b) (4)	38	1	446.1	2.92	(0.074, 16.29)
<i>Cumulative 3-Year (Day 1 – 1095)</i>					
IMPLANON	56	0	1535.1	0	(0, 3.14)
(b) (4)	52	1	1612.0	0.81	(0.020, 4.51)

Source:

- Portion of table not including the one pregnancy within 14 days after removal: Table 14.2.1-1.2.A on page 9 of Attachment A of January 13, 2010 submission and Table 14.2.1-1.4.A on page 190 of Study 34528 Report.
- Portion of table including the one pregnancy within 14 days after removal: Table 14.2.1-1.2.B on page 10 of Attachment A of January 13, 2010 submission and Table 14.2.1-1.4.B on page 191 of Study 34528 Report.

**Table A.4**  
**Study 34530: Pearl Index Calculation of Treatment Failure Rates for On-Treatment Pregnancies Occurring During**  
**The First Two Years of a Three-Year Study:**  
**All Cycles for ITT Population – Subjects 18-35 Years of Age AND Subjects Over 35 Years of Age**

Treatment Period	N	Number of Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval*
<i>Subjects 18-35 Years of Age</i>					
(b) (4)					
Year 1 (Day 1 – 365)	240	0	2856.57	0	(0, 1.68)
Year 2 (Day 366 – 730)	190	0	2129.04	0	(0, 2.26)
<i>Cumulative 2-Year (Day 1 – 730)</i>	240	0	4985.61	0	(0, 0.96)
<i>Subjects Over 35 Years of Age</i>					
(b) (4)					
Year 1 (Day 1 – 365)	61	0	753.57	0	(0, 6.39)
Year 2 (Day 366 – 730)	53	0	629	0	(0, 7.65)
<i>Cumulative 2-Year (Day 1 – 730)</i>	61	0	1382.57	0	(0, 3.48)

Source: Tables 2[a] and 2[b] on pages 2 and 3 of Response to FDA Information Request of March 26, 2010 from the April 8, 2010 submission.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	SUPPL-7	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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/s/

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SONIA CASTILLO  
04/09/2010

MAHBOOB SOBHAN  
04/09/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021529Orig1s007**

**MICROBIOLOGY/VIROLOGY REVIEW(S)**

# Product Quality Microbiology Review

09-OCT-2009

**NDA 21-529/SES-007**

**Drug Product Name**

**Proprietary:** Implanon™

**Non-proprietary:** Etonogestrel implant (product number Org 3236)

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

Letter	Stamp	Review Request	Assigned to Reviewer
29-JUL-2009	30-JUL-2009	N/A	20-AUG-2009

**Applicant/Sponsor**

**Name:** Organon USA, Inc.  
(A Schering-Plough Subsidiary)  
**Address:** 56 Livingston Avenue  
Roseland, New Jersey 07068  
**Representative:** Ed Nellis  
Senior Manager, Global Regulatory Affairs  
**Telephone:** (b) (6)

**Name of Reviewer:** Steven Fong, Ph.D.

**Conclusion:** Recommended for approval from a microbiology quality standpoint.

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## Product Quality Microbiology Data Sheet

- A.
- 1. TYPE OF SUBMISSION:** Prior approval chemistry and manufacturing controls supplement.
  - 2. SUBMISSION PROVIDES FOR:** A new radiopaque version of the Implanon contraceptive implantation device, and a novel product delivery device, the Next Generation Implanon Applicator (NGIA).
  - 3. MANUFACTURING SITE:** The product is manufactured by NV Organon facilities based in the Netherlands, Germany, New Jersey, and Pennsylvania. (b) (4)  
(b) (4)  
Detailed addresses for these operations are provided in section P.3.1, Table 2 of this review.
  - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** The proposed product will be provided as a 40 X 2 mm coaxial rod consisting of a core composed of a composite of the drug substance (68 mg etonogestrel), barium sulfate, and ethylene vinylacetate copolymer, and a vinylacetate skin. The implant is placed within the stainless steel needle of a disposable applicator and packaged in a blister pack. The rod is administered subdermally with the aid of the NGIA.
  - 5. METHOD(S) OF STERILIZATION:** (b) (4).
  - 6. PHARMACOLOGICAL CATEGORY:** Progestin hormone contraceptive.
- B. **SUPPORTING/RELATED DOCUMENTS:**
- C. **REMARKS:**
- The supplement was provided electronically in CTD format.
  - (b) (4) of the current Implanon contraceptive device was assessed in 04-DEC-2008 and 11-FEB-2004 quality microbiology reviews.
  - On 05-OCT-2009 an information request was forwarded to the sponsor through the project manager regarding the (b) (4). As of 09-OCT-2009 a response was not received. The reviewer has since noted that sufficient information regarding the test was provided in the stability data and that a sponsor response is no longer necessary.

filename: N021529s007r1.doc

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## **Executive Summary**

### **I. Recommendations**

- A. Recommendation on Approvability** - Recommended for approval from a microbiology quality standpoint.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

### **II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The core of the proposed applicator rod differs from the approved rod in containing barium sulfate (15 mg/implant) in addition to etonogestrel drug substance (68 mg/implant) and ethylene vinylacetate copolymer (b) (4) (b) (4). The lidding material for container closure blister has been changed to (b) (4) (b) (4). A novel product administration device for subdermal insertion of the rod, the NGIA, is also proposed.
- B. Brief Description of Microbiology Deficiencies** – None.
- C. Assessment of Risk Due to Microbiology Deficiencies** – Acceptable risk.

### **III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
Steven Fong, M.S., Ph.D.
- B. Endorsement Block** \_\_\_\_\_  
Stephen Langille, Ph.D.  
Senior Microbiology Reviewer
- C. CC Block**  
N/A

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	SUPPL-7	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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/s/

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STEVEN E FONG

10/09/2009

Recommended for approval from a microbiology quality standpoint

STEPHEN E LANGILLE

10/09/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021529Orig1s007**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM**

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NDA: 021529	Submission Dates: 07/30/2009, 01/29/2010, 02/03/2010, 05/07/2010, and 05/09/2011
Brand Name	Nexplanon
Generic Name	Etonogestrel
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Schering-Plough
Relevant IND	42,877
Submission Type	Efficacy Supplemental NDA
Formulation; Strength	Subdermal Implant; etonogestrel 68 mg
Indication	Prevention of pregnancy

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**Table of Contents**

1	Executive Summary .....	2
1.1	Recommendation .....	2
2	Final Agreed Upon Labeling.....	3

## 1 Executive Summary

The Clinical Pharmacology review of efficacy supplemental NDA 021529 (DARRTS, 07/23/2010) stated that the NDA 021529 was acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert labeling. The agreement on the language in the package insert labeling between the sponsor and the Division was reached on 05/09/2011. The highlights of the prescribing information and Clinical Pharmacology relevant sections of the final agreed upon package insert labeling are included in Section 2 of this addendum.

In addition, this addendum is to correct the errors in the Clinical Pharmacology review of efficacy supplemental NDA 021529 (DARRTS, 07/23/2010). In this review, bioequivalence (BE) reanalysis with 95 subjects showed that 90% confidence interval (CI) for  $C_{max}$  was between 0.918 and 1.264 which was above the upper limit of 1.25 by 0.014. Therefore, the sentences in sections 2.2 (page 8) and 2.6 (page 18) of the Clinical Pharmacology review dated 07/23/2010 should be corrected as following: Strike is used for deletion and double underline is used for addition.

*Implanon is for single insertion over 3 years. Since there would be one time period during which  $C_{max}$  occurs over 3 years, there is less concern for 90% CI of  $C_{max}$  being over 1.25 by ~~0.14~~0.014.*

### 1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the NDA 021529 acceptable and there are no pending issues.

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/s/  
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HYUNJIN KIM  
05/12/2011

MYONG JIN KIM  
05/12/2011

EDWARD D BASHAW  
05/12/2011

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

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NDA: 021529	Submission Dates: 07/30/2009, 01/29/2010, 02/03/2010, and 05/07/2010
Brand Name	(b) (4) (pending)
Generic Name	Etonogestrel
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Schering-Plough
Relevant IND	42,877
Submission Type	Efficacy Supplemental NDA
Formulation; Strength	Subdermal Implant; etonogestrel 68 mg
Indication	Prevention of pregnancy

An Optional Inter-Division Level Clinical Pharmacology Briefing was held on March 23, 2010 in conference room 3200 of White Oak Bldg 51. Attendees included Drs' Darrell Abernethy, Scott Monroe, Daniel Davis, Hae Young Ahn, Chinmay Schukla, Immo Zdrojewski, Christian Grimstein, E. Dennis Bashaw, Chongwoo Yu, Lin Zhou, Arun Agarwal, LaiMing Lee, Doanh Tran, Jeannie Fourie, and Hyunjin Kim

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**Table of Contents**

1	Executive Summary .....	2
1.1	Recommendation .....	2
1.2	Phase IV Commitments .....	2
1.3	Summary of Important Clinical Pharmacology and Biopharmaceutics Findings ..	2
2	Question Based Review .....	4
2.1	General Attributes.....	4
2.2	General Clinical Pharmacology.....	5
2.3	Intrinsic Factors .....	10
2.4	Extrinsic Factors .....	13
2.5	General Biopharmaceutics.....	13
2.6	Analytical Section.....	14
3	Detailed Labeling Recommendation .....	19
4	Appendix .....	23
4.1	Individual Clinical Study Review .....	23

## 1 Executive Summary

The sponsor submitted an efficacy supplemental NDA (sNDA) under 505(b)(1) for (b) (4) (68 mg etonogestrel implant). (b) (4) is a long-acting (up to 3 years), reversible, hormonal contraceptive method. It should be inserted subdermally in the upper arm. It is a radiopaque version of currently approved etonogestrel implant, Implanon (approval, July 17, 2006, NDA 021529).

To facilitate correct implantation and to provide an additional method of localization by X-ray, the sponsor developed a radiopaque version of Implanon. (b) (4) is identical to Implanon except that it contains additional 15 mg barium sulfate (b) (4). The sponsor also developed a modified applicator to facilitate correct implantation of (b) (4) and to add a safety feature which locks the needle inside the body of the applicator, once the (b) (4) is implanted under the skin.

In support of this sNDA, the sponsor submitted two studies to support the approval of (b) (4). A pivotal bioequivalence (BE) study 34528 employed (b) (4) and currently approved, commercially available Implanon conducted over 36 months. In addition, the sponsor submitted a study 34530 to evaluate X-ray visibility of the (b) (4) and assess subjects' satisfaction (PSQ-18 questionnaire) conducted over 36 months. *Study 34530 was reviewed by Dr. Theresa Van Der Vlugt (Medical Officer, DRUP).*

A request for inspection of the clinical and analytical sites of the pivotal BE study was made to the Division of Scientific Investigation (DSI, DARRTS, September 23, 2009). The form 483s were issued for both clinical and analytical sites. However, the sponsor properly addressed all the findings listed in the form 483s.

### 1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in sNDA 021529 acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert.

### 1.2 Phase IV Commitments

None.

### 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

BE analysis between Implanon and (b) (4)

<BE analysis conducted before the DSI inspection findings were available>

The BE between those two products was demonstrated in study 34528. Etonogestrel pharmacokinetic (PK) parameter values and statistical evaluation of 103 out of 108 healthy subjects are provided in Table 1. Five subjects (subjects (b) (6), (b) (6), (b) (6), (b) (6), and (b) (6)) were excluded from the PK analysis because they took prohibited contraceptive medications during the study period or the day before the implant insertion. The 90% Confidence Intervals (CIs) for the difference between the Test and Reference Least Square Means (LSMs) for the PK parameters,  $C_{max}$ ,  $AUC_{0-6months}$ ,  $AUC_{0-12months}$ ,  $AUC_{0-24months}$ ,  $AUC_{12-24months}$ ,  $AUC_{0-36months}$ , and  $AUC_{24-36months}$  were within 80 to 125% bioequivalence limits for etonogestrel, hence showed the bioequivalence between Implanon and (b) (4).

**Table 1. Bioequivalence between Implanon and (b) (4) study 34528 (n=103)**

Parameters	Geometric mean [CV]		Ratio (test/reference)	90% Confidence interval
	Implanon (reference)	(b) (4) (test)		
$C_{max}^a$ (pg/mL)	1,021.2 [50.4 %]	1,083.3 [50.4 %]	1.06	0.91-1.23
$AUC_{0-6months}^b$ (pg·month/mL)	2,210.4 [27.2 %]	2,212.1 [28.4 %]	1.00	0.91-1.10
$AUC_{0-12months}^c$ (pg·month/mL)	3,594.0 [28.2 %]	3,495.4 [26.5 %]	0.97	0.88-1.07
$AUC_{0-24months}^d$ (pg·month/mL)	5,873.9 [31.1 %]	5,783.1 [25.1 %]	0.98	0.88-1.10
$AUC_{12-24months}^d$ (pg·month/mL)	2,355.5 [34.0 %]	2,207.3 [25.3 %]	0.94	0.84-1.05
$AUC_{0-36months}^e$ (pg·month/mL)	7,487.0 [31.9 %]	7,453.2 [24.9 %]	1.00	0.89-1.11
$AUC_{24-36months}^e$ (pg·month/mL)	1,652.5 [33.7 %]	1,613.0 [26.9 %]	0.98	0.87-1.10
$t_{max}$ (h) <sup>a*</sup>	120.2 [29.1–232.8]	141.2 [47.4–334.5]		

n1: number of subjects implanted with Implanon, n2: number of subjects implanted with (b) (4) <sup>a</sup> n1=53, n2=50; <sup>b</sup> n1=46, n2=46; <sup>c</sup> n1=41, n2=42; <sup>d</sup> n1=32, n2=37; <sup>e</sup> n1=30, n2=32; \* Data presented as median [range]

<BE reanalysis conducted after the DSI inspection findings were available>

Based on the findings of DSI inspection, 13 subjects (5 subjects in the original analysis + 8 additional subject due to the DSI findings) were excluded from the final dataset and BE reanalysis was conducted on 95 subjects. The reanalysis showed that all the PK parameters ( $AUC_{0-6months}$ ,  $AUC_{0-12months}$ ,  $AUC_{0-24months}$ ,  $AUC_{12-24months}$ ,  $AUC_{0-36months}$ , and  $AUC_{24-36months}$ ) met the BE criteria except for the  $C_{max}$ . The 90% CI for  $C_{max}$  was between

0.918 and 1.264. Although the upper bound of 90% CI for  $C_{max}$  was higher than 1.25 to meet the BE criteria, this reviewer believes that this finding is not clinically meaningful and that the efficacy and safety of (b) (4) can be relied upon the efficacy and safety of Implanon. See section 2.6 for details.

<Effect of Body Mass Index (BMI)>

Potential effect of BMI (18-29 kg/m<sup>2</sup>) on etonogestrel serum concentration following the Implanon or (b) (4) insertion was performed. There were no clear trends observed between the BMI and etonogestrel exposure. In addition, there were no statistical significances observed between the BMI and etonogestrel exposure in both groups. Therefore, there was no clear effect of BMI (18-29 kg/m<sup>2</sup>) on the concentration of etonogestrel following implantation of Implanon or (b) (4) in study 34528. (see Figure 4 under section 2.3.3).

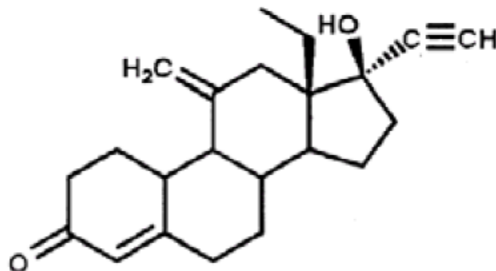
## 2 Question Based Review

### 2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

<Physico-chemical properties>

- Structural formula:



- IUPAC Name: 17a-ethyl-17-hydroxy-18-methyl-11-methylene-4-estren-3-one
- Molecular Weight: 324.46
- Molecular Formula: C<sub>22</sub>H<sub>28</sub>O<sub>2</sub>
- Chemical Name: (17a)13-ethyl-17-hydroxy-11-methylene-18,19-dinorpregn-4-en-20-yn- 3-one

<Drug Formulation>

The drug formulation of (b) (4) differs from Implanon in the composition, i.e., the addition of 15 mg barium sulfate (b) (4).

**Table 2. Composition Comparison of Implanon and (b) (4)**

Component	Function	Quantity per implant
-----------	----------	----------------------

		Implanon	(b) (4)
Etonogestrel (b) (4)	Drug substance	68 mg	68 mg
Barium sulfate	Radio opacifier	-	15 mg
Ethylene vinyl acetate copolymer (28 % vinyl acetate)	Core polymer	(b) (4)	(b) (4)
Ethylene vinyl acetate copolymer (14 % vinyl acetate)	Skin polymer	(b) (4)	(b) (4)
Total weight		129 mg	141 mg

### 2.1.2 What is the proposed mechanism of action?

The contraceptive effect of (b) (4) is achieved by several mechanisms that include suppression of ovulation, increased viscosity of the cervical mucus, and alterations in the endometrium.

### 2.1.3 What are the proposed indication, dosage and route of administration?

The proposed indication of (b) (4) is the prevention of pregnancy. There is only one strength of (b) (4) which contains 68 mg of etonogestrel. (b) (4) is a long acting (up to three years), reversible, contraceptive method. It should be inserted subdermally just under the inner skin of non-dominant arm to avoid the large blood vessels and nerves that lie deeper in the subcutaneous tissue in the sulcus between the triceps and biceps muscles. (b) (4) must be removed by the end of third year and may be replaced by a new (b) (4) at the time of removal, if continued contraceptive protection is desired.

### 2.1.4 What are the differences between (b) (4) and Implanon?

(b) (4) is a radiopaque version of Implanon with a modified applicator to provide an additional method of localization by X-ray and to facilitate correct implantation.

- (b) (4) is identical to Implanon except that the (b) (4) contains additional 15 mg barium sulfate (b) (4).
- The modified applicator is designed to facilitate implantation of (b) (4) just below the skin. In addition, the applicator has a safety feature which locks the needle inside the body of the applicator, once the (b) (4) is implanted under the skin.

## 2.2 General Clinical Pharmacology

There was no pregnancy occurred during the 3 years of Implanon use in four clinical trials (studies 069001, 34505, 34507, and 34507 CDN) submitted in the original NDA cycle. In these clinical trials, bleeding changes were the single most common reason for stopping treatment with Implanon (*Clinical Review of Implanon, NDA 21-529, by Dr. Barbara Wesley, DARRTS, October 28, 2004*).

The safety and efficacy of (b) (4) are based on the original NDA submission of Implanon, NDA 021529. Therefore, no efficacy and safety study was conducted with (b) (4). Instead, a pivotal BE study 34528 between two products (Implanon and (b) (4)) and a study to evaluate the X-ray visibility and to assess subjects' satisfaction (PSQ-18 questionnaire) following implantation of (b) (4) (study 34530) were conducted.

Refer to clinical review by Dr. Daniel Davis for details of study 34530.

Study 34528 was a randomized parallel group BE study. As both Implanon and (b) (4) are long-acting (up to 3 years) contraceptive implants, a cross-over design was not feasible. A total of 108 healthy females with age between 18 and 40 were randomized to Implanon or (b) (4). Blood samples were withdrawn at pre-dose, Days 3, 5, 7, 9, 11, 15, and 22, and Months 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 27, 30, 33, and 36. C<sub>max</sub> and multiple AUCs (AUC<sub>0-6months</sub>, AUC<sub>0-12months</sub>, AUC<sub>0-24months</sub>, AUC<sub>12-24months</sub>, AUC<sub>0-36months</sub>, and AUC<sub>24-36months</sub>) from different periods were calculated for the comparison of peak concentration and exposure of two products, since they are long-acting (up to 3 years) products.

### 2.2.1 Is (b) (4) bioequivalent to Implanon?

<BE analysis conducted before the DSI inspection findings were available>

Etonogestrel PK parameter values and statistical evaluation of 103 out of 108 subjects are provided in Table 3. Five subjects (subjects (b) (6), (b) (6), (b) (6), (b) (6), and (b) (6)) were excluded from the PK analysis because they took prohibited contraceptive medications during or the day before the implant. Arithmetic mean (± standard deviation (SD)) serum etonogestrel concentration – time profiles following implantation of either Implanon or (b) (4) are provided in Figure 1. Approximately 30% of etonogestrel was released within first 6 months from both Implanon and (b) (4). Mean concentration of etonogestrel after Month 6 was relatively stable compared to mean concentration of etonogestrel over first 6 months. It gradually decreased after Month 6 (approximately 270 and 150 pg/mL at Month 6 and 36, respectively). The 90% CIs for the difference between the Test and Reference LSMs for the parameters, C<sub>max</sub>, AUC<sub>0-6months</sub>, AUC<sub>0-12months</sub>, AUC<sub>0-24months</sub>, AUC<sub>12-24months</sub>, AUC<sub>0-36months</sub>, and AUC<sub>24-36months</sub> were within 80 to 125% bioequivalence limits for etonogestrel, hence show the bioequivalence between Implanon and (b) (4).

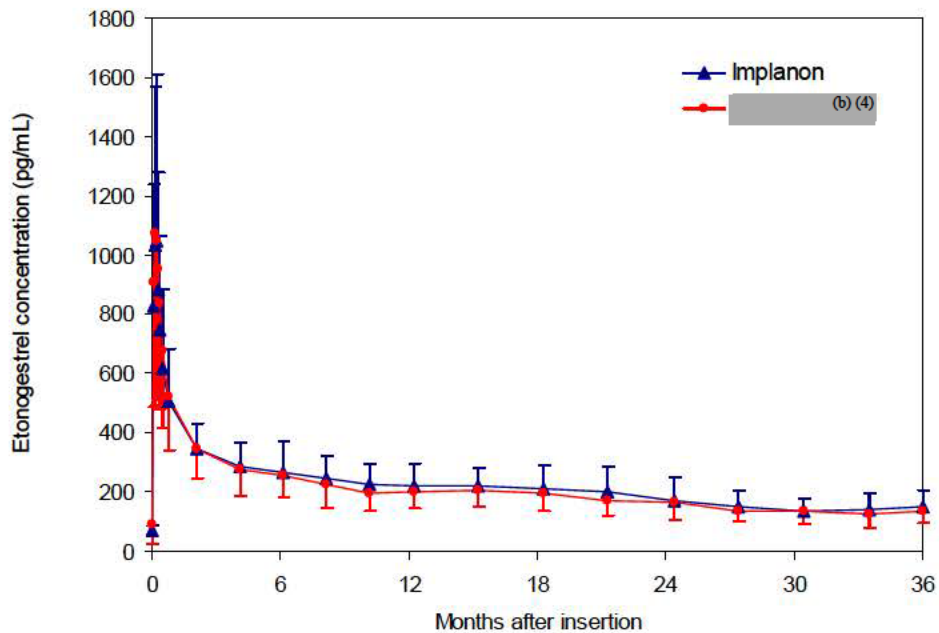
**Table 3. Bioequivalence between Implanon and (b) (4) study 34528**

Parameters	Geometric mean [CV]		Ratio (test/reference)	90% Confidence interval
	Implanon (reference)	(b) (4) (test)		
C <sub>max</sub> <sup>a</sup> (pg/mL)	1,021.2 [50.4 %]	1,083.3 [50.4 %]	1.06	0.91-1.23

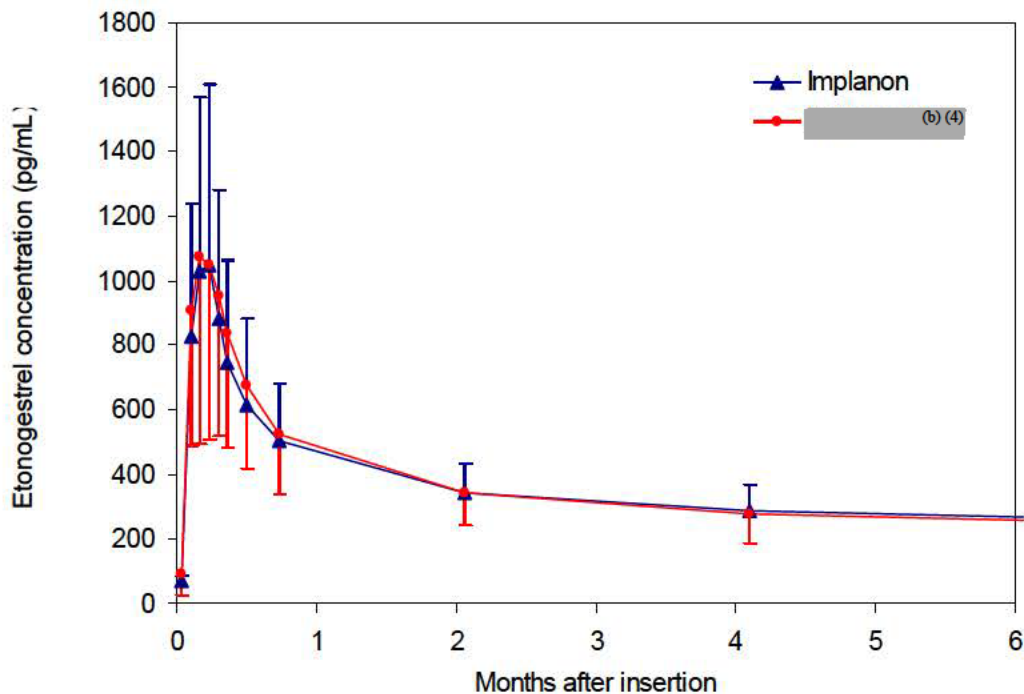
AUC <sub>0-6months</sub> <sup>b</sup> (pg·month/mL)	2,210.4 [27.2 %]	2,212.1 [28.4 %]	1.00	0.91-1.10
AUC <sub>0-12months</sub> <sup>c</sup> (pg·month/mL)	3,594.0 [28.2 %]	3,495.4 [26.5 %]	0.97	0.88-1.07
AUC <sub>0-24months</sub> <sup>d</sup> (pg·month/mL)	5,873.9 [31.1 %]	5,783.1 [25.1 %]	0.98	0.88-1.10
AUC <sub>12-24months</sub> <sup>d</sup> (pg·month/mL)	2,355.5 [34.0 %]	2,207.3 [25.3 %]	0.94	0.84-1.05
AUC <sub>0-36months</sub> <sup>e</sup> (pg·month/mL)	7,487.0 [31.9 %]	7,453.2 [24.9 %]	1.00	0.89-1.11
AUC <sub>24-36months</sub> <sup>e</sup> (pg·month/mL)	1,652.5 [33.7 %]	1,613.0 [26.9 %]	0.98	0.87-1.10
t <sub>max</sub> (h) <sup>a*</sup>	120.2 [29.1–232.8]	141.2 [47.4-334.5]		

n1: number of subjects implanted with Implanon, n2: number of subjects implanted with (b) (4); <sup>a</sup> n1=53, n2=50; <sup>b</sup> n1=46, n2=46; <sup>c</sup> n1=41, n2=42; <sup>d</sup> n1=32, n2=37; <sup>e</sup> n1=30, n2=32; \* Data presented as median [range]

The serum concentration of etonogestrel versus time curves during the 36 months and first 6 months are presented in Figures 1 and 2, respectively. They show that the two curves are similar during the entire period, including the first 6 months in which the etonogestrel release is highest. Figure 2 shows that after the implantation of Implanon and (b) (4) etonogestrel is rapidly released and maximum serum etonogestrel concentrations are reached within one month.



**Figure 1. Arithmetic mean ( $\pm$  SD) etonogestrel concentration-time profiles following implantation of Implanon and (b) (4) over 36 months; study 34528**



**Figure 2. Arithmetic mean (± SD) etonogestrel concentration-time profiles following implantation of Implanon and (b) (4) over first 6 months; study 34528**

<BE reanalysis conducted after the DSI inspection findings were available>

Based on the findings of DSI inspection, 13 subjects (5 subjects in the original analysis + 8 additional subject due to the DSI findings) were excluded from the final dataset and BE reanalysis was conducted on 95 subjects. The reanalysis showed that all the PK parameters ( $AUC_{0-6\text{months}}$ ,  $AUC_{0-12\text{months}}$ ,  $AUC_{0-24\text{months}}$ ,  $AUC_{12-24\text{months}}$ ,  $AUC_{0-36\text{months}}$ , and  $AUC_{24-36\text{months}}$ ) met the BE criteria except for the  $C_{\text{max}}$ . Although the upper bound of 90% CI for  $C_{\text{max}}$  was higher than 1.25, this reviewer believes that this finding is not clinically meaningful for the following reason.

1] (b) (4) is long term use contraceptive over 3 years. The 90% CI for not only AUC over 3 years, but also sectional AUCs ( $AUC_{0-6\text{months}}$ ,  $AUC_{0-12\text{months}}$ ,  $AUC_{0-24\text{months}}$ ,  $AUC_{12-24\text{months}}$ , and  $AUC_{24-36\text{months}}$ ) met the BE criteria.

2] Implanon is for single insertion over 3 years. Since there would be one time period during which  $C_{\text{max}}$  occurs over 3 years, there is less concern for 90% CI of  $C_{\text{max}}$  being over 1.25 by 0.14.

3] The review of the safety data in the application and of the requested safety data did not demonstrate safety concerns for the radiopaque etonogestrel implant related to the slightly higher upper limit of the 90% CI for  $C_{\text{max}}$  (Dr. Theresa Van Der Vlugt's medial review).

Overall, this reviewer believes that this finding is not clinically meaningful and that the efficacy and safety of (b) (4) can be relied upon the efficacy and safety of Implanon. See section 2.6 for details.

There were a total of 44 (out of 108) subjects who discontinued study during the study period. The number and reasons for discontinuation of study are listed in Tables 5 and 6.

**Table 4. Number of subjects who discontinued the study in different periods; study 34528**

	Months 0 - 6	Months 6 - 12	Months 12 - 24	Months 24 - 36
Implanon	7	5	9	2
(b) (4)	4	4	5	5

**Table 5. Reasons for discontinuation of study from Implanon and (b) (4) arms; study 34528**

	Implanon (out of n=56)	(b) (4) (out of n=52)	Combined (out of n=108)
Bleeding irregularities			
Frequent irregular bleeding	4	4	8
Prolonged menstrual flow	3	2	5
Spotting	1	3	4
Other bleeding problems	0	1	1
Sub total	8	10	18
Adverse Events			
Dysmenorrhea	1	0	1
Cardiovascular	0	1	1
Acne	2	1	3
Other skin problems	1	1	2
Weight change	1	0	1
Nausea	1	0	1
Other adverse events	3	2	5
Sub total	9	5	14
Other reasons			
Used other contraceptive	0	1	1
Planning pregnancy	4	1	5
Moving device	0	1	1
Personal	2	1	3
Sub total	6	4	10
Lost to follow up	1	1	2
Total	24	20	44

Overall discontinuation rate from the study 34528 was 41%. This discontinuation rate is comparable to ones observed in four studies which supported the principal efficacy and safety of Implanon in the original NDA 021529 as following.

- Study 069001: 49% (161/330)
- Study 34505: 32% (32/100)
- Study 34507: 32% (205/636)
- Study 34507 CDN: 37% (19/52)

*Data for discontinuation rates of four studies is from Clinical Review of NDA 21-529 by Dr. Barbara Wesley (DARRTS, October 28, 2004).*

### 2.2.2 Are the active moieties in the serum appropriately identified?

Yes. Blood samples were withdrawn at pre-dose, Days 3, 5, 7, 9, 11, 15, and 22, and Months 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 27, 30, 33, and 36 for determination of serum etonogestrel concentration following implantation of Implanon and (b) (4).

## 2.3 Intrinsic factors

### 2.3.1 Does hepatic disease influence the PK of (b) (4)?

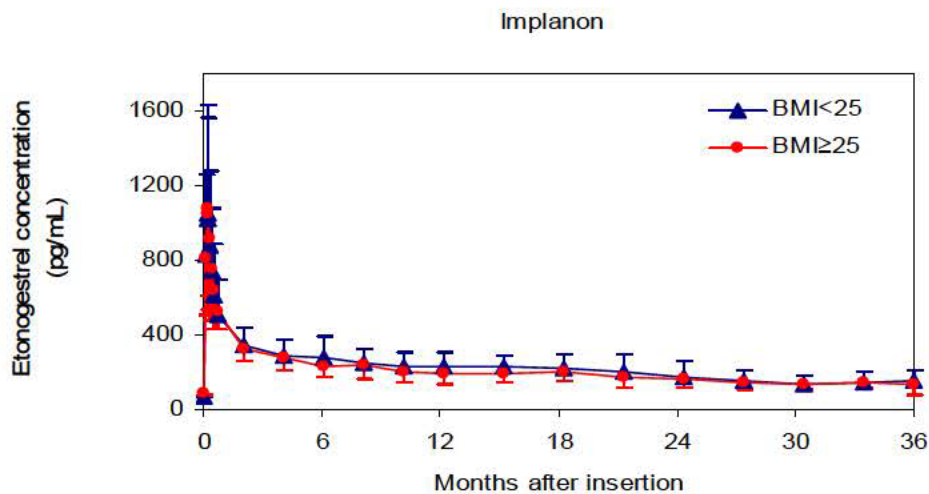
No studies were conducted to evaluate the effect of hepatic disease on the PK of (b) (4). However, steroid hormones may be poorly metabolized in patients with liver impairment.

### 2.3.2 Does renal disease influence the PK of (b) (4)?

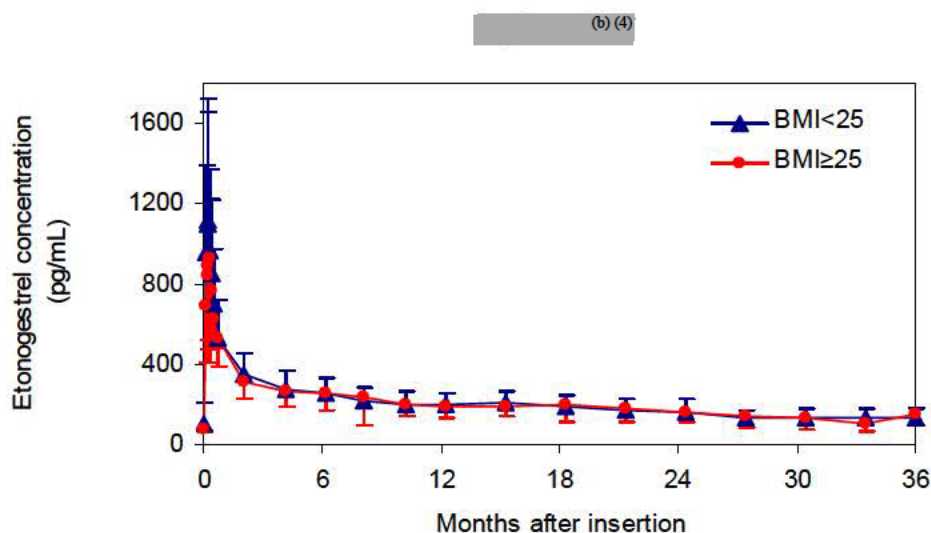
No studies were conducted to evaluate the effect of renal disease on the PK of (b) (4).

### 2.3.3 Does body weight / BMI influence the PK of (b) (4)?

An inverse relationship between body weight / BMI and etonogestrel concentration was observed in the original NDA submission for Implanon (Clinical Pharmacology review of NDA 021529 by Dr. Myong-Jin Kim, DARRTS, October 27, 2004). In order to explore the effect of body weight / BMI on etonogestrel concentration in study 34528, the mean etonogestrel concentration ( $\pm$  SD)-time profiles by two groups, BMI<25 and BMI $\geq$ 25, following implantation of Implanon and (b) (4) were plotted (Figure 3 and 4). There were 8 subjects (out of 53) with BMI $\geq$ 25 in the Implanon arm and 10 subjects (out of 50) with BMI $\geq$ 25 in the (b) (4) arm. As shown in Figure 3 and 4, the differences in mean concentrations of etonogestrel from these two BMI groups at each time point over 36 months were within the range of SD for each corresponding time point. Therefore, there were no observed differences in the etonogestrel concentration over 36 months between the two BMI groups (BMI<25 vs. BMI $\geq$ 25).



**Figure 3. Arithmetic mean ( $\pm$  SD) etonogestrel concentration-time profiles following implantation of Implanon by BMI (<25 and  $\geq$ 25) over 36 months; study 34528**

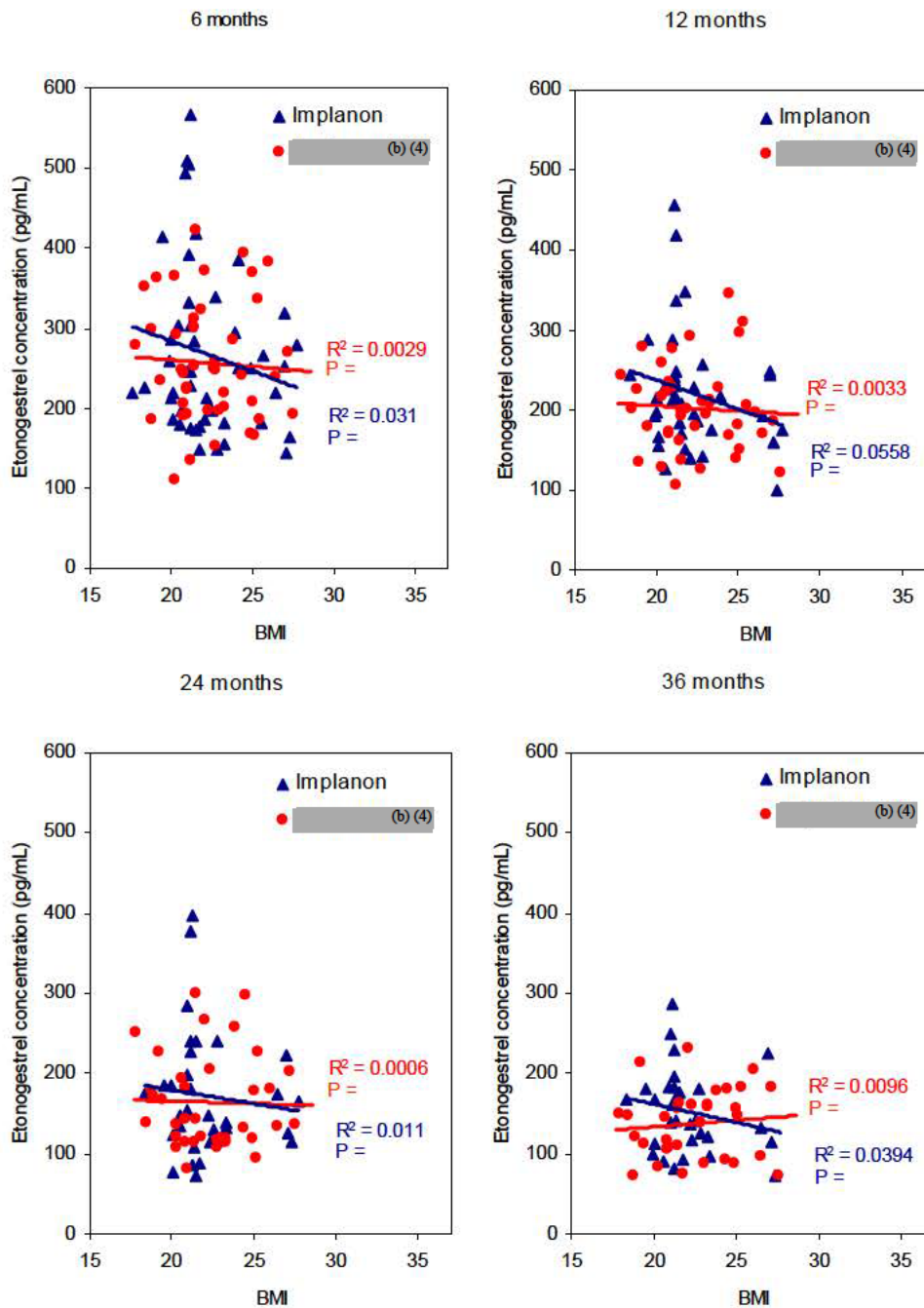


**Figure 4 . Arithmetic mean ( $\pm$  SD) etonogestrel concentration-time profiles following implantation of (b) (4) by BMI (<25 and  $\geq$ 25) over 36 months; study 34528**

Further analysis was performed to assess the effect of BMI on etonogestrel serum concentration for subjects treated with either Implanon or (b) (4). There were no clear trends observed between the BMI and etonogestrel exposure. In addition, there were no statistical significances observed between the BMI and etonogestrel exposure in both groups (Figure 5). Therefore, the PK (b) (4) was not influenced by BMI between 18 - 29 kg/m<sup>2</sup> in study 34528.

Potential effect of BMI (18-29 kg/m<sup>2</sup>) on etonogestrel serum concentration following the Implanon or (b) (4) insertion was performed. There were no clear trends

observed between the BMI and etonogestrel exposure. In addition, there were no statistical significances observed between the BMI and etonogestrel exposure in both groups. Therefore, there was no clear effect of BMI (18-29 kg/m<sup>2</sup>) on the concentration of etonogestrel following implantation of Implanon or (b) (4) in study 34528. (see Figure 4 under section 2.3.3).



**Figure 5. Etonogestrel concentration–BMI profiles following implantation of Implanon and (b) (4) during 6, 12, 24, and 36 months; study 34528**

## 2.4 Extrinsic factors

2.4.1 Does taking medications with (b) (4) influence exposure of (b) (4)?

No drug-drug interaction studies were conducted with (b) (4). However, the following is the modified class label of drug-drug interaction section adopted from oral contraceptives containing both estrogen and progestin.

### Changes in Contraceptive Effectiveness Associated with Coadministration of Other Products

Drugs or herbal products that induce enzymes, including CYP3A4, that metabolize progestins may decrease the plasma concentrations of progestins, and may decrease the effectiveness of hormonal contraceptives. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

### HIV Antiretrovirals

Significant changes (increase or decrease) in the plasma levels of the progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

### Increase in Plasma Hormone Levels Associated with Co-Administered Drugs

Drugs (For example, ketoconazole or itraconazole) that inhibit microsomal enzymes, such as CYP3A4, may increase plasma hormone levels.

## 2.5 General Biopharmaceutics

- (b) (4) was manufactured by NV Organon (Kloosterstraat 6, 5349 AB Oss, Netherlands).
- The drug formulation of (b) (4) is identical to Implanon except that the (b) (4) contains additional 15 mg barium sulfate (b) (4).

**Table 6. Composition of Implanon and (b) (4)**

Component	Function	Quantity per implant
-----------	----------	----------------------

		Implanon	(b) (4)
Etonogestrel (b) (4)	Drug substance	68 mg	68 mg
Barium sulfate	Radio opacifier	-	15 mg
Ethylene vinyl acetate copolymer (28 % vinyl acetate)	Core polymer	(b) (4)	(b) (4)
Ethylene vinylacetate copolymer (14 % vinyl acetate)	Skin polymer	(b) (4)	(b) (4)
Total weight		129 mg	141 mg

### 2.5.1 Are the clinical trial and the to-be-marketed formulations the same?

Yes. The formulation and manufacturing site of (b) (4) used in clinical studies 34528 and 34530 (batches CX180 and CZ143, respectively) are identical to the “to-be-marketed” product. Implanon and (b) (4) used in the clinical studies 34528 and 34530 were manufactured at the commercial sites using the commercial equipment. The commercial sites and implant manufacturing equipment used for (b) (4) are also the same as the currently approved Implanon.

	Manufacturer	Manufacturing Site	Responsibility
1	NV Organon	Kloosterstraat 6 5349 AB Oss The Netherlands	Drug product manufacturing; Packaging; Quality control testing; Release
2	(b) (4)	(b) (4)	Quality control testing
3	(b) (4)	(b) (4)	(b) (4) of finished product in final packaging

## 2.6 Analytical Section

Etonogestrel was isolated from serum solid phase extraction with (b) (4) cartridges and concentrations of etonogestrel were determined using radio-immunoassay. The acceptance criteria for both accuracy and precision in the method validation report, NL0032509, were 25% for lower limit of quantification and 20% for the other concentrations of quality control samples. Although the above 20/25 acceptance criteria is 5% higher than 15/20 general acceptance criteria described in Bioanalytical Method Validation (Guidance for industry – Bioanalytical method validation, FDA, May 2001),

the guidance allows wider acceptance criteria for ligand-binding assay where radio-immunoassay, one of the ligand-binding assays, was used in the study 34528. Furthermore, actual accuracy and precision for both intra- and inter-assay in both method validation report, NL0032509, and bioanalytical report, INT00104788 were within 15% deviation from the nominal value and coefficient of variation less than 15%, respectively. Therefore method validation report, NL0032509 satisfied the requirements of Bioanalytical Method Validation (Guidance for industry – Bioanalytical method validation, FDA, May 2001).

		Method validation report, NL0032509	Bioanalytical report, INT00104788
Component to measure		Etonogestrel	Etonogestrel
Type of Biological Fluid		Human serum	Human serum
Range of Standard Curve		30 – 9,000 pg/mL	30 – 9,000 pg/mL
Linearity (R <sup>2</sup> )		0.9997 ± 0.0002	
QC Sample Accuracy	Intra-assay	94.7 – 107.4 %	94.3 – 102.0 %
	Inter-assay	98.5 – 112.4 %	98.7 – 99.6%
QC Sample Precision	Intra-assay	4.2 – 13.8 %	2.6 – 9.5 %
	Inter-assay	3.7 – 8.5 %	8.2 - 9.7 %
Stability		24 hrs at room temperature; 2 years at -20°C; 3 cycles of freezing/thawing <sup>1</sup>	

All human serum samples of study 34528 were analyzed for the content of etonogestrel according to the validated method validation report, NL0032509 as reported in bioanalytical report, INT00104788.

#### **DSI report of the pivotal BE study (34528)**

The Division of Clinical Pharmacology III requested for DSI to conduct audits of the both clinical and bioanalytical sites of the pivotal BE study on September 18, 2009. See 4.2 DSI site inspection request and 4.3 DSI site inspection report for detail.

- Clinical site (Dinox BV, Netherlands)
  - Following the inspection of clinical site from February 22<sup>nd</sup> to 26<sup>th</sup>, 2010, there were two findings resulted in issuance of form FDA-483.
    1. The firm did not retain reserve samples for the study (No. 34528). The study drug products were provided in three shipments as follows. One shipment of four units was designated as back-up supplies and was

<sup>1</sup> Method validation report (SDG RR No. 4691)

returned to the sponsor. The other two shipments provided by the sponsor consisted of 24 units and eight units, 32 units in total, and were used for subject dosing with none remaining.

*Although there were no remaining samples to confirm the identity of implant samples used in the BE study, the sponsor maintained the X-ray records to verify whether the implants used in the BE study were electron dense or not. DSI reviewer recommended using the X-ray data as supportive evidence and this reviewer concurs with this recommendation.*

2. Administration of informed consent to the first 12 subjects utilized a consent form version (15 March 2005) that had not been approved by the reviewing ethics committee. The approved version (8 April 2005) was administered to the subjects at a subsequent visit. The approved version included changes to information on study risks and information on subject confidentiality.

*DSI reviewer evaluated that the usage of non-approved version of informed consent form used for 12 subjects in the BE study would have little or no consequence on the study result. This reviewer concurs with this recommendation..*

- o Bioanalytical site (Merck Sharp Dohme *previously known as Schering-Plough*, Netherlands)

Following the inspection of bioanalytical site from March 1<sup>st</sup> to 5<sup>th</sup>, 2010, there were four findings resulted in issuance of form FDA-483.

1. Stability during long-term frozen storage was not validated pre-study for the same assay procedure used in study 34528 ( (b)(4) solid phase extraction with radioimmunoassay). Study samples were stored as long as 650 days (mean 231 days) before assay. However, within the study, stability of QCs was demonstrated for 105 days.

*In response to the form 483 issued by the DSI, the sponsor reestablished the stability of Implanon and (b)(4) for more than two years, which is longer than 650 days (maximum storage period of implants used in the BE study).*

2. Run acceptance/rejection decisions were made inappropriately, by averaging replicate determinations of QC sample concentrations. When QC data were calculated in the same way as study sample data, the originally-failed run 27 would pass, and the passed runs 14 and 36 would fail.

*1> In the original BE analysis, data from run 27 were rejected. However, samples for run 27 were reassayed in run 31 and accepted. Therefore, no adjustment in the evaluation of original BE analysis in regard to failed run 27 is necessary.*

*2> There were 34 subjects whose data were analyzed in runs 14 and 36.*

*1] Data from 13 ( (b)(6)*

(b) (6) and (b) (6) out of 34 subjects in runs 14 and 36 were for data at months 2 and/or 4.

2] Data from 7 (b) (6) and (b) (6) out of 34 subjects in runs 14 and 36 were for data at months 15 and/or 18.

3] Data from 10 (b) (6) and (b) (6) out of 34 subjects in runs 14 and 36 were for data at months 18 and/or 21.

The sponsor recalculated both  $C_{max}$  and AUC of etonogestrel from 30 (13+7+10) subjects listed above excluding data from runs 14 and 36. Since  $C_{max}$  occurs within one month, recalculation of  $C_{max}$  excluding data from runs 14 and 36 did not affect the  $C_{max}$ . However, recalculation of AUCs excluding data from runs 14 and 36 changed the AUCs. Recalculation of AUC without data at “months 2 and/or 4”, OR “months 15 and/or 18”, OR “months 18 and/or 21” is acceptable, since logarithmic concentration-time profile from month 1 to 36 are relatively linear.

4] Data from 4 (b) (6) and (b) (6) out of 34 subjects in runs 14 and 36 were for multiple data sets for period including first 2 months after implant insertion, during which  $C_{max}$  occurs and concentration of etonogestrel greatly varies and affects the AUC. Therefore, these four subjects listed above were excluded from the sponsor’s reanalysis of the BE data.

3> The sponsor’s approach to reanalyze the BE data was acceptable. In the sponsor’s reanalysis of the BE data with total 99 subjects, all the PK parameters ( $AUC_{0-6months}$ ,  $AUC_{0-12months}$ ,  $AUC_{0-24months}$ ,  $AUC_{12-24months}$ ,  $AUC_{0-36months}$ , and  $AUC_{24-36months}$ ) except  $C_{max}$  used to assess the BE between implanon and (b) (4) met the BE criteria. The upper bound of 90% CI for  $C_{max}$  was 1.259, which is higher than 1.25 (upper bound limit for 90% CI). The sponsor explained that this observation is caused by the exclusion of four subjects, resulting in too low sample size.

3. Six serum samples (subjects (b) (6) and (b) (6) with insufficient volume to confirm measurable pre-dose ENG concentrations were listed as “not reportable.” However, other measurable pre-dose ENG concentrations were confirmed to be accurate.

1> Data from 2 (b) (6) and (b) (6) out of 6 subjects listed above showed pre-dose concentration of etonogestrel less than 5% of each subject’s  $C_{max}$ . Per “Guidance for Industry – Bioavailability and bioequivalence studies for orally administered drug products (March 2003, FDA)”, data from these two subjects (b) (6) and (b) (6) still can be used for BE evaluation. Therefore, these two subjects (b) (6) and (b) (6) were not excluded for BE reanalysis.

2> Because of the pre-dose concentration of etonogestrel higher than 5% of each subject’s  $C_{max}$  in four (b) (6) and (b) (6) out

of six subjects listed above, this reviewer reassayed the data excluding these 4 subjects ( (b) (6), and (b) (6) ) in addition to excluding 4 subjects ( (b) (6), and (b) (6) ) with inappropriate run acceptance/rejection decision (item #2 from bioanalytical site in DSI report). BE reanalysis with 95 subjects showed that all the PK parameters except  $C_{max}$  met the BE criteria. 90% CI for  $C_{max}$  was between 0.918 and 1.264. Although the upper bound of 90% CI for  $C_{max}$  was higher than 1.25, this reviewer believes that this finding is not clinically meaningful for the following reason.

1] (b) (4) is long term use contraceptive over 3 years. The 90% CI for not only AUC over 3 years, but also sectional AUCs ( $AUC_{0-6months}$ ,  $AUC_{0-12months}$ ,  $AUC_{0-24months}$ ,  $AUC_{12-24months}$ , and  $AUC_{24-36months}$ ) met the BE criteria.

2] Implanon is for single insertion over 3 years. Since there would be one time period during which  $C_{max}$  occurs over 3 years, there is less concern for 90% CI of  $C_{max}$  being over 1.25 by 0.14.

3] The review of the safety data in the application and of the requested safety data did not demonstrate safety concerns for the radiopaque etonogestrel implant related to the slightly higher upper limit of the 90% CI for  $C_{max}$  (Dr. Theresa Van Der Vlugt's medial review).

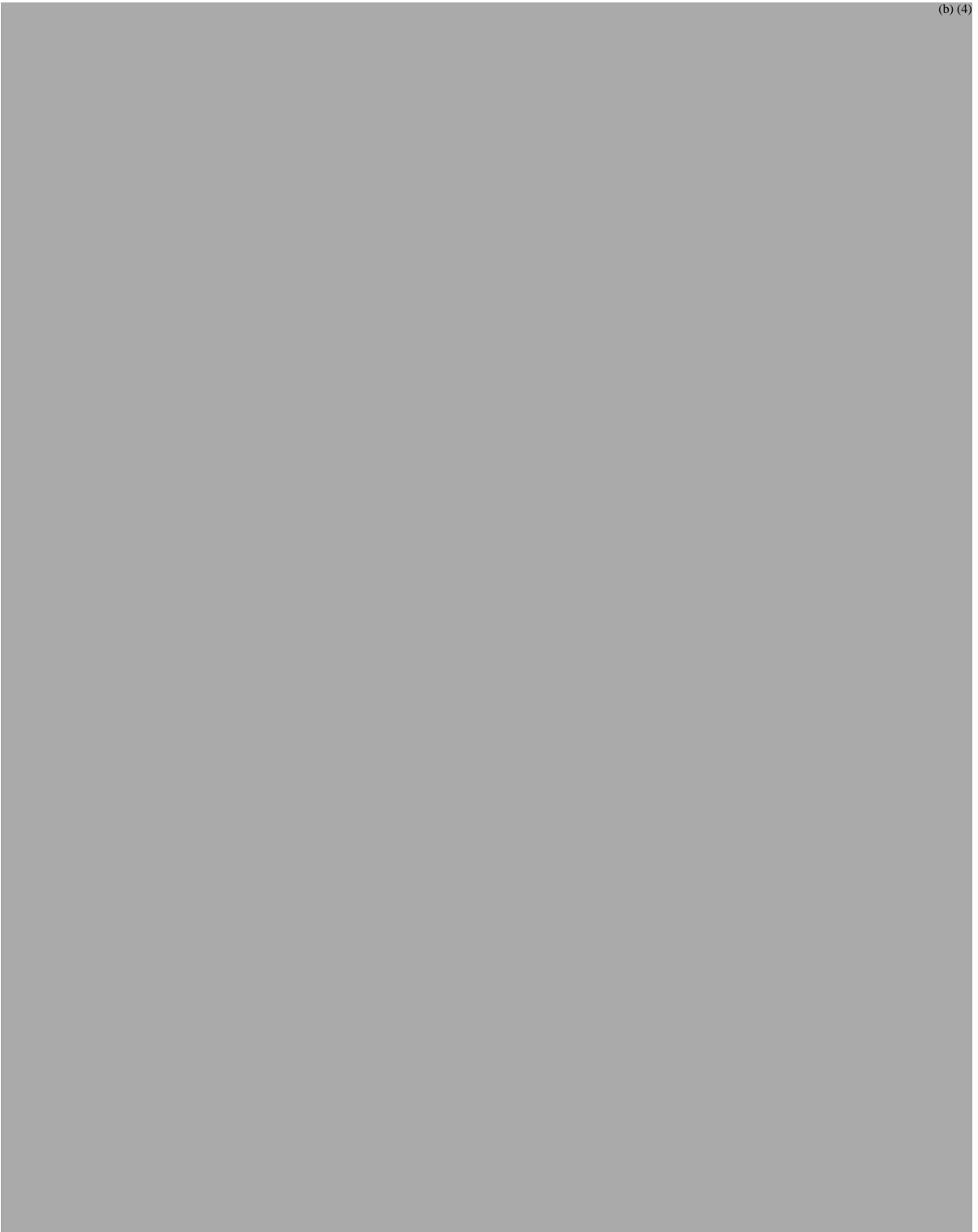
4. Failure to evaluate incurred sample reproducibility (ISR). Although 44 study samples in analytical run 27 were reassayed in run 31, because of the inappropriate process cited in observation #2, these 44 reassayed samples represent only about 2% of total study samples.

The sponsor reestablished the ISR with more than 10% (which is the recommended % for ISR by DSI) of the total samples in response to this finding from DSI.

Overall, the sponsor's response to the form 483s for both clinical and analytical sites of the BE study addressed all the findings from the DSI inspection. Therefore, the sponsor's data is valid to be reviewed and BE reanalysis showed that the efficacy and safety of (b) (4) can be relied upon the efficacy and safety of Implanon, although BE study between (b) (4) and Implanon did not meet the BE criteria for  $C_{max}$ .

### **3 Detailed Labeling Recommendations**

The following Clinical Pharmacology related labeling comments are addressed below. Strikes are used for deletion and double underline is used for addition.

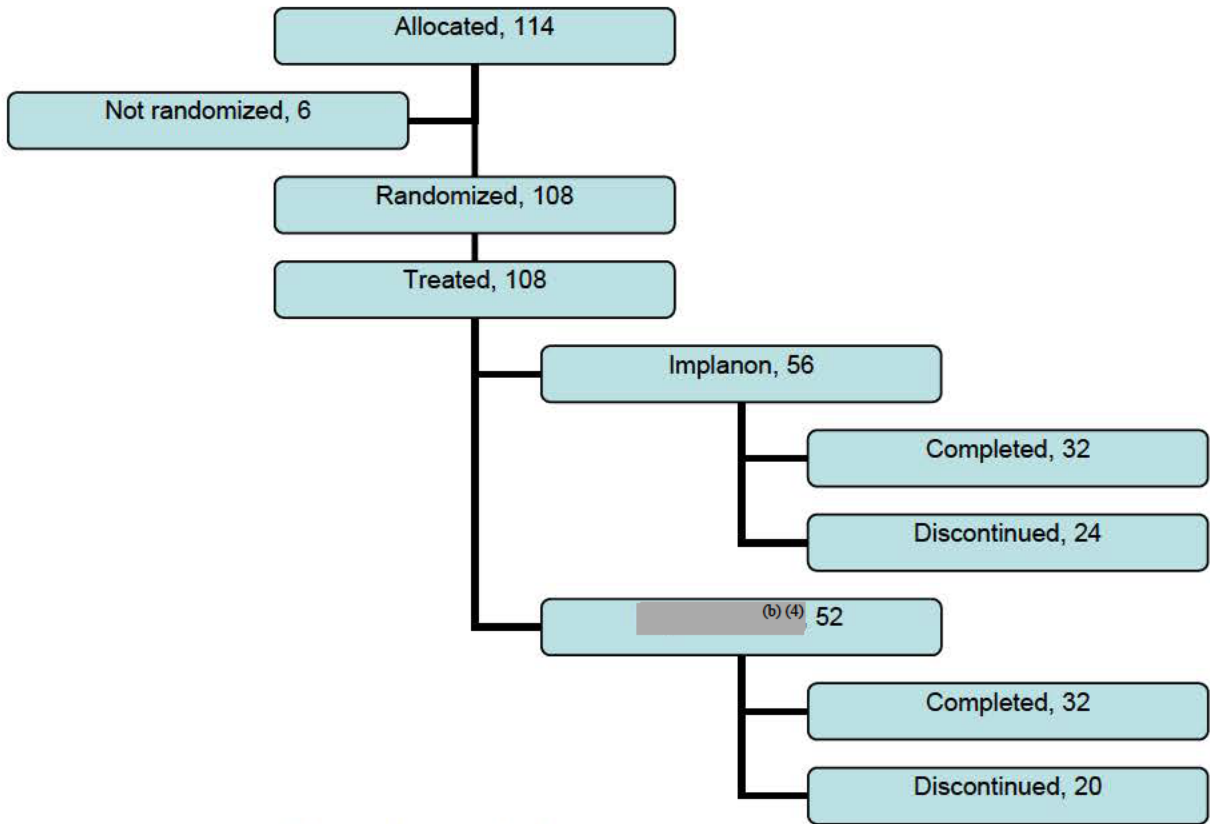


(b) (4)

## 4 Appendix

### 4.1 Individual Clinical Study Review

- Title of the clinical study (34528)
  - A randomized, double-blind, parallel group, bioequivalence study of Implanon and (b) (4)
- Clinical study centers (number of subjects): total of 114 healthy female subjects
  - Switzerland
    - [CH\_021] Inselspital, Universitäts-Frauenklinik, Effingerstrasse 102, 3010 Bern (12);
    - [CH\_022] Universitätsspital Basel Frauenklinik, Spitalstrasse 21, 4031 Basel (12);
    - [CH\_036] Humboldtstrasse 24, 3013 Bern (12);
    - [CH\_064] Universitäts Spital Zürich, Klinik für Endokrinologie, Departement Frauenheilkunde, Frauenklinikstrasse 10, 8091 Zurich (12);
  - France
    - [FR\_127] 8 rue Anatole France, 91860 Epinay-sous-Sénart (13);
    - [FR\_226] Hôpital Jeanne de Flandres, rue Eugène Avinée, 59037 Lille (2);
    - [FR\_343] CH Dr Schaffner, Lens, 99 route de La Bassée, 62307 Lens (13);
    - [FR\_358] Cabinet de Gynécologie, 88 rue de Sèvres, 75007 Paris (5);
  - The Netherlands:
    - [NL\_201] Dincox BV, Hanzeplein 1, entrance 53, 9713 GZ Groningen (33)
- Study period (years)
  - May, 2005 to February, 2009.
- Objectives
  - Primary: To demonstrate bioequivalence of Implanon and (b) (4)
  - Secondary: To assess X-ray visibility of (b) (4)
- Study design
  - Multicenter, randomized, double-blind, parallel group, bioequivalence study
- Number of subjects
  - A total of 90 subjects were planned; 45 Implanon subjects and 45 (b) (4) subjects.
  - A total of 108 subjects were treated; 56 subjects received Implanon and 52 subjects received (b) (4)



- Not randomized subjects, 6
  - (b)(6): Pregnancy screening failure
  - (b)(6): Subject not included due to the decision of the project team leader
  - (b)(6): Inclusion criteria violation – Subject had irregular menstrual cycle
  - (b)(6): Withdrawal of consent
  - (b)(6): Inclusion criteria violation – Subject’s Age was not between 18 and 40
  - (b)(6): Lost to follow up
- Discontinued subjects, 44

	Implanon (out of n=56)	(b)(4) (out of n=52)	Combined (out of n=108)
Bleeding irregularities			
Frequent irregular bleeding	4	4	8
Prolonged menstrual flow	3	2	5
Spotting	1	3	4
Other bleeding problems	0	1	1
Sub total	8	10	18

Adverse Events			
Dysmenorrhea	1	0	1
Cardiovascular	0	1	1
Acne	2	1	3
Other skin problems	1	1	2
Weight change	1	0	1
Nausea	1	0	1
Other adverse events	3	2	5
Sub total	9	5	14
Other reasons			
Used other contraceptive	0	1	1
Planning pregnancy	4	1	5
Moving device	0	1	1
Personal	2	1	3
Sub total	6	4	10
Lost to follow up	1	1	2
Total	24	20	44

Overall discontinuation rate from the study 34528 was 41%. This discontinuation rate is comparable to ones observed in four studies considered having the principal efficacy and safety in the original NDA 21-529, Implanon.

- Study 069001: 49% (161/330)
- Study 34505: 32% (32/100)
- Study 34507: 32% (205/636)
- Study 34507 CDN: 37% (19/52)
  
- Inclusion criteria
  - At least 18 but not older than 40 years of age at the time of screening
  - Be in good physical and mental health
  - Have regular cycles with a usual length between 24 and 35 days
  - Have a body mass index between 18 and 29
  - Be willing to give informed consent in writing.
- Exclusion criteria
  - Have any of the following contraindications
    - Known or suspected pregnancy
    - Active venous thromboembolic disorder (e.g., deep vein thrombosis, pulmonary embolism)
    - Presence or history of severe hepatic disease as long as liver function values had not returned to normal
    - Malignancy or pre-malignancy
    - Undiagnosed vaginal bleeding
    - Hypersensitivity to any of the components of (b) (4)
    - Have hypertension, i.e. systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg
    - Have a history during pregnancy or during previous use of sex steroids of: jaundice and/or severe pruritus related to cholestasis,

- gallstone formation, porphyria, systemic lupus erythematosus, haemolytic uraemic syndrome, Sydenham's chorea, herpes gestationis, or otosclerosis-related hearing loss
    - have present use or use during 2 months prior to the start of Implanon, phenytoin, phenobarbital, primidone, carbamazepine, rifampicin, oxcarbazepine, topiramate, felbamate, ritonavir, nelfinavir, griseofulvin or the herbal remedy St John's wort
    - Have administration of investigational drugs within 2 months prior to the start of study
  - Test product
    - (b) (4) differs from the Implanon rod in the composition of the core, i.e., the addition of 15 mg barium sulfate (b) (4) v/v of the implant core) (b) (4). The radiopaque rod is otherwise identical to the Implanon rod. Batch number CX 180 was used.
  - Reference product
    - Implanon is a single rod contraceptive implant of 4 cm length and 2 mm in diameter. Implanon contains approximately 68 mg etonogestrel dispersed in a matrix of ethylene vinyl acetate copolymer, surrounded by its membrane. Batch number CX179 was used.

*For blinding purpose the test and reference products were implanted using original Implanon applicator.*

- Duration of treatment
  - Three years
- Criteria for evaluation
  - Pharmacokinetics
    - Etonogestrel concentrations were measured in serum at
      - Pre-dose
      - Days 3, 5, 7, 9, 11, 15, and 22
      - Months 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 27, 30, 33, and 36
    - The following pharmacokinetic parameters were calculated:  $C_{max}$ ,  $t_{max}$ ,  $AUC_{0-6months}$ ,  $AUC_{0-12months}$ ,  $AUC_{0-24months}$ ,  $AUC_{12-24months}$ ,  $AUC_{0-36months}$ , and  $AUC_{24-36months}$ .
  - Efficacy
    - Contraceptive efficacy was assessed from the occurrence of pregnancies.
    - Palpability was assessed by localization of the implant by palpation.
    - X-ray visibility was assessed by X-ray imaging after implant implantation and before removal. After removal, the return of menses was evaluated at the post-treatment contact, per protocol scheduled at  $3 \pm 1$  months after implant removal.
  - Safety
    - Safety was assessed by reporting of adverse events (AEs), serious adverse events (SAEs), serious study procedure-related events

(SPEs), vital signs, complications at implantation/removal, implant status, physical and pelvic examinations.

- Statistical methods
  - Pharmacokinetics
    - Descriptive statistics for the concentrations of etonogestrel in serum and the pharmacokinetic parameters were calculated. Bioequivalence testing using an analysis of variance with the 90% confidence interval (CI) approach (acceptance range 0.80-1.25) on the loge-transformed pharmacokinetic parameters as following:  $C_{max}$ ,  $AUC_{0-6months}$ ,  $AUC_{0-12months}$ ,  $AUC_{0-24months}$ ,  $AUC_{12-24months}$ ,  $AUC_{0-36months}$ , and  $AUC_{24-36months}$ .
  - Efficacy
    - Pregnancies were categorized as pre-treatment when the estimated date of conception was before implant implantation.
    - Pregnancies were considered in-treatment according to two definitions
      - In-treatment pregnancies were pregnancies with an estimated date of conception from the day of implant implantation up to and including the day of implant removal and
      - In-treatment pregnancies were pregnancies with an estimated date of conception from the day of implant implantation up to and including the day of implant removal extended with a period of 14 days.
    - Overall, annual Pearl Index (PI, for the first, second, and the third year of exposure) and cumulative PI (through the first, through the second, and through the third year of exposure) were calculated.
    - The number and percentage of subjects with palpability result “palpable” or “not palpable” was assessed at all assessments up to the implant removal assessment. The 95% CIs for the incidence of palpability was tabulated per treatment group.
    - The number and percentage of subjects with X-ray visibility result “clearly visible” or “not (clearly) visible” was assessed after implant implantation and before removal. The 95% CIs for the incidence of clear visibility was tabulated per treatment group and assessment.
    - Return of menses at post-treatment was tabulated for those subjects who had a post-treatment assessment, were not pregnant, and did not use post-treatment hormonal contraceptives.
  - Safety
    - Safety was primarily assessed by the reporting of AEs, as well as discontinuations due to AEs. In addition, the reporting of complications at implant implantation and removal, status of the implant site, and abnormalities in pelvic and clinically significant findings for the physical examinations were assessed. Descriptive statistics were used to evaluate these parameters.

- For vital signs, descriptive statistics were used; markedly abnormal vital signs values were determined.
  - Results
    - All 108 subjects that were treated in this study were females and had a mean (SD) of 27.1 (6.7) years of age. The mean (SD) BMI and body weight were 22.40 (2.42) kg/m<sup>2</sup> and 63.32 (8.27) kg, respectively. Most of the subjects were Caucasian (n=103, 95.4%). A total of 64 subjects completed the study, 32 subjects in each treatment group.
    - Pharmacokinetics

Parameters	Geometric mean [CV]		Ratio (test/reference)	90% Confidence interval
	Implanon (reference)	(b) (4) (test)		
C <sub>max</sub> <sup>a</sup> (pg/mL)	1,021.2 [50.4 %]	1,083.3 [50.4 %]	1.06	0.91-1.23
AUC <sub>0-6months</sub> <sup>b</sup> (pg·month/mL)	2,210.4 [27.2 %]	2,212.1 [28.4 %]	1.00	0.91-1.10
AUC <sub>0-12months</sub> <sup>c</sup> (pg·month/mL)	3,594.0 [28.2 %]	3,495.4 [26.5 %]	0.97	0.88-1.07
AUC <sub>0-24months</sub> <sup>d</sup> (pg·month/mL)	5,873.9 [31.1 %]	5,783.1 [25.1 %]	0.98	0.88-1.10
AUC <sub>12-24months</sub> <sup>d</sup> (pg·month/mL)	2,355.5 [34.0 %]	2,207.3 [25.3 %]	0.94	0.84-1.05
AUC <sub>0-36months</sub> <sup>e</sup> (pg·month/mL)	7,487.0 [31.9 %]	7,453.2 [24.9 %]	1.00	0.89-1.11
AUC <sub>24-36months</sub> <sup>e</sup> (pg·month/mL)	1,652.5 [33.7 %]	1,613.0 [26.9 %]	0.98	0.87-1.10
t <sub>max</sub> (h) <sup>a*</sup>	120.2 [29.1–232.8]	141.2 [47.4-334.5]		

n1: number of subjects implanted with Implanon, n2: number of subjects implanted with (b) (4) <sup>a</sup> n1=53, n2=50; <sup>b</sup> n1=46, n2=46; <sup>c</sup> n1=41, n2=42; <sup>d</sup> n1=32, n2=37; <sup>e</sup> n1=30, n2=32; \* Data presented as median [range]

- Bioequivalence of Implanon and (b) (4) was demonstrated for C<sub>max</sub>, AUC<sub>0-6months</sub>, AUC<sub>0-12months</sub>, AUC<sub>0-24months</sub>, AUC<sub>12-24months</sub>, AUC<sub>0-36months</sub>, and AUC<sub>24-36months</sub>.

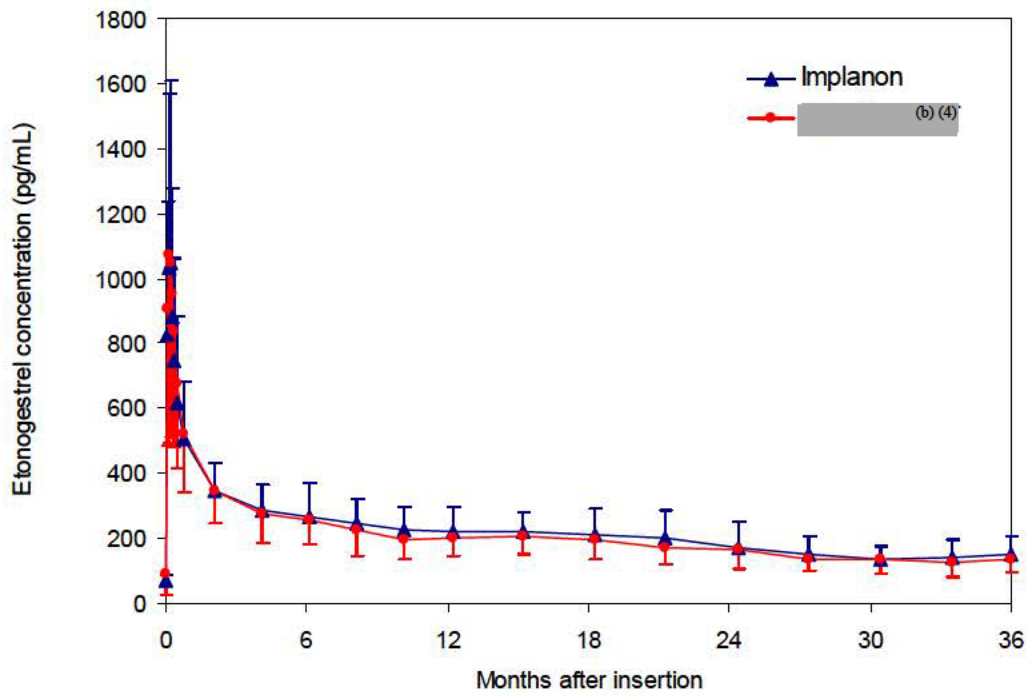


Figure 5. Arithmetic mean ( $\pm$  SD) etonogestrel concentration-time profiles following implantation of Implanon and (b) (4).

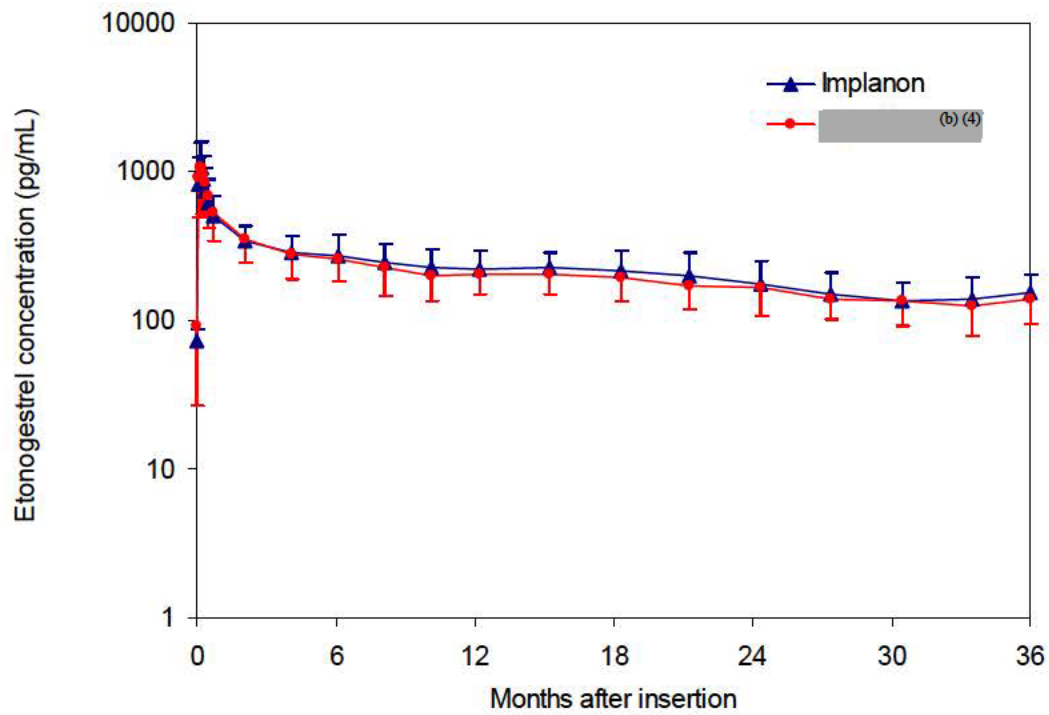


Figure 6. Arithmetic mean ( $\pm$  SD) etonogestrel concentration-time profiles following implantation of Implanon and (b) (4) (logarithmic scale).

- Efficacy and Safety

*Please see the medical officer's review by Dr. Daniel Davis for efficacy and safety.*

- Contraceptive efficacy
- Palpability
- X-ray visibility

- Conclusions

- For total etonogestrel exposures in different periods ( $AUC_{0-6\text{months}}$ ,  $AUC_{0-12\text{months}}$ ,  $AUC_{0-24\text{months}}$ ,  $AUC_{12-24\text{months}}$ ,  $AUC_{0-36\text{months}}$ , and  $AUC_{24-36\text{months}}$ ) and peak concentration ( $C_{\text{max}}$ ), the Implanon and (b) (4) were bioequivalent.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	SUPPL-7	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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/s/

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HYUNJIN KIM  
07/22/2010

MYONG JIN KIM  
07/23/2010

EDWARD D BASHAW  
07/23/2010  
Division Director Comments

At the time of the OCP Briefing (3/23/10) the DSI audit was still pending. At that time all of the pk parameters passed the 80-125% confidence interval. However, following the audit DSI indicated that some of the subjects should be removed from the analysis and new statistics generated.

When these subjects were removed, the 90% confidence interval for Cmax exceeded by upper limit of 125% 1.4% (ie.,126.4%).

Even so, the point estimate for Cmax was within the 80-125% limits and the overall confidence interval contained "1". Given that Cmax represents a transient time period for this product and that other measures over the entire "dosing" period meet their statistical tests, it is unlikely that this represents a meaningful difference.

I concur with the conclusion as written by the reviewer and his Team Leader in all aspects.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021529Orig1s007**

**OTHER REVIEW(S)**

## **Memo to the file**

**Date:** 5-11-2011

**NDA #:** 21-529 S-007

**Date of submission:** 7-29-09

**Sponsor:** Organon, Inc.

**Drug Product:** Nexplanon (etonogestrel implant), formulation: radio opaque rods

**Indication:** Pregnancy prevention

**Subject:** Labeling review

**Reviewer:** Krishan L. Raheja, D.V.M., Ph.D.

**Through Expert Reviewer:** Alex Jordan, Ph.D.

**Regulatory action:** From the P/T perspective labeling is adequate and acceptable

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/s/  
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KRISHAN L RAHEJA  
05/11/2011

ALEXANDER W JORDAN  
05/11/2011

## SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 021529/S007
APPLICANT	Organon USA, Inc.
PRODUCT NAME	Nexplanon (etonogestrel implant)
SUBMISSION DATE	30 July 2009
PDUFA DATE	30 August 2010
SEALD SIGN-OFF DATE	10 May 2011
OND ASSOCIATE DIRECTOR FOR STUDY ENDPOINTS AND LABELING	Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies noted in the SEALD Labeling Review filed 29 April 2011, have been addressed in the final agreed-upon PI. SEALD has no objection to PI approval at this time.

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/s/  
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LAURIE B BURKE  
05/10/2011

## SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 021529/S007
APPLICANT	Organon USA, Inc.
PRODUCT NAME	Nexplanon (etonogestrel implant)
SUBMISSION DATE	30 July 2009
PDUFA DATE	30 August 2010
SEALD REVIEW DATE	29 April 2011
SEALD LABELING REVIEWER	Jun Yan, Pharm.D.

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

# Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**
  - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
- **Product Title**
  - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol. (b) (4)
- **Initial U.S. Approval**
  - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action. **Change the year to 2001.**
- **Boxed Warning**
  - All text in the boxed warning is **bolded**.
  - Summary of the warning must not exceed a length of 20 lines.
  - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
  - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
- **Recent Major Changes (RMC)**
  - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
  - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
  - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

### • General Format

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

### • Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

### • Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). 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.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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JUN YAN  
04/29/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: March 31, 2011

Application Type/Number: NDA 021529

To: Scott Monroe, MD, Director  
Division of Reproductive and Urologic Products

Through: Carlos Mena-Grillasca, RPh, Team Leader  
Carol A. Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Lissa C. Owens, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis  
(DMEPA)

Subject: Label and Labeling Review

Drug Name(s)/Strength: Nexplanon (etonogestrel implant) 68 mg

Applicant/Sponsor: Merck & Co., Inc.

OSE RCM #: 2010-2417

## **1 INTRODUCTION**

This review evaluates the revised Nexplanon (etonogestrel implant) 68 mg labels and labeling submitted on March 17, 2011 in response to the Division of Medication Error Prevention and Analysis's (DMEPA) previous comments to the Applicant.

## **2 MATERIAL REVIEWED**

The revised label and labeling submitted on March 17, 2011 (see Appendix A), the OSE review #2009-1974 dated November 15, 2010, and additional comments sent to the Applicant via email on February 24, 2011 were evaluated to assess whether the revisions adequately addresses our concerns from a medication error perspective.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

The revised label and labeling submitted by the Applicant adequately addresses our concerns from a medication error perspective. We do not have any additional comments at this time.

If you have further questions or need clarifications, please contact OSE Project Manager Maria Wasilik, at 301-796-0567.

## **4 REFERENCES**

*OSE Review #2009-1974, Label and Labeling Review for Etonogestrel Implant 68 mg. Park, Judy. November 15, 2010.*

**Appendix A**  
**Container Labels**



**Carton Labeling**



**Patient Chart Labeling**



**Patient Card Labeling**



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/s/  
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LISSA C OWENS  
03/31/2011

CARLOS M MENA-GRILLASCA  
03/31/2011

CAROL A HOLQUIST  
03/31/2011

**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**

Date: November 15, 2010

To: Scott Monroe, MD, Director  
Division of Reproductive and Urologic Products

Thru: Carlos M. Mena-Grillasca, R.Ph., Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Judy Park, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Etonogestrel Implant  
68 mg

Application Type/Number: NDA 021529

Applicant/Applicant: Merck & Co., Inc.

OSE RCM #: 2009-1974

## 1 INTRODUCTION

This review responds to a request from the Division of Reproductive and Urology Products for an evaluation of the blister labels, chart labeling, user card, carton and insert labeling of (b) (4) to identify areas that could lead to medication errors.

## 2 METHODS AND MATERIALS

### 2.1 LABELS AND LABELING

Using Failure Mode and Effects Analysis,<sup>1</sup> the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the labels and labeling submitted on August 20, 2010 and October 10, 2010 to identify vulnerabilities that could lead to medication errors (see Appendices A through F).

### 2.2 ADVERSE EVENT REPORTING SYSTEM (AERS)

Since Implanon is a marketed product, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on April 7, 2010 for any medication errors relevant to the labels or labeling of Implanon using the following criteria: Trade name “Implanon”, verbatim term “Implano%” and the MedDRA reaction terms “Medication Errors” (HGLT) and “Product Quality Issues” (HLGT).

The search retrieved four cases, none of which were related to labels or labeling. The four cases described the following: implant broken while implanted, drug exposure via breastmilk, pregnancy, and wrong duration of therapy (left the implant in a year longer than maximum recommended duration of 3 years in the insert labeling).

## 3 RECOMMENDATION

We acknowledge that the proposed proprietary name is still under review therefore, we are providing preliminary comments on the current labels and labeling. Our comments for the insert labeling are in Section 3.1 *Comments to the Division* and our comments for container labels and carton labeling are in Section 3.2 *Comments to the Applicant*. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

If you have further questions or need clarifications on this review, please contact Maria Wasilik, OSE Project Manager, at 301-796-0567.

### 3.1 COMMENTS TO THE DIVISION

#### A. Insert Labeling

1. Under Section 2.2. *Insertion Procedure* - Step 3 indicates to make two marks and refers to Figure 2. However, the picture on Figure 2 shows (b) (4). In addition, (b) (4)

Clarify what each mark should indicate and use terms that correspond to the Figure.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2. Under Section 2.2. *Insertion Procedure*- Step 7 indicates not to touch the “purple slider.” Since the insert labeling may be presented in black and white, indicate the “purple slider” on Figure 3.
3. Under Section 2.2. *Insertion Procedure* - include directions “lift skin” and “slide needle” next to the corresponding arrows in Figure 6 under Step 10 to better clarify the directions.

### **3.2 COMMENTS TO THE APPLICANT**

We acknowledge that the proposed proprietary name has not been granted therefore, we are providing preliminary comments on your current labels and labeling

#### ***A. General Comment***

1. Ensure that all labels and labeling for the proposed product are well differentiated from the marketed Implanon to ensure the products will not be confused for one another at the point of product selection and dispensing.
2. Per 21 CFR 201.10(g)(2), ensure that the established name is at least half the size of the proprietary name and have the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
3. Delete [REDACTED] (b) (4) [REDACTED] we recommend you include the statement “Contains radiopaque ingredient” on the principal display panel. Consider placing an asterisk at the end of the statement and next to the inactive ingredient, barium sulfate, on the rear panel to instruct practitioners of the actual radiopaque ingredient.

**APPENDICES**

**Appendix A** : Sample Blister Label



**Appendix B** : Sample Carton Labeling



**Appendix C** : Trade Blister Label



**Appendix D** : Trade Carton Labeling



**Appendix E** : User Card



(b) (4)

**Appendix F** : Chart Label



(b) (4)

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CARLOS M MENA-GRILLASCA  
11/15/2010

CAROL A HOLQUIST  
11/17/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
White Oak Building 66  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Date:** August 24, 2010

**From:** Nikhil Thakur, Combination Products Team Leader  
General Hospital Devices Branch, DAGID, ODE, CDRH

**To:** Dr. Theresa Van der Vlugt, Medical Officer  
DRUP/ODE3/OND/CDER

**Subject:** NDA 021529, Amendment to Supplemental NDA (S-007)

1. **Issue**

Device review to support NDA 021529 was first provided on April 29, 2010.

Follow-up consult was provided on July 7, 2010.

CDER issued Information Requests to the sponsor on July 7, 2010 and July 27, 2010.

CDER is requesting that CDRH review the sponsor's responses, dated August 2, 2010 and August 9, 2010. CDRH has provided an updated review of these responses on August 19, 2010.

CDRH has also provided consults regarding the Human Factors elements associated with this device on July 22, 2010. We amended our consult on August 3, 2010, to reflect an assessment of a 2008 clinical study that the Sponsor had performed in support of device usability. CDRH's concerns regarding Human Factors were submitted to the Sponsor. The Sponsor provided additional information regarding the Human Factors Study on August 20, 2010.

CDER and CDRH had a discussion regarding CDRH's concerns on August 23, 2010. At this meeting, CDER discussed CDRH's concerns regarding device performance and human factors. Based on this discussion, CDRH has updated our review memo to reflect the most current information associated with this submission.

2. **Documents**

Device Performance:

August 2, 2010 amendment to S-007

August 9, 2010 amendment to S-007

Human Factors:

NDA 2159 Use testing materials (Response to May 11, 2010 FDA Information Request);  
prior review Alan Stevens (4/29/2010)

Subsequent review of Study 34530, Clinical Trial Report (as per this amended review)

**3. Review**

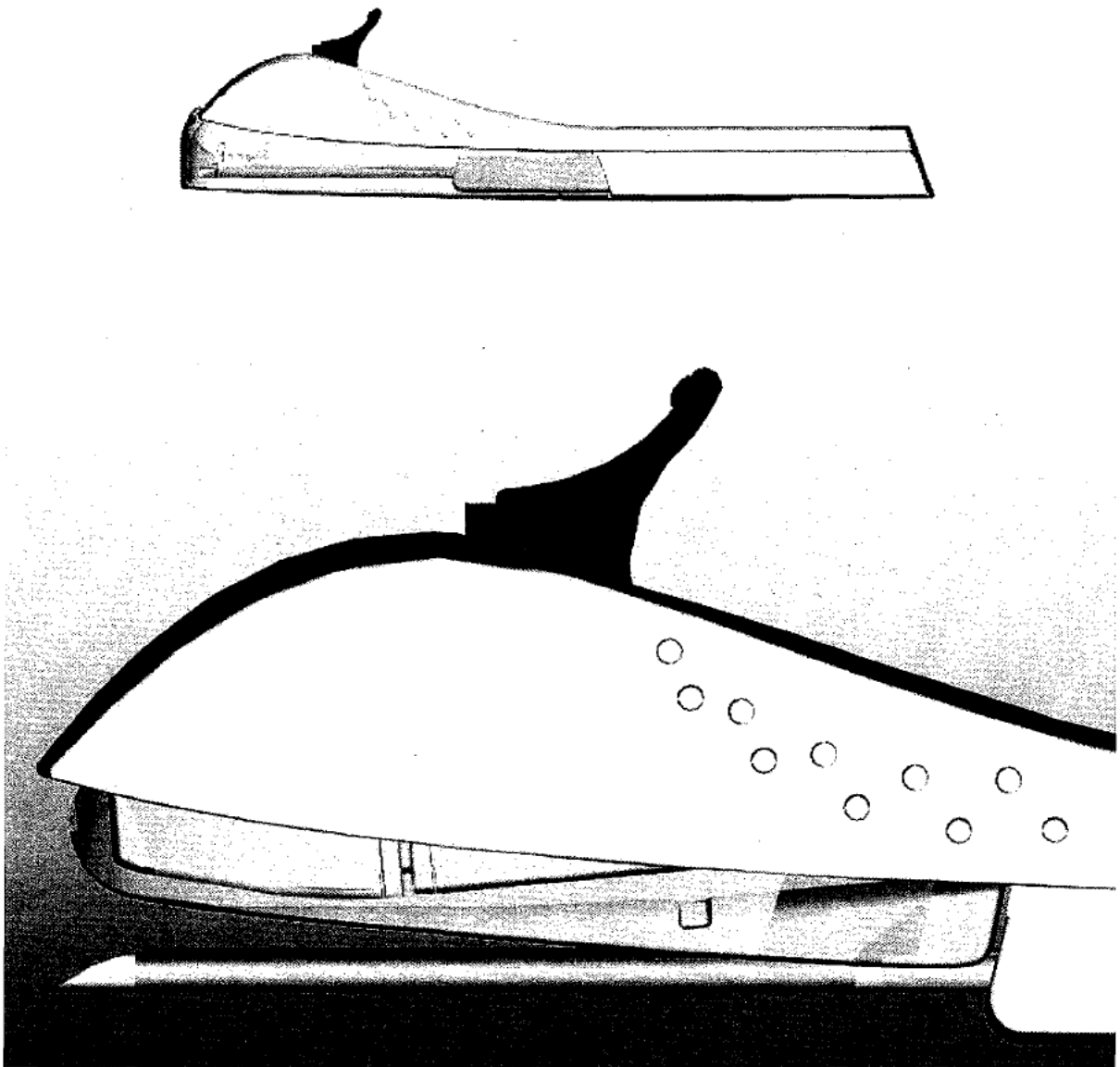
The product consists of an implant, placed inside an applicator. The implant consists of a core containing a mixture of the drug substance etonogestrel (Org 3236), barium sulfate and ethylene vinylacetate copolymer with a vinylacetate content of 28% and a skin consisting of ethylene vinylacetate copolymer with a vinylacetate content of 14%. Each implant contains 68 mg of etonogestrel. The implant has a length of 4.0 cm and a diameter of 2.0 mm.

CDRH consult is requested for the implant insertion device.

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Device Description

The implant is placed inside a stainless steel needle which is fitted to an applicator. The loaded applicator is placed in a (b) (4) tray which is subsequently sealed with lidding foil.



The implant is meant to be inserted subdermally. It should be palpable after insertion. In order to facilitate the manual handling of the applicator by healthcare providers the Next Generation Implanon Applicator (NGIA, new applicator) has been developed. As is the case for the current applicator, the new applicator is a ready-for-use disposable applicator where the implant is pre-filled in the stainless steel needle of the applicator.

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ON ORIGINAL

**Device Function**

- Step 1: The needle protection cap assures that the implant remains inside the needle (1). In case of absence of an implant in the needle, the needle protection cap can not easily be removed as the lever (3 in Step 2) will block the needle protection cap movement.
- Step 2: Upon removal of the protection cap away from the needle (2) the lever (3) holds the implant in place in the needle.
- Step 3: The shape of the applicator and position of the handle relative to the needle should support proper subdermal insertion of the needle. Upon insertion the lever (4) is pushed upward thereby “releasing” the implant.
- Step 4: While keeping the applicator in the same position after the needle has been inserted superficially into the subdermal connective tissue, the slider (5) on top of the applicator can be unlocked by pushing it slightly down. By sliding the slider backwards until it is arrested in the back of the slider, the needle is retracted into the applicator housing while the implant (6), held in place by an obturator, is left behind under the skin.
- Step 5: After complete retraction of the slider, the purple tip of the obturator (7) is visible (out of the housing), and the needle is completely retracted into the housing and locked (8); this assures single use of the applicator and should prevent needle stick accidents.

Materials of Construction

<b>Part</b>	<b>Material</b>
<b>Applicator</b>	
Stainless steel needle	Stainless steel
Needle holder/knob and obturator	(b) (4) colored with a purple dye
Needle protection cap	(b) (4)
Lever	(b) (4)
Spring	Stainless steel
Housing parts	(b) (4) colored with a blue dye and (b) (4)
<b>Blister pack</b>	
Blister forming film	(b) (4)
Blister lidding film	(b) (4)

FINAL COMMENTS

On August 23, 2010, CDER and CDRH had a face-to-face meeting to discuss the Sponsor's August 2, 2010 and August 9, 2010, responses regarding device performance, and to discuss the Sponsor's August 20, 2010 clarification regarding the Human Factors studies.

*Regarding the Device Performance Deficiencies:*

CDRH had originally reviewed the Sponsor's August 2, 2010 and August 9, 2010, responses per our review memorandum dated August 19, 2010. In this memorandum we had identified the following deficiencies associated with device performance. Based on the August 23, 2010, meeting with CDER, CDRH has updated our position regarding these deficiencies. The updated language is clarified below.

1. With respect to deep insertions, CDRH was previously unable to conclude that the residual risks of deep insertions are acceptable, because the Sponsor had not provided an analysis of the associated risk to health. We asked that the Sponsor to provide validation that the labeling mitigations are effective and provide a full analysis of the risks to health associated with deep insertions (including risks associated with x-ray and additional steps to correct the deep insertion), which provides a supportable

conclusion that the residual risks are acceptable. The Sponsor's August 9, 2010 response did not appear to adequately argue that the labeling and training mitigations are valid. The response also does not completely analyze the risks to health from deep insertion. We believe the response is deficient in two areas:

- a. Failures appear to be occurring despite the Sponsor's implemented Risk Mitigation Activities. The Sponsor's report 121 US cases of deep insertion. However, they have not analyzed how these deep insertions occurred and why their occurrence does not indicate failure of the risk mitigations. We requested that the Sponsor identify the root cause of the deep insertions (e.g., physician technique, physiological parameters of the patient, etc.), determine if the device design, labeling, or training contributed to the failures, and identify any additional mitigation necessary to prevent deep insertion.
- b. The Sponsor had not provided an analysis of risk to health if the implant cannot be located and removed. We requested that an analysis of risk to health if the implant cannot be located and removed.

*Update based on August 23, 2010, discussion with CDER:*

During this meeting, we reviewed the August 19, 2010 concerns regarding deep insertions. However, CDER explained their belief that the risk of deep insertion could not really be mitigated to "zero." CDRH wanted to ensure that for each occurrence of deep insertion, that the Sponsor was able to determine the root cause of the insertion. CDER felt that there was a reduction in the occurrence of deep insertions with the Implanon device versus the previously approved product. Based on our discussions with CDER, we defer to the CDER clinical team with regard to deep insertions.

2. The Sponsor's August 2, 2010 amendment addresses drop test failures and failures of the device to meet specifications of the test, "*Force to disassemble protection cap from housing (implant not inserted in needle)*".
  - a. For the force to disassemble test, the Sponsor asserted that the failures are likely due to manufacturing defect (assembly error). It is unclear how they have reached this as the likely cause of the failures. The amendment states that since the failed samples met the specification when retested, it implies an assembly error. However, it is unclear how the Sponsor eliminated other possible failure mechanisms as the root cause. It is also unclear how they have retested the device to simulate the actual use of the product. They have not provided the protocol/report for the test. The Sponsor also describes a test of an additional 128 samples (all pass), which was performed "manually" to exclude test artifact. They have not defined manual automatic testing. CDRH asked the Sponsor to provide an analysis detailing the potential failure mechanisms that could lead to the lock-

out feature failing, define manual vs. automated testing, and provide the test protocol/report for the 128 additional samples.

*Update based on August 23, 2010, discussion with CDER:*

During this meeting, we reviewed the August 19, 2010 concerns regarding the failure to meet the specification for the force to disassemble the protection cap from the housing. When the Implanon device is activated, the applicator needle is safely retracted into the body of the device, once the implanon rod is inserted into the patient. Once the needle is retracted, a locking mechanism within the device prevents the user from unintentionally unsheathing the needle from the implanon applicator body. Thus, CDRH agrees with CDER that the protection cap is a secondary mechanism to prevent unintended needle sticks with the implanon needle. CDRH recommends that the labeling for the Implanon device be updated to reflect the appropriate disposal of the applicator in a sharps container or other needle stick prevention receptacle.

*Regarding the Human Factors Deficiencies:*

CDRH had originally reviewed Human Factors studies per our review memorandum dated July 22, 2010. We had amended our review on August 3, 2010, to reflect our assessment of the Sponsor's 2008 clinical study which tested device usability. Based on these reviews, CDRH had the following concerns regarding Human Factors. Based on subsequent review of a later clinical trial that focused on the insertion characteristics of the "next generation applicator" (Study 34530, July 2008) it appears that good performance was obtained for multiple users and actual insertions. It is, however, not clear in that study whether the modifications to the training video and the design of the applicator were made prior to the 2008 study, and whether improvements in terms of user error reduction can be demonstrated from the results of that study. Please provide a summary of the modifications to the device and the training video that were made prior to the 2008 clinical trial and a clarification of their effectiveness based on the results of that study.

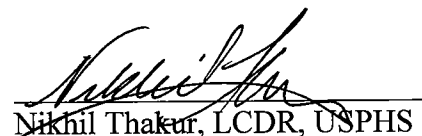
We had also reviewed the Sponsor's August 20, 2010, response clarifying various elements of the human factor studies performed for this device. Based this updated response, and the August 23, 2010, discussion with CDER regarding the Human Factors concerns, we have updated our assessment of the human factors for this device.

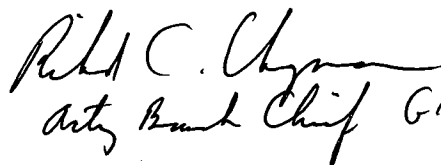
*Update based on August 23, 2010, discussion with CDER:*

Based on our discussion with CDER, it appears that the 2008 clinical study provided data that demonstrated that the Implanon device could be successfully used by multiple users in actual insertions of the Implanon rod into a patient's arm. Although there were still deep insertions associated with the new device, CDER explained that the risk of deep

insertion can never be eliminated due the location where the Implanon rod is inserted. CDER also stated that the clinical risk of deep insertion is minimal given that the Implanon rod contains radiopaque material to locate the rod through x-ray. CDRH defers to CDER with regard to the clinical significance of deep insertions. We believe that the following advisory statement be conveyed to the Sponsor for future human factors efforts.

*“Please be advised that the Agency expects Human Factors/Usability validation testing for all medical devices for which safety and effectiveness outcomes can be impacted by the ability of users to use the device. Specific evaluations involving simulated or actual use should focus on user's interaction with the device and prioritize consideration of the most critical tasks for data collection and reporting. Problems with use should be described in terms of user actions, failure to act or misperceptions or misinterpretations. Data from Human Factors/Usability tests and evaluations should include assessment of user performance as well as subjective assessment by users involved and these apply most importantly to instances where errors, close calls or outright failures occurred during use. Modifications to the design of the device, training, IFU or accessories intended to improve use should be reevaluated to demonstrate effectiveness. The Agency will no longer accept Human Factors/Usability validation studies for which these considerations are not clearly presented.”*

  
Nikhil Thakur, LCDR, USPHS  
Combination Products Team Leader  
General Hospital Devices Branch  
Division of Anesthesiology, General Hospital  
Infection Control and Dental Devices  
Center for Devices and  
Radiological Health

  
Acty Branch Chief GHOB 8/25/10

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	SUPPL-7	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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/s/

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ZETA-MAE C WILLIAMSON  
08/30/2010

## SEALD LABELING REVIEW

This review identifies aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 021529
APPLICANT	Organon USA, Inc.
DRUG NAME	TRADENAME (etonogestrel implant)
SUBMISSION DATE	July 30, 2009
PDUFA DATE	August 30, 2010
SEALD REVIEW DATE	August 24, 2010
SEALD LABELING REVIEWER	Jun Yan, Pharm.D.

Outlined below are the following outstanding labeling issues that must be corrected before the final draft labeling is approved. Issues are listed in the order mandated by the regulations or guidance.

If there are no issues for a particular heading in highlights (HL) or for sections in the full prescribing information (FPI), “none” is stated. If clearly inapplicable sections are omitted from the FPI, “not applicable” is stated. In addition, “not applicable” is stated if optional headings (i.e., Drug Interactions or Use in Specific Populations) are omitted from HL.

### Highlights (HL):

- **Highlights Limitation Statement:** None.
- **Product Title Line:** None.
- **Initial U.S. Approval:** None.
- **Boxed Warning:** N/A.
- **Recent Major Changes:** N/A.
- **Indications and Usage:** N/A.
- **Dosage and Administration:** None.
- **Dosage Forms and Strengths:** None.
- **Contraindications:** None.
- **Warnings and Precautions:** None.

## SEALD LABELING REVIEW

- **Adverse Reactions:** None.
- **Drug Interactions:** None.
- **Use in Specific Populations:** None.
- **Patient Counseling Information Statement:** None.
- **Revision Date:** Ensure the date is filled in by the review division at the time of approval. Do not leave blank.

### Table of Contents (TOC):

None.

### Full Prescribing Information:

**Boxed Warning:** N/A.

**1 Indications and Usage:** None.

**2 Dosage and Administration:** None.

**3 Dosage Forms and Strengths:** None.

**4 Contraindications:** None.

**5 Warnings and Precautions:** None.

**6 Adverse Reactions:** Ensure that the final labeling discusses adverse *reactions*, not events, in this section. See 21 CFR 201.57(c)(7).

**7 Drug Interactions:** None.

**8 Use in Specific Populations:** None.

**9 Drug Abuse and Dependence:** N/A.

**10 Overdosage:** None.

**11 Description:** None.

**12 Clinical Pharmacology:** None.

## SEALD LABELING REVIEW

**13 Nonclinical Toxicology:** None.

**14 Clinical Studies:** None.

**15 References:** N/A.

**16 How Supplied/Storage and Handling:** None.

**17 Patient Counseling Information:** None.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	SUPPL-7	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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/s/

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JUN YAN  
08/24/2010

LAURIE B BURKE  
08/26/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
White Oak Building 66  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Date:** August 19 2010

**From:** Mechanical Engineer  
General Hospital Devices Branch, DAGID, ODE, CDRH

**To:** Dr. Theresa Van der Vlugt, Medical Officer  
DRUP/ODE3/OND/CDER

**Subject:** NDA 021529, Amendment to Supplemental NDA (S-007)

**1. Issue**

Device review to support NDA 021529 was first provided on April 29, 2010.

Follow-up consult was provided on July 7, 2010.

CDER issued Information Requests to the sponsor on July 7, 2010 and July 27, 2010.

CDER is now requesting that CDRH review the sponsor's responses, dated August 2, 2010 and August 9, 2010.

**2. Documents**

August 2, 2010 amendment to S-007

August 9, 2010 amendment to S-007

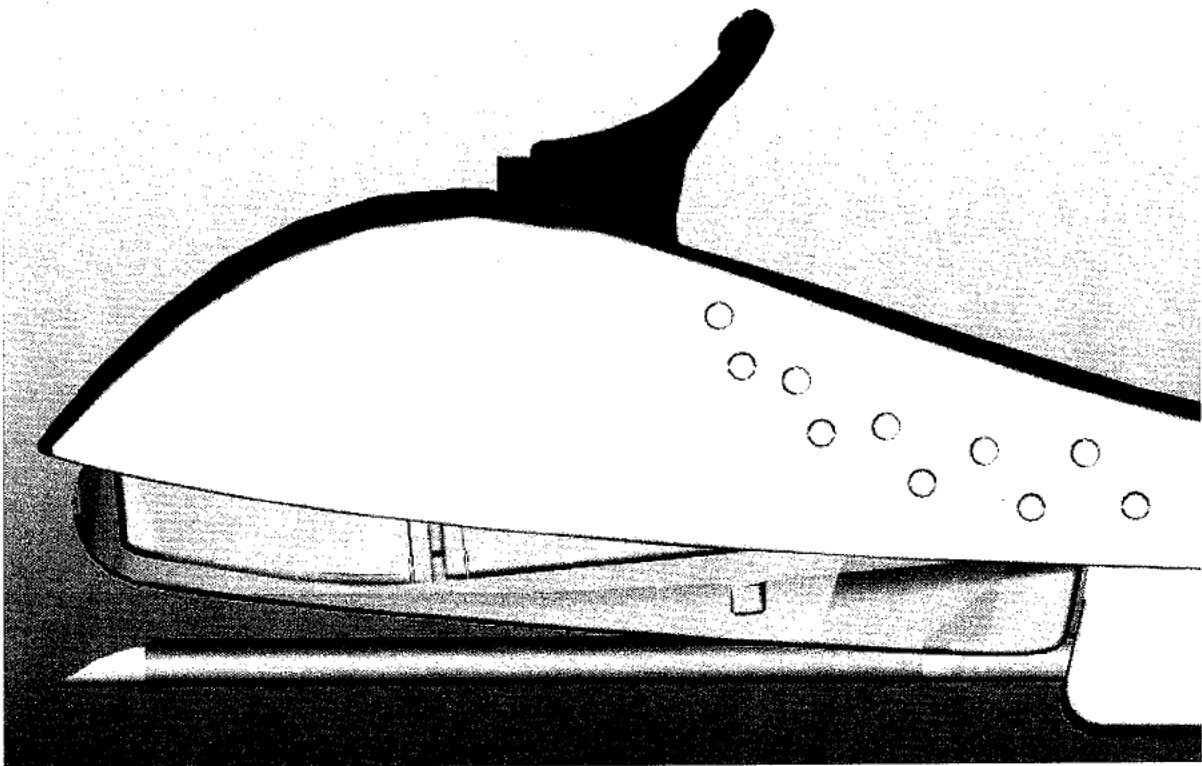
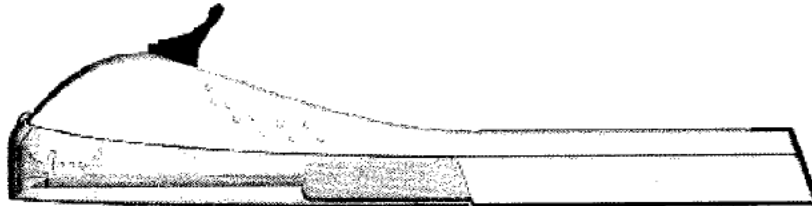
**3. Review**

The product consists of an implant, placed inside an applicator. The implant consists of a core containing a mixture of the drug substance etonogestrel (Org 3236), barium sulfate and ethylene vinylacetate copolymer with a vinylacetate content of 28% and a skin consisting of ethylene vinylacetate copolymer with a vinylacetate content of 14%. Each implant contains 68 mg of etonogestrel. The implant has a length of 4.0 cm and a diameter of 2.0 mm.

CDRH consult is requested for the implant insertion device.

Device Description

The implant is placed inside a stainless steel needle which is fitted to an applicator. The loaded applicator is placed in a (b) (4) tray which is subsequently sealed with lidding foil.



The implant is meant to be inserted subdermally. It should be palpable after insertion. In order to facilitate the manual handling of the applicator by healthcare providers the Next Generation Implanon Applicator (NGIA, new applicator) has been developed. As is the case for the current applicator, the new applicator is a ready-for-use disposable applicator where the implant is pre-filled in the stainless steel needle of the applicator.

**Device Function**

- Step 1: The needle protection cap assures that the implant remains inside the needle (1). In case of absence of an implant in the needle, the needle protection cap can not easily be removed as the lever (3 in Step 2) will block the needle protection cap movement.
- Step 2: Upon removal of the protection cap away from the needle (2) the lever (3) holds the implant in place in the needle.
- Step 3: The shape of the applicator and position of the handle relative to the needle should support proper subdermal insertion of the needle. Upon insertion the lever (4) is pushed upward thereby “releasing” the implant.
- Step 4: While keeping the applicator in the same position after the needle has been inserted superficially into the subdermal connective tissue, the slider (5) on top of the applicator can be unlocked by pushing it slightly down. By sliding the slider backwards until it is arrested in the back of the slider, the needle is retracted into the applicator housing while the implant (6), held in place by an obturator, is left behind under the skin.
- Step 5: After complete retraction of the slider, the purple tip of the obturator (7) is visible (out of the housing), and the needle is completely retracted into the housing and locked (8); this assures single use of the applicator and should prevent needle stick accidents.

Materials of Construction

Part	Material
<b>Applicator</b>	
Stainless steel needle	Stainless steel
Needle holder/knob and obturator	(b) (4) colored with a purple dye
Needle protection cap	(b) (4)
Lever	(b) (4)
Spring	Stainless steel
Housing parts	(b) (4) colored with a blue dye and (b) (4)
<b>Blister pack</b>	
Blister forming film	(b) (4)
Blister lidding film	(b) (4)

**Sponsor Response to July 7, 2010 Deficiencies Request**

- I. *In your risk management report, you had identified several residual risks. One of these is identified as "too deep insertions" whereby the implant is delivered at a greater than desired depth into the tissue.*

*Your FMEA states that the applicator is designed to prevent incorrect positioning of the applicator relative to the skin. However, the FMEA also documents clinical results, which demonstrate that the implant may be delivered deeper than desired. You conclude that the residual risks are acceptable. However, you have not provided an analysis of the risks to health from a deep insertion. Your report concluded that the implant may be imaged on x-ray. It is unclear what further steps are to be taken after imaging the deep implant. Your report identifies several labeling mitigations. However, no data or information is presented to demonstrate that these mitigations are effective.*

*CDRH is unable to conclude that the residual risks are acceptable, because you have not provided an analysis of the associated risk to health. Provide validation that the labeling mitigations are effective and provide a full analysis of the risks to health associated with deep insertions (including risks associated with x-ray and additional steps to correct the deep insertion), which provides a supportable conclusion that the residual risks are acceptable.*

## **SPONSOR RESPONSE**

Implanon and radiopaque Implanon should be inserted subdermally just under the skin. During the use of Implanon, there is a small risk that the implant is inserted too deeply. As outlined below, the risk of deep insertion as well as the risk to health from a deep insertion is considered small.

The next generation Implanon applicator (NGIA) is designed to facilitate correct insertion. The shape of the applicator and position of its body relative to the needle should help ensure proper superficial subdermal insertion of the needle. Although the NGIA design should minimize very deep insertion, the design cannot fully prevent deep insertions (per Failure Mode and Affect Analysis (FMEA) of the NGIA during development). Consequently, this was one of the remaining risks as reported in the final risk management report. However, by its design the NGIA is expected to further reduce the already low risk of deep insertion and associated risk to health.

### Data from the Active Monitoring Program (AMP)

The Sponsor is currently performing an AMP for Implanon. US Health Care Professionals (HCPs) who have been trained in the Implanon Clinical Training Program (CTP) are encouraged to participate in the AMP. Data are collected by means of an Insertion Evaluation Form (IEF) and a Removal Evaluation Form (REF), which are completed by the participating HCP after each insertion and removal. From market introduction in the US through 16JUL2010 a total of (b) (4) IEFs have been received from the AMP program ((b) (4) insertions). Of these, only 19 cases of deep insertions have been reported. This corresponds to a reporting rate of (b) (4)%.

### Data from spontaneous post-marketing reporting in the US

From market introduction through 16JUL2010 it is estimated that (b) (4) implants have been inserted in the US outside the AMP. From US launch through 16JUL2010 a total 121 US cases of deep insertions have been reported spontaneously to the Sponsor. This corresponds to a reporting rate of (b) (4)%.

### Health Risks Related to Deep Insertions (Data for Implanon in the US)

Deep insertions can be associated with the following health risks:

- Injury to neurovascular structures
- Difficult implant localization
- Difficult implant removals

### Risk Mitigation Activities

The following activities to mitigate the risk of deep insertion are currently in place for Implanon in the US and are proposed for the radiopaque implant inserted using the NGIA:

1. Mandatory CTP and Controlled Distribution

All US HCPs must enroll in a Mandatory CTP where they learn how to correctly insert and remove the implant. The Mandatory CTP is coupled to a controlled distribution, whereby only trained HCPs can order the implant.

2. Correct instructions and warnings in the labeling

The labeling contains clear instructions on the correct insertion, localization and removal of the implant. Furthermore, the labeling contains specific warnings on deep insertion and the possible consequences of deep insertion.

### **CDRH REVIEW**

**The sponsor was asked to argue that the labeling mitigations are valid and analyze the risks to health from deep insertion. The sponsor has failed to adequately respond to this request in two ways.**

- 1. Failures are occurring despite the sponsor's implemented Risk Mitigation Activities. The sponsor reports 121 US cases of deep insertion. They have not analyzed how these deep insertions occurred and why their occurrence does not indicate failure of the risk mitigations. The sponsor should identify the root cause of the deep insertions (e.g., physician technique, physiological parameters of the patient, etc.).**
- 2. The sponsor was asked to analyze the risks to health. The sponsor provides no analysis of risk to health if the implant cannot be located and removed.**

**The sponsor concludes that risks are acceptable because reporting rates are low. The stated design requirement for the Implanon device is to facilitate correct subdermal insertion. It is not clear that the sponsor has adequately verified and validated this design requirement.**

**The sponsor should analyze all cases of deep insertion to determine how and why they occurred. The analysis should determine if the device design, labeling, or training contributed to the failures.**

*II. For the design verification test, "Force to disassemble protection cap from housing (implant not inserted in needle)" [SOP 0002 (document # 3-0271-TRAP- 0049, v.3.0)], the requirement is Force (b)(4) The test results demonstrate several results (b)(4) (b)(4) It does not appear that you have addressed these failures.*

*For the drop test, your stated design requirements are no device deformation and device functionality. The results demonstrate several test samples with deformation, which were also non-functional. You have not addressed these failures.*

*Please address failures for both tests, including the cause of the failures, corrections to prevent recurrence of the failures, and provide verification that the corrections are effective.*

**SPONSOR RESPONSE**

**Force to Removal Failures**

The sponsor indicates that the failures are due to operator error during assembly of the applicator.

All applicators with results from the pull-off force below (b) (4) were visually inspected. The applicators with initial results below (b) (4) showed very minor damage. The applicators with initial results above (b) (4) showed more substantial damage of the locking features. (It should be emphasized that pulling the protection cap off while the locking mechanism is activated will result in the deformation of applicator parts, due to the design of the applicator.) Following visual inspection, the protection cap was placed back on all applicators. Upon manual testing, it was noted that the locking mechanism functioned properly in all devices.

The same parts with results from the pull-off force below (b) (4) were subsequently retested according to 3-0271-SOP-003 (NDA 21-529/S-007, Serial Submission No. 110, Appendix 4). The results are summarized in Table 1 below.

Table 1: Summary of pull-off force results (3-0271-SOP-003)

(b) (4)

Based on these results, the likely cause of the initial failures is operator error during applicator assembly. Since specific part combinations were assembled for these tests, the assembly had to be performed manually. If the cap is not assembled properly on the device, the locking mechanism will not function properly.

A functional assessment of the locking mechanism was done for an additional 128 applicators. This test was performed manually to exclude any potential effect of the test setup. It was confirmed that all 128 applicators showed a properly working locking mechanism.

## **CDRH REVIEW**

**The sponsor asserts that the failures are likely due to manufacturing defect (assembly error). It is unclear how the sponsor has reached this as the only possible conclusion. The sponsor states that since the failed samples met the specification when retested, it implies the assembly error. However, it is unclear how the sponsor retested the device to simulate the actual use of the product. The sponsor has not provided the protocol/report for the test. They describe a test of an additional 128 samples (all pass), which was performed “manually” to exclude test artifact. The sponsor has not defined manual vs. automatic testing. Additional information is required.**

### Drop Test Failures

A risk-based approach was taken to determine if these failures could be accepted. Based on this approach it was decided to accept the failures because of the following rationale:

- The likelihood that the applicator is unintentionally dropped by the physician after removing from its primary pack is considered low.
- The functional test is performed in a worst-case condition, by dropping the applicator with the housing back facing exactly downward, from a 1 meter height onto a steel plate. This test setup leads to a direct impact on the plunger part of the applicator. If an applicator is unintentionally dropped, the likelihood is considered low that an applicator will fall exactly with the housing back pointing downward. During unintended dropping, the applicator will be at a random orientation since the applicator is likely to rotate somewhat because of the weight distribution.
- If the applicator would be dropped at the worst-case position, the likelihood that the plunger breaks is considered low because even under this condition, only 2 plungers out of 100 tested applicators broke (and in only 1 of these led to a non functional device).
- If an applicator would be dropped at the worst-case position and if the plunger would break, the likelihood that the product would actually be used by the physician is considered low because the plunger part is clearly broken or fallen apart. In addition the insertion has to be performed under aseptic conditions, as the physician is clearly instructed in the physician package insert. Therefore, an applicator dropped on the floor will be discarded in the clinical setting as aseptic conditions are compromised.

## **CDRH REVIEW**

**The sponsor accepts the results based on their above-stated points. The sponsor states that the applicator will not be used if dropped. It is unclear to me that this assertion is true. If the sponsor wants to accept these data, I recommend that they modify the**

**labeling and training to identify that dropped applicators may not be used because data demonstrate functional damage may occur and non-aseptic conditions may occur.**

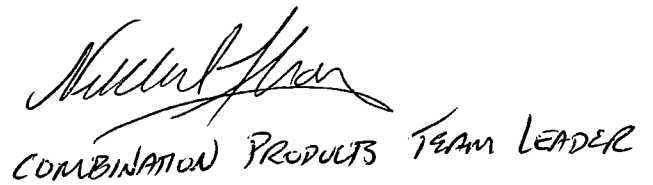
**RECOMMENDED DEFICIENCIES**

1. We were previously unable to conclude that the residual risks of deep insertions are acceptable, because you had not provided an analysis of the associated risk to health. We asked that you provide validation that the labeling mitigations are effective and provide a full analysis of the risks to health associated with deep insertions (including risks associated with x-ray and additional steps to correct the deep insertion), which provides a supportable conclusion that the residual risks are acceptable. Your August 9, 2010 response does not adequately argue that the labeling and training mitigations are valid. The response also does not completely analyze the risks to health from deep insertion. We believe the response is deficient in two areas:
  - a. Failures appear to be occurring despite your implemented Risk Mitigation Activities. You report 121 US cases of deep insertion. However, you have not analyzed how these deep insertions occurred and why their occurrence does not indicate failure of the risk mitigations. Identify the root cause of the deep insertions (e.g., physician technique, physiological parameters of the patient, etc.), determine if the device design, labeling, or training contributed to the failures, and identify any additional mitigation necessary to prevent deep insertion.
  - b. You have not provided an analysis of risk to health if the implant cannot be located and removed. Provide an analysis of risk to health if the implant cannot be located and removed.
  
2. Your August 2, 2010 amendment addresses drop test failures and failures of the device to meet specifications of the test, "*Force to disassemble protection cap from housing (implant not inserted in needle)*".
  - a. For the force to disassemble test, you assert that the failures are likely due to manufacturing defect (assembly error). It is unclear how you have reached this as the likely cause of the failures. Your amendment states that since the failed samples met the specification when retested, it implies an assembly error. However, it is unclear how you eliminated other possible failure mechanisms as the root cause. It is also unclear how you have retested the device to simulate the actual use of the product. You have not provided the protocol/report for the test. You also describe a test of an additional (b)(4) samples (all pass), which was performed (b)(4) to exclude test artifact. You have not defined (b)(4) testing. Provide an analysis detailing the potential failure mechanisms that could lead to the lock-out feature failing, define (b)(4) testing, and provide the test protocol/report for the (b)(4) additional samples.

- b. For the drop test, you have determined to accept the failures because an applicator dropped on the floor will be discarded in the clinical setting as aseptic conditions are compromised. Based on your assessment, we believe it is appropriate to include statements in the labeling warning that dropped applicators should not be used because aseptic conditions may be compromised and preclinical data demonstrate that functional damage to the applicator may occur, rendering the applicator inoperable. Please update the labeling accordingly.



LCDR Alan Stevens



COMBINATION PRODUCTS TEAM LEADER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-21529	----- SUPPL-7	----- ORGANON USA INC	----- IMPLANON (ETONOGESTREL IMPLANT) 68MG

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/s/

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ZETA-MAE C WILLIAMSON  
08/20/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
White Oak Building 66  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Date:** July 7, 2010

**From:** Mechanical Engineer  
General Hospital Devices Branch, DAGID, ODE, CDRH

**To:** Dr. Catherine Tran-Zwanetz, Consumer Safety Officer  
ONDQA, OPS, CDER

**Subject:** NDA 021529, Amendment to Supplemental NDA (S-007)

1. **Issue**

Device review to support NDA 021529 was first provided on April 29, 2010.

CDER issued an Information Request to the sponsor on May 11, 2010.

CDER requests CDRH review the sponsor's response, dated June 7, 2010.

2. **Documents**

NDA 021529 (S-007)  
June 7, 2010 Amendment

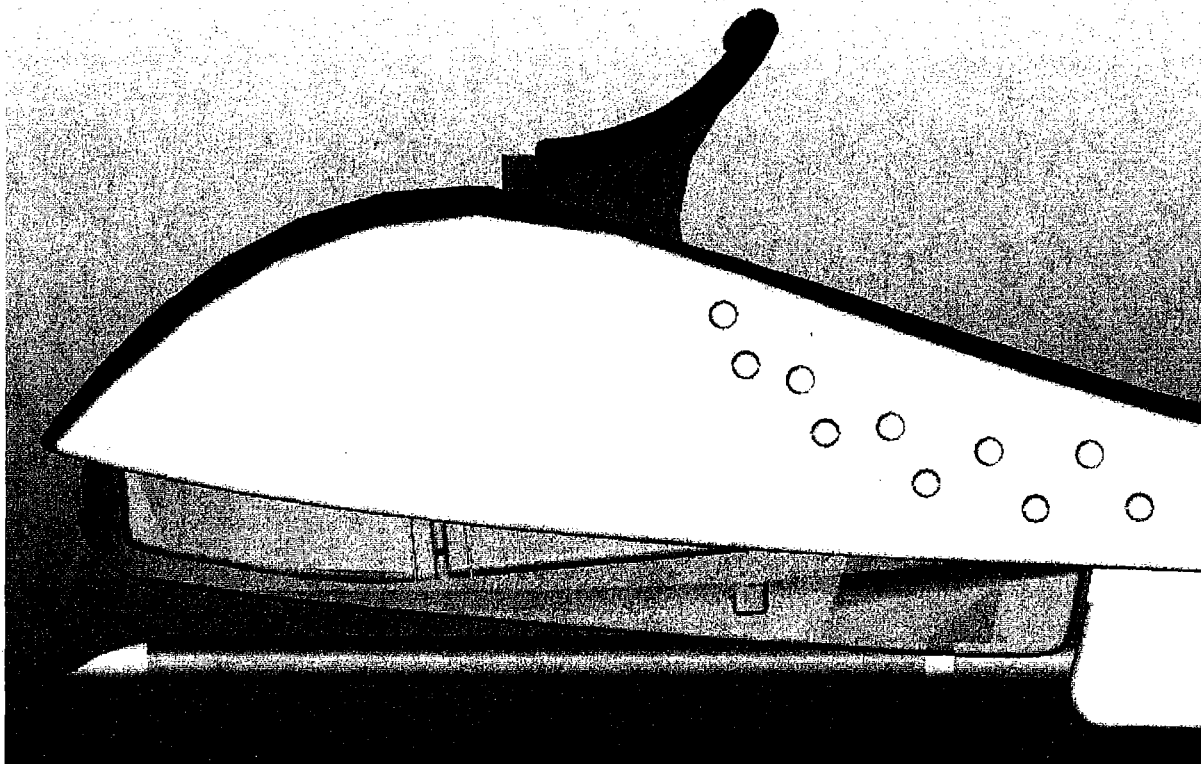
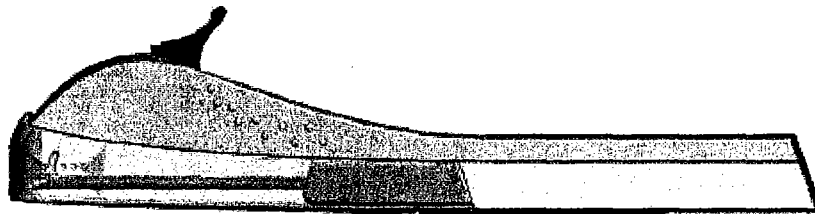
3. **Review**

The product consists of an implant, placed inside an applicator. The implant consists of a core containing a mixture of the drug substance etonogestrel (Org 3236), barium sulfate and ethylene vinylacetate copolymer with a vinylacetate content of 28% and a skin consisting of ethylene vinylacetate copolymer with a vinylacetate content of 14%. Each implant contains 68 mg of etonogestrel. The implant has a length of 4.0 cm and a diameter of 2.0 mm.

CDRH consult is requested for the implant insertion device.

**Device Description**

The implant is placed inside a stainless steel needle which is fitted to an applicator. The loaded applicator is placed in a (b) (4) tray which is subsequently sealed with lidding foil.



The implant is meant to be inserted subdermally. It should be palpable after insertion. In order to facilitate the manual handling of the applicator by healthcare providers the Next Generation Implanon Applicator (NGIA, new applicator) has been developed. As is the case for the current applicator, the new applicator is a ready-for-use disposable applicator where the implant is pre-filled in the stainless steel needle of the applicator.

**Device Function**

- Step 1: The needle protection cap assures that the implant remains inside the needle (1). In case of absence of an implant in the needle, the needle protection cap can not easily be removed as the lever (3 in Step 2) will block the needle protection cap movement.
- Step 2: Upon removal of the protection cap away from the needle (2) the lever (3) holds the implant in place in the needle.
- Step 3: The shape of the applicator and position of the handle relative to the needle should support proper subdermal insertion of the needle. Upon insertion the lever (4) is pushed upward thereby “releasing” the implant.
- Step 4: While keeping the applicator in the same position after the needle has been inserted superficially into the subdermal connective tissue, the slider (5) on top of the applicator can be unlocked by pushing it slightly down. By sliding the slider backwards until it is arrested in the back of the slider, the needle is retracted into the applicator housing while the implant (6), held in place by an obturator, is left behind under the skin.
- Step 5: After complete retraction of the slider, the purple tip of the obturator (7) is visible (out of the housing), and the needle is completely retracted into the housing and locked (8); this assures single use of the applicator and should prevent needle stick accidents.

Materials of Construction

Part	Material
<b>Applicator</b>	
Stainless steel needle	Stainless steel
Needle holder/knob and obturator	(b) (4) colored with a purple dye
Needle protection cap	(b) (4)
Lever	(b) (4)
Spring	Stainless steel
Housing parts	(b) (4) colored with a blue dye and (b) (4)
<b>Blister pack</b>	
Blister forming film	(b) (4)
Blister lidding film	(b) (4)

Sponsor Response to May 11, 2010 Information Request

<p>1. Your submission references risk management, design verification and validation efforts with respect to the implant delivery system. The underlying elements have not been provided for review, and we are therefore unable to determine if your conclusions regarding the device component safety and effectiveness are adequate. Please provide the following information related to your device component:</p>	
<p><b>Risk Management Report</b></p>	<p><b><u>SPONSOR RESPONSE</u></b></p> <p>Risk management has been applied at various development stages. The risk management process covers the various components of the NGIA (design), the manufacturing process (process) and clinical use (use), based on the relevant parts of the FDA-recognized international standard ISO14971:2003. The Failure Mode and Effect Analyses method (FMEA) was adapted as a risk management technique.</p> <p>Risk management has been applied at 3 levels:</p> <ol style="list-style-type: none"> <li>1. At the applicator level using the list of possible hazards as stated in the ISO 14971:2003 standard (Design FMEA).</li> <li>2. At the process level considering the risks per detailed step from manufacturing until disposal of the applicator by the physician after use (Product Process Tree FMEA)</li> </ol>

3. At the component level considering the risks of malfunction for each individual part of the applicator (Product Parts FMEA)  
 The final "Risk Management Report" (version 8.00) and the above mentioned FMEAs are given in Appendix 1.

**CDRH REVIEW – INADEQUATE**

The sponsor's report describes the risk estimation, evaluation and analysis process.

The sponsor identifies the following residual risks and the associated risk/benefit analysis:

Residual risk	Risk benefit analysis
- Cap coming loose after dropping the applicator	Cap needs to be easily removable during the procedure because otherwise the physician might cut himself when the cap suddenly comes off after using more force. This contradicts with the cap staying in place when the applicator is dropped. Therefore it is accepted that the cap can come loose when the applicator is dropped. The physician is obliged to and urged to discard contaminated applicators. The instructions are very clear on this point.
- too deep insertions	Due to the design of the next generation applicator, too deep insertions are less likely to occur compared to the current applicator. However it is still possible to insert the implant too deep, which may result in a situation that the presence of the implant cannot be checked by palpation and might lead to problems at removal. The Clinical Trial Report (study 34530) concludes: "The Next Generation Applicator is an appropriate device". Considering the change of the applicator design, the situation for this use scenario with the NGIA is definitely improved, compared to the current applicator. In addition, since the implant is now made radio opaque, the presence of the implant can easily be verified by x-ray. The user test results also show that the instruction video is a good complementary way of instruction for the physician. As a result of this clinical study a recommendation to perform the insertion in a sitting position and a warning that the needle needs to be inserted completely has been added to the insertion instructions.
- user forgets to check if Implanon is correctly inserted	A check by palpation for the presence and position of the implant in the arm of the patient shall remain an important part of the instructions for the physician. Use test results (ref 1) show that the instruction video (ref 2) is a good complementary way of instruction for the physician. In addition the SmPC, which includes the insertion instructions, also clearly states that the presence of the implant should always be checked by palpation.

I accept the sponsor's analysis of the first and third residual risks. The sponsor has adequately analyzed these issues.

	<p>The second residual risk is identified as “too deep insertions” whereby the implant is delivered at a greater than desired depth into the tissue.</p> <p>The sponsor’s FMEA states that the applicator is designed to prevent incorrect positioning of the applicator relative to the skin. However, The use tests demonstrate that the implant may be delivered deeper than desired. The sponsor concludes that the residual risks are acceptable. However, there is no analysis of the risk to health from a deep insertion. The sponsor only concludes that the implant may be imaged on x-ray. It is unclear what further steps are to be taken after imaging the deep implant.</p> <p>The design requirement to prevent incorrect positioning on the skin is apparently not verified or validated given that deep insertions occurred during clinical study.</p> <p>The sponsor’s analysis identifies several labeling mitigations. However, no data are presented to demonstrate that these mitigations are effective. The sponsor should validate that the labeling mitigations are effective and provide a full analysis of the risks to health associated with deep insertions, which provides a supportable conclusion that the risks are acceptable.</p>
<p><b>Design Verification</b></p>	<p><b><u>SPONSOR RESPONSE</u></b></p> <p>At the start of the NGIA development the “Detailed Design Requirements” (DDR) were defined. The DDR defines all requirements on the basis of a risk assessment involving the intended user, clinical use of the applicator and experiences with the current applicator. At the various development stages the functional design of the applicator was tested against the DDR. The results were laid down in design qualification reports.</p> <p>During the various stages of development the NGIA was tested against pre-determined acceptance criteria as derived from the Detailed Design Requirements. The final design verification tests were performed with the NGIA that was produced from the multi-cavity moulds that will also be used for commercial production. The “Design Verification Summary Report” 3-0271-REP-0168-2-0 (Appendix 2) summarizes the acceptance criteria and the conclusions, and refers test procedures and results. The individual design verification “procedures” providing detailed descriptions, “test results and conclusions” can be found in Appendix 3 and Appendix 4, respectively.</p> <p>Attached in Appendix 5 is the final version of the “Design Qualification Report”, qualifying the design of the commercial product using the outcome of the above design verification studies. The “Design Qualification Report” lists all requirements from the DDR and additional requirements related to</p>

	<p>risk management of issues that have come up during development. Further, the report qualifies the design of the applicator and lists the references to the relevant reports in which the detailed qualification data are documented.</p>
	<p><b><u>CDRH REVIEW</u></b>          I have completed a review of the documentation provided in Appendices 2-5. The sponsor appears to have met most of the design requirements.</p> <p><b><u>Deficiencies</u></b>          For the design verification test, “Force to disassemble protection cap from housing (implant not inserted in needle)” [SOP 0002 (document # 3-0271-TREP-0049, v.3.0)], the requirement is Force (b) (4). The test results demonstrate several results as (b) (4). The sponsor does not appear to have addressed these failures.</p> <p>For the drop test, the requirements are no device deformation and device functionality. The results demonstrate several test samples with deformation, which were also non-functional. The sponsor has not addressed these failures.</p>
<p><b>Human Factors</b></p>	<p>Refer to review from CDRH Human Factors expert, Ron Kaye.</p>
<p><b>Release Specifications</b></p>	<p><b><u>SPONSOR RESPONSE</u></b>          Quantitative measurement of NGIA functionality is incorporated into the in-process testing during applicator manufacture. After completing assembling of the front assembly and attachment to the back assembly, the force to unlock and retract the needle is measured. As described in Appendix 7 (3-271- SOP-0023 -2_0 force to unlock and retract the needle holder with weight), the following acceptance criteria apply:          The evaluated measuring range is (b) (4)          Warning level: (b) (4)          Maximum force of needle holder retraction: (b) (4)</p> <p>In the final assembly process of the drug product, the implant is placed in the needle and the two applicator parts are fixed together without additional heating or gluing. Therefore, this final process step does not impact the functionality of the applicator in terms of the force to unlock or retract the needle. As a consequence, the final (b) (4) release test for NGIA functionality gives added assurance of product quality in terms of the</p>

	<p>following requirements:</p> <ul style="list-style-type: none"> <li>-The needle holder has been retracted completely without hampering or blocking.</li> <li>-The needle holder has locked in the end position.</li> <li>-The implant has completely been ejected from the needle.</li> </ul> <p>In conclusion, quantitative testing during NGIA assembly and qualitative testing following the final assembly process of the drug product is adequate and sufficient to control functionality requirements of the applicator.</p> <p><b><u>CDRH REVIEW – Acceptable</u></b></p> <p>The sponsor’s response on this point is adequate.</p>
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### **RECOMMENDED DEFICIENCIES**

**NOTE TO CDER: The first deficiency identifies a problem with the sponsor’s design Risk Management Report. The deficiency itself is clinical in nature, and therefore, I will defer to the CDER medical officer to determine if the residual risks associated with “deep insertions” are acceptable. If deemed acceptable by the medical officer based on the current information in the submission, then I would agree that it is unnecessary to submit the first deficiency to the sponsor.**

1. In your risk management report, you identify several residual risks. One of these is identified as “too deep insertions” whereby the implant is delivered at a greater than desired depth into the tissue.

Your FMEA states that the applicator is designed to prevent incorrect positioning of the applicator relative to the skin. However, the FMEA also documents clinical results, which demonstrate that the implant may be delivered deeper than desired. You conclude that the residual risks are acceptable. However, you have not provided an analysis of the risks to health from a deep insertion. Rather, your report concludes that the implant may be imaged on x-ray. It is unclear what further steps are to be taken after imaging the deep implant. Your report identifies several labeling mitigations. However, no data or information is presented to demonstrate that these mitigations are effective.

We are unable to conclude that the residual risks are acceptable, because you have not provided an analysis of the associated risks to health. Please provide validation that the labeling mitigations are effective and provide a full analysis of the risks to health associated with deep insertions (including risks associated with x-ray and additional steps to correct the deep insertion), which provides a supportable conclusion that the residual risks are acceptable.

2. For the design verification test, "Force to disassemble protection cap from housing (implant not inserted in needle)" [SOP 0002 (document # 3-0271-TREP-0049, v.3.0)], the requirement is Force (b) (4). The test results demonstrate several results as (b) (4). It does not appear that you have addressed these failures.

For the drop test, your stated design requirements are no device deformation and device functionality. The results demonstrate several test samples with deformation, which were also non-functional. You have not addressed these failures.

Please address failures for both tests, including the cause of the failures, corrections to prevent recurrence of the failures, and provide verification that the corrections are effective.



LCDR Alan Stevens



TEAM LEADER, COMB. PROJ Aug 2, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-21529	----- SUPPL-7	----- ORGANON USA INC	----- IMPLANON (ETONOGESTREL IMPLANT) 68MG

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

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/s/

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ZETA-MAE C WILLIAMSON  
08/03/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
White Oak Building 66  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Date:** April 29, 2010

**From:** Mechanical Engineer  
General Hospital Devices Branch, DAGID, ODE, CDRH

**To:** Dr. Catherine Tran-Zwanetz, Consumer Safety Officer  
ONDQA, OPS, CDER

**Subject:** NDA 021529

1. **Issue**

Device review to support NDA 021529.

2. **Documents**

NDA 021529

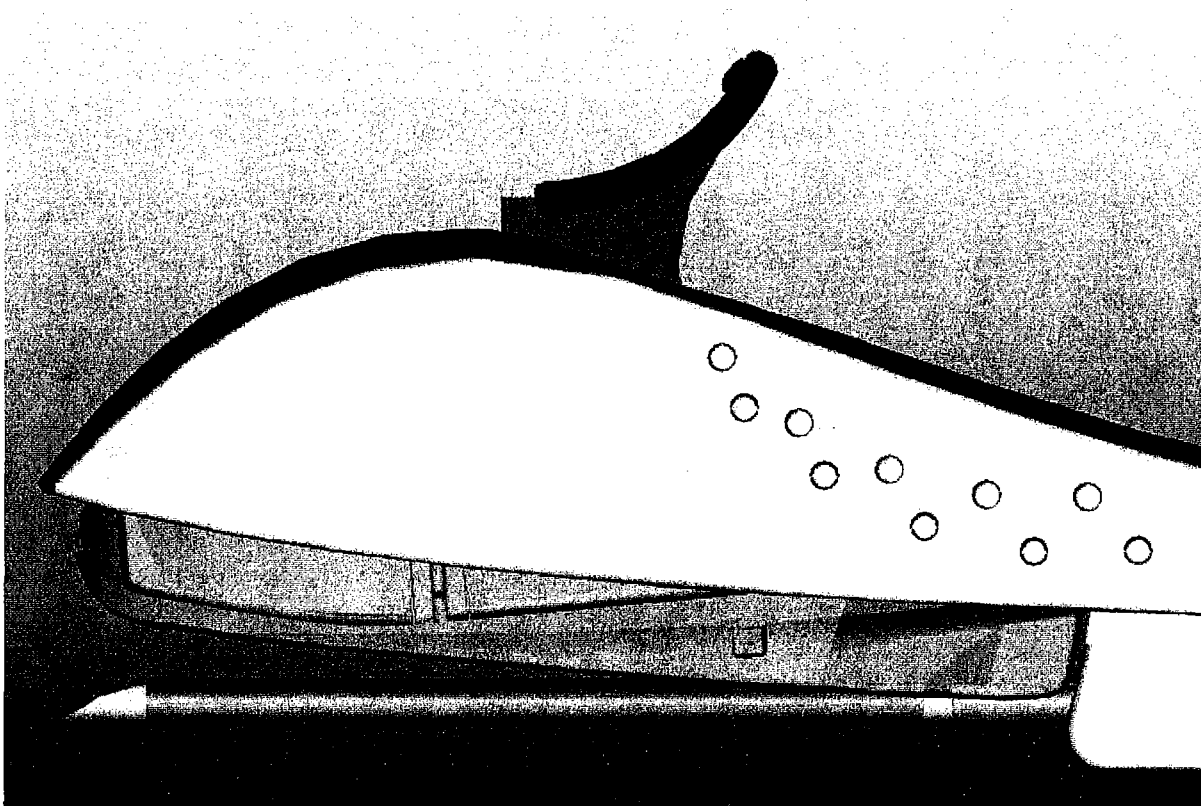
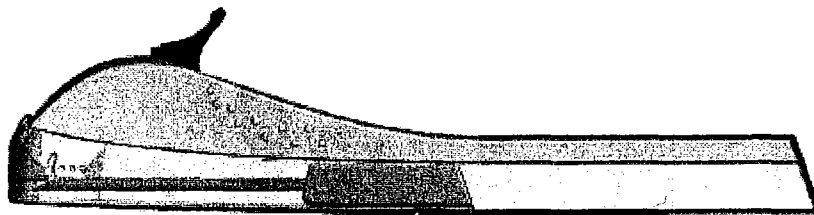
3. **Review**

The product consists of an implant, placed inside an applicator. The implant consists of a core containing a mixture of the drug substance etonogestrel (Org 3236), barium sulfate and ethylene vinylacetate copolymer with a vinylacetate content of 28% and a skin consisting of ethylene vinylacetate copolymer with a vinylacetate content of 14%. Each implant contains 68 mg of etonogestrel. The implant has a length of 4.0 cm and a diameter of 2.0 mm.

CDRH consult is requested for the implant insertion device.

**Device Description**

The implant is placed inside a stainless steel needle which is fitted to an applicator. The loaded applicator is placed in a (b) (4) tray which is subsequently sealed with lidding foil.



The implant is meant to be inserted subdermally. It should be palpable after insertion. In order to facilitate the manual handling of the applicator by healthcare providers the Next Generation Implanon Applicator (NGIA, new applicator) has been developed. As is the case for the current applicator, the new applicator is a ready-for-use disposable applicator where the implant is pre-filled in the stainless steel needle of the applicator.

**Device Function**

- Step 1: The needle protection cap assures that the implant remains inside the needle (1). In case of absence of an implant in the needle, the needle protection cap can not easily be removed as the lever (3 in Step 2) will block the needle protection cap movement.
- Step 2: Upon removal of the protection cap away from the needle (2) the lever (3) holds the implant in place in the needle.
- Step 3: The shape of the applicator and position of the handle relative to the needle should support proper subdermal insertion of the needle. Upon insertion the lever (4) is pushed upward thereby “releasing” the implant.
- Step 4: While keeping the applicator in the same position after the needle has been inserted superficially into the subdermal connective tissue, the slider (5) on top of the applicator can be unlocked by pushing it slightly down. By sliding the slider backwards until it is arrested in the back of the slider, the needle is retracted into the applicator housing while the implant (6), held in place by an obturator, is left behind under the skin.
- Step 5: After complete retraction of the slider, the purple tip of the obturator (7) is visible (out of the housing), and the needle is completely retracted into the housing and locked (8); this assures single use of the applicator and should prevent needle stick accidents.

Materials of Construction

Part	Material
<b>Applicator</b>	
Stainless steel needle	Stainless steel
Needle holder/knob and obturator	(b) (4) colored with a purple dye
Needle protection cap	(b) (4)
Lever	(b) (4)
Spring	Stainless steel
Housing parts	(b) (4) colored with a blue dye and (b) (4)
<b>Blister pack</b>	
Blister forming film	(b) (4)
Blister lidding film	(b) (4)

Risk management

To establish those parameters that are likely to have the greatest impact on the safety and performance of the applicator, risk management using Failure Mode Effect Analysis (FMEA), in accordance with ISO 14971, was applied during the whole applicator development process. In this risk management process, three risk analyses using the FMEA method have been performed:

- Design FMEA, looking at the applicator combined with the list of possible hazards as stated in ISO 14971:2000, Annex A.
- Product Process Tree FMEA, looking at the risks per detailed step of the process of using the applicator.
- Product Parts FMEA, looking at the risks of malfunction per part of the applicator.

Residual risks

Only 3 residual risks were identified, all from the production tree FMEA.

These risks are:

- The needle protection cap gets loose after dropping the applicator,
- Too deep insertions,
- User forgets to check whether the implant is inserted correctly.

These three risks are further mitigated in the insertion procedure included in the instruction for use, instruction video and in the training program:

- The physician is obliged to and urged to discard contaminated applicators,
- The instruction video, instruction for use and the training program show how the applicator should be used to prevent too deep insertions,
- The instruction video, instruction for use and the training program clearly require that the presence of the implant in the arm of the user should always be checked by palpation.

#### Sponsor Conclusions

A Next Generation Implanon Applicator has been developed that possesses several additional functionalities. Extensive risk assessments have been performed in the design development. Use tests using an artificial arm and a clinical study have demonstrated that the new applicator design is suitable for the intended use. The new applicator design facilitates the manual handling of the applicator during the insertion procedure, thereby contributing to successful implant insertions.

**Reviewer Discussion: The risk management report is not provided. Additionally, the mitigations to the presented residual risks rely on user action, rather than device design. The sponsor should demonstrate through a human factors study that the training adequately mitigates these risks.**

#### Biological Safety

##### Biocompatibility

CDRH defers the review of material biocompatibility to the CDER experts. CDRH recommends the use of FDA recognized consensus standard, ISO 10993, for the review of material biocompatibility.

##### Sterility



*CDRH Reviewer Discussion: The description of the sterilization process is acceptable.*

### **Design Validation Studies**

The sponsor states that the final design was evaluated in an international use test in Europe, North America and Asia (total of 32 physicians, with various levels of experience with Implanon insertions).

*CDRH Reviewer Discussion: The studies were not described and the reports could not be located. Please see the recommended deficiencies section for required information.*

### **Design Verification Studies**

The only information located in the submission with respect to design verification are found in the following table.

<b>Test</b>	<b>Method principle</b>	<b>Acceptance criterion</b>	<b>Result</b>
Appearance		(b) (4)	Conform
Tensile strength of needle/needle holder connection			Conform
Force to remove the needle protection cap			Conform
Force to retract the needle			Conform
Assembly with NGIA back assembly			Conform

*CDRH Reviewer Discussion: The only bench data for the device are found in the table above. The acceptance criteria are not adequate because they are [REDACTED] (b) (4) acceptance criteria are expected, where appropriate.*

*The sponsor has not provided design verification test reports.*

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**Release Specifications**

**Table 16: Specification for the new Implanon**

(b) (4)



(b) (4)



***CDRH Reviewer Discussion:*** *The release test specifications do not include [redacted] (b) (4) [redacted] for functionality. The sponsor should explicitly state the functional tests and the quantitative endpoints.*


**Recommended Deficiencies**

1. Your submission references risk management, design verification and validation efforts with respect to the implant delivery system. The underlying elements have not been provided for review, and we are therefore unable to determine if your conclusions regarding the device component safety and effectiveness are adequate. Please provide the following information related to your device component:
  - a. Risk Management Report
  - b. Design Verification test protocols and reports. Please note that quantitative acceptance criteria are required. The studies should be well-designed to meet the stated objectives and should demonstrate that your device successfully performs as intended. This will include rigorous attention to: statistical elements (hypotheses, analyses, sample size and sampling, power, etc.), controls, minimization of bias, test

parameters (endpoints), follow-up, evaluation criteria, etc. For each design verification test, please provide the following:

- i. A detailed description of the test method, including drawings of the test apparatus where appropriate;
  - ii. An explanation of how the test set up simulates actual clinical use;
  - iii. An explicit statement of the acceptance criteria for the test;
  - iv. The results of the test;
  - v. An analysis of the test results; and
  - vi. An explicit statement of any conclusions drawn from the test.
- c. Design Validation protocols and reports. Your submission states that the final design was evaluated in an international use test in Europe, North America and Asia (total of 32 physicians, with various levels of experience with Implanon insertions). The studies were not described and the reports could not be located. Please provide the test protocols and reports of your human factors evaluations. Please review the following list of criteria for human factors evaluations and ensure that your reports address these items:
- i. **Description of the device user interface:** The report will include a description of all essential components of the device with which the user interacts in a level of detail that will support the rationale for how the testing was developed and applied.
  - ii. **Relative priority of tasks:** The human factors validation testing will systematically evaluate user tasks and prioritize those tasks with respect to relative use-safety risks. If a task is performed infrequently, it may still be regarded as high priority for the purposes of a use study, since it is often these infrequent tasks that result in difficulties for users (combination of infrequent use and minimal training). The rationale applied to their priority will be provided.
  - iii. **Comprehensiveness of task set:** The prioritized tasks are comprehensive with respect to all necessary interactions between user and device. The representative users will complete each scenario, thereby performing all high priority tasks. The report will provide a rationale for the group of tasks included in the study. Prior experience with known device problems (e.g., adverse events, recalls, literature, etc.) will directly inform task selection and emphasis in the validation study.
  - iv. **Study participants:** A minimum of 15 representative participants will be enrolled in the study. Study participants are representative of the intended user population. For devices that have two (or more) distinct groups of users, the evaluation will require a minimum of 15 representative users in each group, for example one group might be composed of nurses and the other of lay (“home”) users. Sponsor employees are not appropriate study participants.
  - v. **Realism of simulated use:** The testing environment and realism of the simulated use will be described in sufficient detail to determine if it is reasonable for the

- device, and consistent with more challenging use conditions expected for use of the device.
- vi. **Objective and Subjective data:** The study will include objective evaluations (performance-based) of task success and subjective assessment (formal or informal feedback by study participants). Both measures emphasize tasks according to risk priority. Objective measures focus on use errors that could result in harm to a patient (as discussed above). Subjective assessments elicit feedback from the participants on aspects of device use that may be difficult or confusing.
  - vii. **Pass/fail definitions:** The validation report will describe the performance criteria of pass/fail for the tasks or task scenarios in the test. The evaluation will address each failure, particularly on critical task performance and determine its cause. Performance objectives that allow for a given percentage of failures are not appropriate for validation studies (e.g., 90% of users will succeed). The expectation is that all critical tasks will be performed correctly unless sufficient explanation for failures is provided.
  - viii. **Unexpected failures:** The test plan will identify how unexpected failures will be identified, recorded and reported.
  - ix. **Training:** Training provided to participants will represent the extent of training for actual users. A description of the training provided to test participants and a rationale for its consistency with the training provided to actual users will be provided.
  - x. **Data analysis and Conclusions:** The final report will describe all performance failures for critical tasks, summarize all subjective comments and provide a root cause for each failure. If use problems are identified during the testing and mitigations are indicated (e.g., improved user instructions, device labeling, training, design modification), then additional human factors evaluations are required to validate the mitigations. (Such studies can be smaller in scale and focus on the specific problem if that is appropriate in the context of use). Based on the study results, the validation report will provide an analysis and conclusion that the device is reasonably safe and effective for the intended users.
2. The release test specifications do not include [REDACTED] <sup>(b) (4)</sup> for functionality. Please explicitly state the functional tests and the [REDACTED] <sup>(b) (4)</sup> for release specifications.




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LCDR Alan Stevens



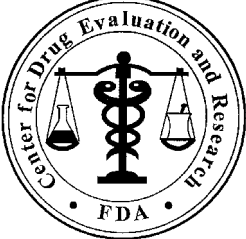
TEAM LEADER (AMB. BOW) Aug 2, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-21529	----- SUPPL-7	----- ORGANON USA INC	----- IMPLANON (ETONOGESTREL IMPLANT) 68MG

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/s/  
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ZETA-MAE C WILLIAMSON  
08/03/2010

	<p><b>Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology</b></p>
Date:	May 19, 2010
To:	<p>Scott Monroe, MD, Director Division of Reproductive and Urologic (DRUP) Office of New Drugs (OND), CDER</p> <p>Audrey Gassman, MD, Deputy Director of Safety Division of Reproductive and Urologic Products (DRUP) Office of New Drugs (OND), CDER</p>
Through:	<p>Robert M. Boucher, MD, MPH, FACS, Director Division of Pharmacovigilance II (DPV II) Office of Surveillance and Epidemiology (OSE), CDER</p> <p>Adrienne Rothstein, PharmD, Team Leader Division of Pharmacovigilance II (DPV II) Office of Surveillance and Epidemiology (OSE), CDER</p>
From:	<p>Mark Miller, PharmD, Safety Evaluator Division of Pharmacovigilance II (DPV II) Office of Surveillance and Epidemiology (OSE), CDER</p>
Subject:	<p>Postmarketing review of Implanon (etonogestrel implant) associated with insertion and removal related events (IRRE), thromboembolic events (VTE and ATE), stroke, myocardial infarction, and deaths</p>
Drug Name(s):	Implanon (etonogestrel implant)
Application Type/NDA Number:	21-529
Applicant/sponsor:	ORGANON USA INC
OSE RCM #:	2010-496

# CONTENTS

EXECUTIVE SUMMARY .....	1
1 INTRODUCTION .....	2
1.1 Background.....	2
1.2 Regulatory history.....	2
1.3 Product labeling .....	2
2 METHODS AND MATERIALS.....	4
2.1 AERS Search Strategy and Selection of cases.....	4
3 RESULTS.....	5
3.1 AERS Overview-Most commonly reported terms.....	5
3.2 AERS Reports with a Fatal Outcome .....	6
3.3 Arterial and Venous Thromboembolism events .....	6
3.4 Stroke related events.....	6
3.5 Myocardial Infarction events .....	7
3.6 Insertion and Removal Related Events (IRRE) .....	7
3.7 Serious unlabeled events.....	7
4 DISCUSSION.....	7
5 Conclusion .....	8
5.1 Thromboembolism, Stroke, and Myocardial Infarction events .....	8
5.2 Insertion and removal related events (IRRE).....	8
6 RECOMMENDATIONS.....	8
6.1 Thromboembolism, Stroke, and Myocardial Infarction events .....	8
6.2 Insertion and removal related events (IRRE).....	9
7 REFERENCES .....	9
8 APPENDICES .....	10

## EXECUTIVE SUMMARY

This review evaluates postmarketing cases of deaths, myocardial infarction, stroke-related, thromboembolic and insertion and removal related events (IRRE) associated with Implanon (etonogestrel implant). The Division of Reproductive and Urologic Products (DRUP) requested this evaluation to assess adverse events with Implanon. The evaluation will assist DRUP's analysis of the labeling and efficacy supplements (S-006, S-007) submitted by the sponsor on July 30, 2009 and June 30, 2009, respectively.

The Division of Pharmacovigilance's (DPV II) assessment is based on review of FDA's Adverse Event Reporting System (AERS) and the sponsor's efficacy and labeling supplements (S-007 and S-006, respectively). DPV II found three fatalities, 29 AERS cases of arterial and venous thromboembolism and 27 cases of IRREs possibly associated with Implanon use. In addition, upon reviewing Implanon IRRE cases, DPV II identified reports of convulsions, a *serious, unlabeled* adverse event.

DPV II recommends revising the label regarding postmarketing cases of arterial and venous thromboembolism to include cases of pulmonary emboli, deep vein thrombosis, myocardial infarction, and strokes in women using the etonogestrel implant. DPV II will complete a separate postmarketing review investigating reports of convulsion(s) with Implanon.

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# 1 INTRODUCTION

## 1.1 BACKGROUND

The purpose of this review is to evaluate AERS postmarketing reports of deaths, myocardial infarction, stroke-related, and thromboembolic events in addition to insertion and removal related events (IRRE) associated with Implanon (etonogestrel implant). The Division of Reproductive and Urologic Products (DRUP) requested this evaluation to assess adverse events with Implanon. The evaluation will assist DRUP's analysis of the labeling and efficacy supplements (S-006, S-007) submitted by the sponsor on July 30, 2009 and June 30, 2009, respectively.

IRRE is defined in this document as any untoward device-related rather than active ingredient-related event due to insertion, localization and/or removal of IMPLANON. As part of a post-approval commitment to FDA the sponsor specifically monitors IRREs received through an Active Monitoring Program (AMP).<sup>1</sup> Sponsor AMP data for Implanon through January 16, 2010 show a total of (b) (4) Implanon rods distributed since US launch in July 2006; there are (b) (4) AMP forms with 355 patients experiencing a total of 716 IRREs. The sponsor's summary of IRRE classification is presented in Appendix B.<sup>1</sup>

The efficacy supplement (S-007) submitted to DRUP for (b) (4) (etonogestrel; a new Implanon product), describes a radiopaque implant (the current implant is non-radiopaque) and a "Next Generation Implanon Applicator" (NGIA). The basis for successful use and subsequent removal of Implanon is a correctly performed insertion. S-007 proposes a modified applicator and radiopaque implant to facilitate correct insertion and to provide an additional method of localization. Several programs which are intended to prevent, mitigate and manage adverse events (including IRREs) are in place for the currently marketed (non-radiopaque) Implanon product. The Sponsor intends to maintain similar programs for the new (radiopaque) Implanon product.<sup>1,2</sup>

## 1.2 REGULATORY HISTORY

**Progestin-only implants for the prevention of pregnancy:** The original Norplant, a set of six small silicone capsules, each filled with 36mg of levonorgestrel, was FDA approved in 1990 and discontinued in 2002. Norplant II, a set of two small silicone rods each containing 75mg of levonorgestrel in a polymer matrix was originally FDA approved in 1996 as being effective for three years. Subsequently, Norplant II (NDA 20544, 1996) was approved, but not marketed, as being effective for five years. Implanon, a reversible contraceptive method and single rod subdermal implant containing 68 mg of etonogestrel, was FDA approved on July 17, 2006 as being effective up to 3 years. Implanon is a progestin-only contraceptive and does not contain estrogen.<sup>3,4</sup>

## 1.3 PRODUCT LABELING

### 1.3.1 Thromboembolic and Vascular Events

Current labeling for Implanon<sup>3</sup> lists warnings for serious thromboembolic events based on experience with Implanon and other progestin-only contraceptives. Additionally, the labeling contains warnings based on experience with combination (progestin plus estrogen) oral contraceptives including thromboembolic disorders and other vascular problems stating the following:

*There have been postmarketing reports of serious thromboembolic events, including cases of pulmonary emboli (some fatal) and strokes, in patients using IMPLANON.*

*Thromboembolism: epidemiological investigations have associated the use of combination hormonal contraceptives with an increased incidence of venous thromboembolism (VTE, deep venous thrombosis, retinal vein thrombosis, and pulmonary embolism). The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism and stroke, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity, and diabetes.*

Proposed labeling from the sponsor in the labeling supplement (S-006) relating to thromboembolic disorders and other vascular events contains a revised single subsection termed (b) (4) in the Warnings and Precautions section as follows:

(b) (4)

(b) (4)

### **1.3.2 Insertion and Removal Related Events (IRRE)**

The sponsor revised the Implanon label<sup>3</sup> about insertion and removal complications for better coherence and clarity of information. The sponsor is proposing to add a Postmarketing Experience section relating to IRRE complications (see below). The proposed labeling also addresses the inability to stop drug-related adverse events and unintended pregnancy. The first paragraph of the current Warnings section and the proposed language in the Warnings and Precautions section is as follows:

#### **Current labeling: Complications of insertion and removal**

*IMPLANON™ should be inserted subdermally so that it is palpable after insertion. Failure to insert IMPLANON™ properly may go unnoticed unless the implant is palpated immediately after insertion. Deep insertions may lead to difficult or impossible removals. Failure to remove IMPLANON™ may result in infertility, ectopic pregnancy, or inability to stop a drug-related adverse event. Undetected failure to insert IMPLANON™ may lead to an unintended pregnancy.*

#### **Proposed Labeling: Complications of Insertion and Removal**

(b) (4)

#### **Post-Marketing Experience**

(b) (4)

## 2 METHODS AND MATERIALS

### 2.1 AERS SEARCH STRATEGY AND SELECTION OF CASES

- 1) A March 31, 2010 AERS search for all adverse events associated with Implanon retrieved 393 reports (see Section 3.1).
- 2) A March 9, 2010 AERS search for adverse events of interest retrieved 82 reports of 59 cases for this analysis (see Table 1). Reports were excluded (N=23) for unrelated adverse events (6), duplicate reports (10), unassessable reports (5), and drug interaction reports (2).

**Table 1: Summary of AERS Search for Implanon (etonogestrel) implant on March 9, 2010**

Adverse Event of Interest	AERS Search Strategy*	Crude Count† N=82	DPV II Analysis N=59
All deaths	Outcome reported as death	7	3**
Arterial and Venous Thromboembolism	Embolic and thrombotic events, arterial (SMQ) Embolic and thrombotic events, venous (SMQ)	24	14
Stroke related events	Haemorrhagic cerebrovascular conditions (SMQ) Ischaemic cerebrovascular conditions (SMQ)	13	11
Myocardial Infarction	Ischaemic coronary artery disorders (HLT) ECG investigations (HLT)	5	4
Insertion and Removal Related Events (IRRE)	Procedural and Device Related Injuries and Complications (HLGT)	33	27

\*See Appendix C for a listing of preferred terms under each Standardized MedDRA Query (SMQ), High Level Group Term (HLGT), and High Level Term (HLT) except Procedural and Device Related Injuries and Complications (HLGT) which includes multiple HLTs.

\*\*Four deaths excluded were neonatal fatalities (2) and unassessable cases due to limited information (2).

† Total count; includes reports subsequently excluded for unrelated adverse events, duplicate reports, unassessable reports, and drug interaction reports.

### 3 RESULTS

#### 3.1 AERS OVERVIEW-MOST COMMONLY REPORTED TERMS

A total of 393 reports with Implanon as a suspect drug (no limitation on reported adverse event term) were retrieved from the AERS database. The most commonly reported preferred terms with a count of  $\geq 8$  are presented in **Table 2**. See Appendix C for the most commonly reported preferred terms with a count of 2-7.

**Table 2:**

**Most Commonly Reported Preferred Terms in Implanon Reports in the AERS Database**

Preferred Term (PT)	N	% of Total* (N=393)	Location in Label/Comments
	March 2010 data		
Drug Exposure During Pregnancy	73	18.58	Clinical trials
Pregnancy With Implant Contraceptive	70	17.81	Clinical trials
Abortion Spontaneous	48	12.21	<i>Unlabeled</i>
Drug Interaction	46	11.70	Labeled drug interactions
Vaginal Haemorrhage	28	7.12	WARNINGS – Bleeding Irregularities
Headache	24	6.11	Adverse Reactions section
Convulsion	23	5.85	<i>Unlabeled</i>
Ectopic Pregnancy	23	5.85	Postmarketing section proposed by sponsor
Weight Increased	23	5.85	Clinical trials
Nausea	18	4.58	Clinical trials
Abortion Induced	15	3.82	<i>Unlabeled</i>
Amenorrhoea	15	3.82	WARNINGS – Bleeding Irregularities
Condition Aggravated	15	3.82	<i>Unlabeled</i>
Depression	15	3.82	Adverse Reactions section
Menorrhagia	15	3.82	WARNINGS – Bleeding Irregularities
Mood Swings	14	3.56	Adverse Reactions section
Haemorrhage	13	3.31	WARNINGS – Bleeding Irregularities
Pregnancy	13	3.31	Adverse Reactions section
Syncope	13	3.31	<i>Unlabeled</i>
Hypoaesthesia	12	3.05	Adverse Reactions section
Pain In Extremity	11	2.80	Adverse Reactions section
Unintended Pregnancy	11	2.80	Clinical trials
Cerebrovascular Accident	10	2.54	WARNINGS section
Device Migration	10	2.54	WARNINGS section under Complications of Insertion and Removal
Dizziness	10	2.54	Adverse Reactions section
Menstruation Irregular	10	2.54	WARNINGS section
Suicidal Ideation	10	2.54	<i>Unlabeled</i>

Preferred Term (PT)	N	% of Total* (N=393)	Location in Label/Comments
	March 2010 data		
Deep Vein Thrombosis	9	2.29	WARNINGS section
Paraesthesia	9	2.29	Adverse Reactions section
Alopecia	8	2.04	Adverse Reactions section
Back Pain	8	2.04	Adverse Reactions section
Weight Decreased	8	2.04	Adverse Reactions section

\* % of Total: the number of occurrences of PTs in the cases over the total number of reports in the individual case series; sum does not equal 100%

### 3.2 AERS REPORTS WITH A FATAL OUTCOME

The AERS database search retrieved three cases of adults with fatal outcomes in conjunction with Implanon use.

The first case (ISR#6314885) was from Australia involving a 27-year-old female with a family history of elevated protein S and anti-thrombin III died due to a pulmonary embolism in (b) (6). The physician involved was conducting genetic studies on the patient. Concomitant medications were Implanon and Effexor. No other information was provided.

The second case (ISR#6574349) was from Great Britain involving a 16-year-old female with a history of cardiac pacemaker insertion who underwent an implanon insertion procedure in September 2008. On an unspecified date, the patient experienced an unspecified infection. She was admitted to the intensive care unit with possible subacute bacterial endocarditis and died on (b) (6). The postmortem investigations and microbiology exam suggested infection originating from the pacemaker and no causal relationship to the implant.

The third case (ISR#6274451) is a spontaneous case sent by a US consumer. The consumer stated a nurse reported a patient of unknown age experienced a broken rod (Implanon) and died. No other information was provided in this report.

### 3.3 ARTERIAL AND VENOUS THROMBOEMBOLISM EVENTS

DPV II identified 14 AERS cases (11 domestic, 3 foreign; average age of 29 years, range 17-43 years) of possible pulmonary embolism (4), deep vein thrombosis (9), and arterial thromboembolism (1) associated with Implanon therapy.

The reviewer notes that all 14 cases contain possible risk factors for thromboembolism such as limb immobilization, comorbidities, smoking, obesity, history of thromboembolism, and a hypercoagulable state.

### 3.4 STROKE RELATED EVENTS

DPV II identified 11 AERS cases (9 domestic, 2 foreign; average age of 31 years, range 21-48 years) of possible stroke (5), transient ischemic attack (3), cerebral embolism (1), an occlusion of cerebral artery (1), and carotid thrombosis and apoplexy (1) associated with Implanon therapy.

The reviewer notes 3 of 11 cases were thromboembolic in nature and 9 of 11 cases contain risk factors for stroke or thromboembolism such as immobilization, obesity (overweight), smoking, hypertension, and diabetes.

### **3.5 MYOCARDIAL INFARCTION EVENTS**

DPV II identified 4 AERS cases (4 domestic, average age of 26 years, range 21-36 years) of possible myocardial infarction associated with Implanon therapy.

The reviewer notes that all 4 AERS cases contain possible risk factors for myocardial infarction such as obesity (overweight) and smoking.

### **3.6 INSERTION AND REMOVAL RELATED EVENTS (IRRE)**

DPV II identified 27 AERS cases (15 domestic, 12 foreign; average age of 28 years, range 16-42 years) of possible IRREs (Procedural and Device Related Injuries and Complications) associated with Implanon therapy.

Based on the sponsor's IRRE classification, there were two insertion-related events, three removal-related events, seven localization-related events, eleven other-related events, three events with greater than one IRRE classification, and one event was unclassifiable.

The reviewer evaluated IRREs for the potential association with corresponding medically significant consequences and found the following consequences: surgery, possible neurological involvement (tremors, twitching, paraesthesias), vascular injury (hematoma), unintended pregnancy, hypersensitivity reactions, and bleeding irregularities. In a majority of the reports, long term effects, positive dechallenge and positive rechallenge were unknown. In one report, the patient experienced permanent finger paralysis.

### **3.7 SERIOUS UNLABELED EVENTS**

The reviewer notes an AERS search for all adverse events associated with Implanon found PT term convulsion occurring 23 times in the reports over the total number of reports (N=393) in the individual case series. Following a specific AERS search for IRREs, the reviewer identified three cases of convulsion, a *serious, unlabeled* adverse event, associated with Implanon use. Two of three cases (ISR#5678773, 6179141) describe patients with no seizure history experiencing seizure activity immediately following Implanon insertion (time frame unknown for ISR#6156304). See the Discussion section for further comments.

See **Appendix A** for a brief summary of the cases relating to all the above adverse events of interest. Data will be separated into Tables corresponding to the AERS searches (for example, Tables exist for stroke and myocardial infarction adverse events).

## **4 DISCUSSION**

DPV II found reports to the FDA of three fatalities, 29 cases of arterial and venous thromboembolism, and 27 cases of IRREs possibly associated with Implanon use.

The reviewer did not find any new safety signals following an evaluation of postmarketing data relating to thromboembolism, stroke, and myocardial infarction in conjunction with Implanon use. Of the three fatality cases, one patient died due to a broken rod (no information provided), one patient died of a pulmonary embolism, and another patient died most likely due to subacute bacterial endocarditis (SBE) originating from a pacemaker. The reviewer found all but two cases (N=27) relating to the above thromboembolic adverse events were confounded by possible preexisting conditions (for example, smoking, obesity, hypertension, diabetes, hypercoagulable state, family history, immobilization).

Venous thromboembolism, stroke, and myocardial infarction are labeled adverse events and currently described in the Warnings section of the Implanon label. The sponsor is proposing that

all information related to (b) (4) in the Implanon label be revised to a (b) (4). In the subsection “(b) (4)”, the sponsor (b) (4)

Following an evaluation of Implanon IRREs in AERS for a potential association with corresponding medically significant consequences, the reviewer identified convulsions as a possible *serious, unlabeled* adverse event. (The reviewer also investigated other unlabeled adverse events identified involving Implanon use such as syncope, condition aggravated, suicidal ideation, abortion spontaneous, and abortion induced. The reviewer concludes these cases cannot be judged for any drug-event association due to insufficient information).

IRREs are labeled adverse events and currently described in the Warnings section of the Implanon label. Specific to IRREs, the sponsor is proposing to add a Postmarketing Experience section and to revise the Warnings section of the label for better coherence and clarity of information. The reviewer identified three AERS cases of seizure activity occurring in patients with Implanon use; two of the cases had a strong temporal relationship with implant insertion and one case reported no prior history of seizures (seizure history unknown in two cases).

## 5 CONCLUSION

### 5.1 THROMBOEMBOLISM, STROKE, AND MYOCARDIAL INFARCTION EVENTS

DPV’s postmarketing safety review of Implanon identified 29 cases of arterial and venous thromboembolism. A majority of the cases (N=27) contain confounding factors such as preexisting conditions (e.g. smoking, obesity, diabetes) making it difficult to determine any causal relationship with Implanon use.

However, after evaluating the postmarketing data, the current Implanon label, and the sponsor’s prior approval labeling supplement, the reviewer recommends strengthening the proposed labeling concerning arterial and venous thromboembolism events (labeled) with Implanon use.

### 5.2 INSERTION AND REMOVAL RELATED EVENTS (IRRE)

DPV II’s postmarketing safety review of Implanon IRREs and a potential association with corresponding medically significant consequences identified convulsions as a possible serious, unlabeled adverse event.

## 6 RECOMMENDATIONS

### 6.1 THROMBOEMBOLISM, STROKE, AND MYOCARDIAL INFARCTION EVENTS

DPV II recommends strengthening the proposed language in subsection “(b) (6)” in the (b) (4) label to the following:

*There have been postmarketing reports of serious arterial and venous thromboembolic events, including cases of pulmonary emboli, deep vein thrombosis, myocardial infarction, and strokes, in women using the etonogestrel implant.*

(b) (4) *(proposed labeling by sponsor)*

(b) (4)

## **6.2 INSERTION AND REMOVAL RELATED EVENTS (IRRE)**

DPV II will complete a separate postmarketing review investigating convulsions in conjunction with Implanon use.

## **7 REFERENCES**

1. Implanon, NDA 21-529, Safety Reporting, dated 02/2010. ORGANON, Inc.
2. Implanon, NDA 21-529, Efficacy Supplement, dated July 30<sup>th</sup>, 2009.
3. Accessed Implanon (etonogestrel implant) label information. NDA 21-529. Label approved on 02/19/2009. ORGANON, Inc.
4. Accessed Norplant and Norplant II (levonorgestrel implant) approval history, label information, and related documents. NDA 19-897 and NDA 20-544. Norplant II Label approved on 11/22/2002, Population Council (company).
5. Accessed UpToDate (electronic clinical information resource), online Version 17.3. Overview of thromboembolism, myocardial infarction, and stroke risk factors.

## 8 APPENDIX A

### Legend for Tables:

<b>Reported Country:</b>	US=United States, GB=United Kingdom, FR=France, CH=Switzerland, DE=Germany, AU=Australia, PT=Portugal
<b>Reported Adverse Events:</b>	PE=pulmonary embolism; DVT=deep vein thrombosis; TIA=transient ischemic attack; CVA=cerebrovascular accident; CP=chest pain
<b>Reported risk factors:</b>	PMH=past medical history; BMI=body mass index; H/O=history of; DM=diabetes mellitus
<b>Reported Outcomes:</b>	DE=death, HO=hospitalizations, LT=life threatening, DS=disabling, OT=other serious outcomes

Brief summary of cases of possible **arterial and venous thromboembolism** associated with Implanon (N=14)

ISR Number	Country	Initial FDA Received Date	Age	Reported Adverse Events	Reviewer comments and reported risk factors	Reported Outcome
5331924	US	5/15/2007	29	PE	lupus, positive antinuclear antibodies, used Ortho Evra prior to Implanon, BMI 20	HO
5347780	US	5/16/2007	43	PE	DM, hypercholesterolemia, morbidly obese (BMI 62), h/o DVT, prior Depo-Provera user	HO
5577788	CH	12/20/2006	35	arterial embolism	smoker, h/o PE, hypertriglyceridemia	HO
5662069	US	2/11/2008	33	DVT	h/o PE/DVT, hypothyroidism	OT
5908896	US	10/1/2008	28	PE	obese, h/o migraines, prior depo-provera and levora user	HO

ISR Number	Country	Initial FDA Received Date	Age	Reported Adverse Events	Reviewer comments and reported risk factors	Reported Outcome
6112191	US	3/10/2009	32	PE	No significant history; BMI 27; family h/o thromboembolism	OT
6469715	FR	11/12/2009	23	thrombophlebitis	smoker, no other PMH reported	OT
6470424	US	11/19/2009	23	DVT	BMI 41, no other risk factors reported	HO
6470437	US	11/19/2009	Unknown	DVT	smoker	OT
6470499	US	11/19/2009	17	DVT	smoker, BMI 23	OT
6470501	US	11/19/2009	Unknown	DVT	No PMH reported, history of leg injury	OT
6470505	US	11/19/2009	22	DVT	BMI 24, family history of thromboembolism	OT
6470514	US	11/19/2009	25	DVT	limb immobilization due to traumatic knee injury	OT

ISR Number	Country	Initial FDA Received Date	Age	Reported Adverse Events	Reviewer comments and reported risk factors	Reported Outcome
6477213	GB	4/22/2009	39	DVT	limb immobilization due to foot fracture	OT

Brief summary of cases of possible **stroke-related events** associated with Implanon (N=11)

ISR Number	Country	Initial FDA Received Date	Age	Reported Adverse Events	Reviewer comments and reported risk factors	Reported Outcome
5851953	US	8/19/2008	21	TIA: suspected stroke: slurred speech, numbness, and headaches	no history of carotid disease	OT
5944170	US	11/4/2008	24	TIA	no cardiovascular risk factors	HO
5978446	US	9/11/2008	28	CVA due to cerebral embolism; history of cardiomyopathy	h/o anxiety, cervical dysplasia, and smoking, mild preeclampsia during pregnancy prior to implant	HO
6063725	US	1/30/2009	Unknown	stroke and cerebral aneurysm	overweight, no risk factors reported	HO
6087996	US	2/19/2009	20	occlusion of cerebral artery	family history of stroke, ex-smoker	HO
6470310	US	11/19/2009	39	stroke	smoker, family history of stroke	HO
6470466	US	11/19/2009	35	stroke	diabetes, obesity, hypertension, African American	HO

ISR Number	Country	Initial FDA Received Date	Age	Reported Adverse Events	Reviewer comments and reported risk factors	Reported Outcome
6475735	US	11/19/2009	28	possible TIA: tingling and radiating tingling down her arm and shortness of breath	PMH not reported	OT
6476851	DE	11/19/2009	41	carotid thrombosis and apoplexy	hemiplegic patient	HO
6477218	DE	11/19/2009	48	stroke	smoker (20-30 cigarettes per day)	OT
6565870	US	1/26/2010	21	stroke	obese (BMI 35),	HO
5851953	US	8/19/2008	21	TIA: suspected stroke: slurred speech, numbness, and headaches	no history of carotid disease	OT

Brief summary of cases of possible **myocardial infarction events** associated with Implanon (N=4)

ISR Number	Country	Initial FDA Received Date	Age	Reported Adverse Events	Reviewer comments and reported risk factors	Reported Outcome
5715241	US	04/22/08	21	myocardial infarction (CP, burning around neck, nausea, left arm pain and numbness)	Overweight (BMI 29), Smoker, Prior infection; h/o of anxiety attacks	OT
5964989	US	11/21/08	36	myocardial infarction (heavy breathing, severe tightness, CP, tingling fingers, and rapid heart rate)	Overweight (BMI 27)	OT
6055275	US	01/23/09	24	myocardial infarction (light chest pain and high blood pressure)	Obese (BMI 38), h/o PE	OT
6470424	US	11/19/09	23	myocardial infarction (chest pain, tightness); DVT	Obese (BMI 41), no thromboembolic history or hypercoagulable state	HO

Brief summary of cases of possible **Insertion and Removal Related Events (IRREs)** associated with Implanon (N=27)  
(See sponsor IRRE classification below)

ISR Number	Country	Initial FDA Received Date	Age	IRRE type (per DPV analysis)	Corresponding Medically Significant Consequence?
5393388	US	7/18/2007	17	Other reported IRREs (implant broken)	None reported
5678773	US	3/21/2008	Unknown	Other reported IRREs	experienced <b>seizure</b> 5 minutes after Implanon insertion; medical history unknown; patient recovered
5912369	US	10/7/2008	20	Other reported IRREs	multiple nonspecific neurological adverse events reported
6156304	US	4/13/2009	32	Other reported IRREs	experienced neurological events including possible partial <b>generalized seizure</b> (prescribed Keppra), tremors, and muscle twitching
6179141	US	4/21/2009	27	Other reported IRREs	experienced <b>seizure</b> immediately after Implanon insertion; no history of seizures
6241927	US	6/22/2009	40	Other reported IRREs	bleeding irregularities
6289078	US	7/8/2009	23	Other reported IRREs	pregnancy due to non-insertion;
6433433	US	11/6/2009	Unknown	Other reported IRREs	pruritis leading to expulsion of rod
6475929	GB	11/19/2009	Unknown	Other reported IRREs	implant cracked may have led to persistent vaginal bleeding, mood swings, and breast lump

ISR Number	Country	Initial FDA Received Date	Age	IRRE type (per DPV analysis)	Corresponding Medically Significant Consequence?
6478206	GB	7/1/2009	25	Localization-related events	unintended pregnancy leading to a spontaneous abortion
6521142	US	12/22/2009	21	Other reported IRREs	"ingrown hair" leading to infection
5604910	US	9/10/2007	40	Removal-related events	None reported;
6540574	FR	6/2/2009	28	Removal-related events	neurological symptoms; motor defect between 4th and 5th finger and paresthesia
6580186	PT	1/20/2010	32	Localization-related events	exploratory surgery performed due to implant migration;
5927977	US	9/29/2008	20	Localization-related events	implant migration; implant was successfully removed under ultrasound guidance by a general surgeon
5974344	US	11/14/2008	31	Localization-related events	None reported
6472731	CH	12/1/2009	Unknown	Removal-related events	paralysis in the fingers and paraesthesias in her hand; patient did not recover
6504776	PT	12/16/2009	32	Localization-related events	possible breast nodules and ovarian cysts
6510236	AU	7/21/2009	16	Localization-related events	unintended pregnancy

ISR Number	Country	Initial FDA Received Date	Age	IRRE type (per DPV analysis)	Corresponding Medically Significant Consequence?
6528473	FR	12/11/2009	42	Localization-related events	possible unintended pregnancy leading to spontaneous miscarriage
6597138	US	2/16/2010	21	Localization-related events	unintended pregnancy
6110164	US	3/6/2009	Unknown	Insertion-related events	"shortness of breath and throat swelling"; patient recovered
6509864	AU	12/17/2009	31	Insertion-related events	pain due to incorrect site
6477690	FR	11/19/2009	28	Localization and removal related events	Paraesthesias; patient recovered with sequelae (abnormal sensation was still present)
6476836	CH	11/19/2009	23	Insertion and localization related events	"difficulty" during insertion which resulted in hematoma
6477723	AU	3/19/2009	34	Insertion and removal-related events	chronic psychological reaction spanning a depression spectrum disorder (dysthymia) and pain (pain disorder associated with psychological factors)
6528735	US	12/1/2009	34	not IRRE related	paranoid thoughts and agitation

## Appendix B: Classification of IRREs (IRRE codes)

IRRE	Read as:	Options in Answer:	Use When:/Description:
<b>Insertion Related Events</b>			
IRRE-BLUE ROD INSERTED	Blue rod present	YES	Instead of IMPLANON® a blue training rod was inserted.
IRRE-DEEP INSERTION	IMPLANON® inserted too deeply	YES	IMPLANON® was inserted too deeply and was located in the muscle or deep in the fat tissue.
IRRE-DIFFICULT INSERTION	Difficult insertion	YES	All problems concerning a difficult insertion.
IRRE-NO ROD	No IMPLANON® was present	YES	ENG level is negative (below 30 pg/mL)
IRRE-MULTIPLE INSERT	Multiple rods were implanted	YES	MORE than one IMPLANON® rod has been inserted AND are (supposedly) present at the same time in the patient.
IRRE-WRONG PLACE	Wrong place	YES	IMPLANON® was not inserted at the correct insertion site (inner site upper arm).
<b>Localization Related Events</b>			
IRRE-PALPABLE PRESENCE	Was IMPLANON® palpable?	YES NO NO/YES/.. DOUBT	IMPLANON® was palpable. IMPLANON® was not palpable. IMPLANON® was not palpable first time, but palpable second time, etc. IMPLANON® was thought to be palpable/not sure.
IRRE-ULTRASOUND PRESENCE	Was IMPLANON® found by ultrasound?	YES NO NO/YES/.. DOUBT	IMPLANON® was found by US. IMPLANON® was not found by US. IMPLANON® was not found first time, but found second time, etc. IMPLANON® was thought to be found/not sure.
IRRE-MRI PRESENCE	Was IMPLANON® found by MRI?	YES NO NO/YES/.. DOUBT	IMPLANON® was found by MRI. IMPLANON® was not found by MRI. IMPLANON® was not found first time, but found second time, etc. IMPLANON® was thought to be found/not sure.
IRRE-DOUBT PRESENCE	Doubt about the presence of IMPLANON®	YES	In case there is doubt about the presence or when it has been reported that IMPLANON® could not be found/localized, but it is not specified if palpation/US/MRI/surgery were used.
<b>Removal Related Events</b>			
IRRE-SUR. REMOVAL GEN. ANESTHESIA	Surgical removal with general anesthesia	YES	Surgical removal of IMPLANON® under general anesthesia.
IRRE-SURG INTERVENTION	Surgical intervention(s)	YES	Surgical intervention other than the normal procedures (Company Core Datasheet).
IRRE-ENG POSITIVE, ROD NOT FOUND	ENG level positive, but no IMPLANON® was found	YES	ENG level was found to be positive, but IMPLANON® could not be found.
IRRE-MIGRATION	IMPLANON® has migrated	YES	IMPLANON® was reported to have moved from the insertion site.
IRRE-REMOVAL PROBLEM	Removal problems	YES	IMPLANON® could not be removed according to the normal procedures.

IRRE	Read as:	Options in Answer:	Use When:/Description:
<b>Other Reported IRREs</b>			
IRRE-OTHER	Other 'problems'	YES	Any other IRRE not mentioned in this list.
IRRE-EXPULSION	Extrusion/expulsion	YES	IMPLANON® protruded through the skin (extrusion/expulsion etc <b>but not</b> directly after insertion). <i>If directly after insertion then</i> IRRE-DIFFICULT INSERTION
IRRE-BROKEN OR CUT	IMPLANON was broken	YES	IMPLANON® was damaged, broken, or cut.
IRRE-ROD BENT	Rod bent	YES	IMPLANON® was bent, but not cut, broken, or damaged.

Source: sponsor safety reporting 02/2010

APPEARS THIS WAY  
ON ORIGINAL

## **APPENDIX C**

### **Embolic and thrombotic events, arterial and venous (SMQ), MedDRA Version 12.1**

Acute myocardial infarction, Amaurosis, Amaurosis fugax, Aortic bypass, Aortic embolus, Aortic surgery, Aortic thrombosis, Aortogram abnormal, Arterectomy with graft replacement, Arterial bypass operation, Arterial graft, Arterial occlusive disease, Arterial stent insertion, Arterial therapeutic procedure, Arterial thrombosis, Arterial thrombosis limb, Arteriogram abnormal, Arteriogram carotid abnormal, Atherectomy, Axillary vein thrombosis, Basal ganglia infarction, Basilar artery occlusion, Basilar artery thrombosis, Blindness transient, Budd-Chiari syndrome, Capsular warning syndrome, Carotid arterial embolus, Carotid artery bypass, Carotid artery occlusion, Carotid artery stent insertion, Carotid artery thrombosis, Carotid endarterectomy, Catheterisation venous, Cavernous sinus thrombosis, Central venous catheterisation, Cerebellar artery occlusion, Cerebellar artery thrombosis, Cerebellar embolism, Cerebral artery embolism, Cerebral artery occlusion, Cerebral artery thrombosis, Cerebral hypoperfusion, Cerebral venous thrombosis, Cerebrovascular insufficiency, Cerebrovascular stenosis, Compression stockings application, Coronary arterial stent insertion, Coronary artery bypass, Coronary artery embolism, Coronary artery occlusion, Coronary artery reocclusion, Coronary endarterectomy, Coronary revascularisation, Deep vein thrombosis, Deep vein thrombosis postoperative, Embolia cutis medicamentosa, Embolism, Embolism venous, Endarterectomy, Femoral artery embolism, Femoral artery occlusion, Hepatic artery embolism, Hepatic artery occlusion, Hepatic artery thrombosis, Hepatic vein occlusion, Hepatic vein thrombosis, Hypothenar hammer syndrome, Iliac artery embolism, Iliac artery occlusion, Iliac artery thrombosis, Iliac vein occlusion, Inferior vena caval occlusion, Intra-aortic balloon placement, Intracranial venous sinus thrombosis, Intraoperative cerebral artery occlusion, Intravenous catheter management, Ischaemic cerebral infarction, Ischaemic stroke, Jugular vein thrombosis, Lacunar infarction, Mesenteric arteriosclerosis, Mesenteric artery embolism, Mesenteric artery stenosis, Mesenteric artery thrombosis, Mesenteric vein thrombosis, Myocardial infarction, Obstetrical pulmonary embolism, Paget-Schroetter syndrome, Papillary muscle infarction, Pelvic venous thrombosis, Penile artery occlusion, Penile vein thrombosis, Percutaneous coronary intervention, Peripheral arterial occlusive disease, Peripheral arterial reocclusion, Peripheral artery angioplasty, Peripheral embolism, Phlebectomy, Phleboplasty, Portal vein occlusion, Portal vein thrombosis, Post procedural myocardial infarction, Post procedural pulmonary embolism, Post thrombotic syndrome, Postinfarction angina, Postoperative thrombosis, Postpartum venous thrombosis, Precerebral artery occlusion, Pulmonary artery therapeutic procedure, Pulmonary artery thrombosis, Pulmonary embolism, Pulmonary infarction, Pulmonary microemboli, Pulmonary thrombosis, Pulmonary vein occlusion, Pulmonary veno-occlusive disease, Pulmonary venous thrombosis, Renal artery occlusion, Renal artery thrombosis, Renal embolism, Renal vein embolism, Renal vein occlusion, Renal vein thrombosis, Retinal artery embolism, Retinal artery occlusion, Retinal artery thrombosis, Retinal vein occlusion, Retinal vein thrombosis, SI QIII TIII pattern, Silent myocardial infarction, Spinal artery embolism, Splenic embolism, Splenic vein occlusion, Splenic vein thrombosis, Stress cardiomyopathy, Stroke in evolution, Subclavian artery embolism, Subclavian artery thrombosis, Subclavian vein thrombosis, Superior mesenteric artery syndrome, Superior sagittal sinus thrombosis, Superior vena caval occlusion, Thromboembolism, Thrombophlebitis, Thrombophlebitis migrans, Thrombophlebitis neonatal, Thrombosed varicose vein, Thrombosis corpora cavernosa, Thrombotic microangiopathy, Thrombotic thrombocytopenic purpura, Transient ischaemic attack, Transverse sinus thrombosis, Truncus coeliacus thrombosis, Vascular graft, Vena cava embolism, Vena cava filter insertion, Vena cava thrombosis, Venipuncture site thrombosis, Venogram abnormal, Venooclusive disease, Venooclusive liver disease, Venous occlusion, Venous operation, Venous recanalisation, Venous stent insertion, Venous thrombosis, Venous thrombosis in pregnancy, Venous thrombosis limb, Venous thrombosis neonatal, Vertebral artery occlusion, Vertebral artery thrombosis, Visual acuity reduced transiently

### **Haemorrhagic and Ischaemic cerebrovascular conditions (SMQ)**

Basal ganglia haemorrhage, Basal ganglia infarction, Basilar artery occlusion, Basilar artery stenosis, Basilar artery thrombosis, Brain stem haemorrhage, Brain stem infarction, Brain stem ischaemia, Brain stem stroke, Brain stem thrombosis, Capsular warning syndrome, Carotid aneurysm rupture, Carotid arterial embolus, Carotid arteriosclerosis, Carotid artery bypass, Carotid artery disease, Carotid artery insufficiency, Carotid artery occlusion, Carotid artery stenosis, Carotid artery stent insertion, Carotid artery thrombosis, Carotid endarterectomy, Cerebellar artery occlusion, Cerebellar artery thrombosis, Cerebellar embolism, Cerebellar haematoma, Cerebellar haemorrhage, Cerebellar infarction, Cerebellar ischaemia, Cerebral arteriosclerosis, Cerebral arteriovenous malformation haemorrhagic, Cerebral artery embolism, Cerebral artery occlusion, Cerebral artery

stenosis, Cerebral artery thrombosis, Cerebral haematoma, Cerebral haemorrhage, Cerebral haemorrhage foetal, Cerebral haemorrhage neonatal, Cerebral infarction, Cerebral infarction foetal, Cerebral ischaemia, Cerebral microhaemorrhage, Cerebral revascularisation synangiosis, Cerebral thrombosis, Cerebral vasoconstriction, Cerebral venous thrombosis, Cerebrovascular accident, Cerebrovascular disorder, Cerebrovascular insufficiency, Cerebrovascular spasm, Cerebrovascular stenosis, Embolic cerebral infarction, Embolic stroke, Foetal cerebrovascular disorder, Haematomyelia, Haemorrhage intracranial, Haemorrhagic cerebral infarction, Haemorrhagic stroke, Haemorrhagic transformation stroke, Intracerebral haematoma evacuation, Intracranial haematoma, Intraventricular haemorrhage, Intraventricular haemorrhage neonatal, Ischaemic cerebral infarction, Ischaemic stroke, Lacunar infarction, Lateral medullary syndrome, Meningorrhagia, Millard-Gubler syndrome, Moyamoya disease, Post procedural stroke, Precerebral artery occlusion, Putamen haemorrhage, Reversible ischaemic neurological deficit, Ruptured cerebral aneurysm, Spinal artery embolism, Spinal cord haemorrhage, Spinal epidural haemorrhage, Spinal haematoma, Stroke in evolution, Subarachnoid haemorrhage, Subarachnoid haemorrhage neonatal, Subdural haemorrhage, Subdural haemorrhage neonatal, Thalamic infarction, Thalamus haemorrhage, Thrombotic cerebral infarction, Thrombotic stroke, Transient ischaemic attack, Vascular encephalopathy, Vertebral artery occlusion, Vertebral artery stenosis, Vertebral artery thrombosis, Vertebrobasilar insufficiency, Wallenberg syndrome,,

### **Ischaemic coronary artery disorders (HLT) and ECG investigations (HLT)**

Acute coronary syndrome, Acute myocardial infarction, Angina pectoris, Angina unstable, Arteriospasm coronary, Cardiac telemetry, Cardiac telemetry abnormal, Cardiac telemetry normal, Chest discomfort, Chest pain, Coronary no-reflow phenomenon, ECG P wave inverted, ECG signs of myocardial ischaemia, ECG signs of ventricular hypertrophy, Electrocardiogram, Electrocardiogram abnormal, Electrocardiogram ambulatory, Electrocardiogram ambulatory abnormal, Electrocardiogram ambulatory normal, Electrocardiogram change, Electrocardiogram delta waves abnormal, Electrocardiogram low voltage, Electrocardiogram normal, Electrocardiogram P pulmonale, Electrocardiogram P wave abnormal, Electrocardiogram P wave biphasic, Electrocardiogram P wave normal, Electrocardiogram pacemaker spike, Electrocardiogram poor R-wave progression, Electrocardiogram PQ interval, Electrocardiogram PQ interval prolonged, Electrocardiogram PR interval, Electrocardiogram PR prolongation, Electrocardiogram PR shortened, Electrocardiogram Q wave abnormal, Electrocardiogram Q waves, Electrocardiogram Q waves normal, Electrocardiogram QRS complex, Electrocardiogram QRS complex abnormal, Electrocardiogram QRS complex normal, Electrocardiogram QRS complex prolonged, Electrocardiogram QRS complex shortened, Electrocardiogram QT interval, Electrocardiogram QT interval abnormal, Electrocardiogram QT interval normal, Electrocardiogram QT prolonged, Electrocardiogram QT shortened, Electrocardiogram R on T phenomenon, Electrocardiogram repolarisation abnormality, Electrocardiogram RR interval prolonged, Electrocardiogram ST segment, Electrocardiogram ST segment abnormal, Electrocardiogram ST segment depression, Electrocardiogram ST segment elevation, Electrocardiogram ST segment normal, Electrocardiogram ST-T change, Electrocardiogram ST-T segment abnormal, Electrocardiogram ST-T segment depression, Electrocardiogram ST-T segment elevation, Electrocardiogram T wave abnormal, Electrocardiogram T wave amplitude decreased, Electrocardiogram T wave amplitude increased, Electrocardiogram T wave biphasic, Electrocardiogram T wave inversion, Electrocardiogram T wave normal, Electrocardiogram T wave peaked, Electrocardiogram U wave inversion, Electrocardiogram U-wave abnormality, Electrocardiogram U-wave biphasic, Exercise electrocardiogram, Exercise electrocardiogram abnormal, Exercise electrocardiogram normal, Kounis syndrome, Microvascular angina, Myocardial infarction, Myocardial ischaemia, Myocardial reperfusion injury, Papillary muscle infarction, Post procedural myocardial infarction, Postinfarction angina, Prinzmetal angina, QRS axis, QRS axis abnormal, QRS axis normal, SI QIII TIII pattern, Silent myocardial infarction, Stress cardiomyopathy, Subclavian coronary steal syndrome, Subendocardial ischaemia

### **Procedural and Device Related Injuries and Complications NEC (HLGT) includes:**

HLTs: Anaesthetic complications, Cardiac and vascular procedural complications, Device component findings, Device malfunction events, Device related complications, Endocrine procedural complications, Eye and ear procedural complications, Gastrointestinal and hepatobiliary procedural complications, Induced abortion complications, Musculoskeletal procedural complications, Neurological and psychiatric procedural complications, Non-site specific procedural complications, Reproductive tract and breast procedural complications, Respiratory tract and thoracic cavity procedural complications, Site

specific procedural complications NEC, Skin procedural complications, Transfusion related complications, Urinary tract procedural complications, Vaccination related complications

**FDA-AERS Standard Report: All Preferred Terms Reporting a count of 2 to 7 (Number of PT terms:132)**

Acne, Implant Site Pain, Loss Of Consciousness , Abdominal Pain, Anxiety Bipolar Disorder , Breast Cancer Female, Drug Ineffective, Dyspnoea, Fatigue, Malaise, Migraine, Ovarian Cyst, Pain, Abdominal Pain Upper, Anaemia, Chest Pain, Complication Of Device Removal, Device Breakage, Epilepsy, Hypertension, Implant Site Haematoma, Metrorrhagia, Muscle Spasms, Pulmonary Embolism, Blood Pressure Increased, Breast Mass, Breast Tenderness, Haemoglobin Decreased, Implant Site Pruritus, Infection, Maternal Drugs Affecting Foetus, Multiple Sclerosis, Nephrolithiasis, Palpitations, Pregnancy With Contraceptive Device, Thrombosis, Urticaria, Abortion, Agitation, Benign Intracranial Hypertension, Blindness Transient, Breast Cancer, Breast Cancer In Situ, Caesarean Section, Cholelithiasis, Complication Of Device Insertion, Fear, Feeling Abnormal, General Physical Health Deterioration, Hot Flush, Impaired Work Ability, Implant Site Reaction, Motor Dysfunction, Neck Pain, No Therapeutic Response, Oedema Peripheral, Oestrogen Receptor Assay Positive, Pancreatitis, Panic Attack, Pneumonia, Post Procedural Complication, Progesterone Receptor Assay Positive, Psychotic Disorder, Pyrexia, Refusal Of Treatment By Patient, Scar, Sleep Disorder, Visual Impairment, Vomiting, Abdominal Distension, Abdominal Pain Lower, Aggression, Anger, Angioedema, Application Site Pruritus, Asthma, Blood Glucose Increased, Burning Sensation, Cardiomyopathy, Cellulitis, Coital Bleeding, Cough, Crying, Cytogenetic Abnormality, Death, Decreased Appetite, Dehydration, Dysaesthesia, Economic Problem, Erythema Nodosum, Eye Pain, Fall, Feeling Cold, Heart Rate Increased, Hormone Level Abnormal, Hypersomnia, Hyperthyroidism, Hysterectomy, Implant Expulsion, Implant Site Infection, Implant Site Necrosis, Injury, Irritability, Lip Swelling, Loss Of Libido, Medical Device Complication, Menometrorrhagia, Mood Altered, Muscle Twitching, Musculoskeletal Pain, Nasopharyngitis, Nerve Injury, Neuralgia, Ovarian Cyst Ruptured, Overweight, Papilloedema, Paranoia, Polymenorrhoea, Post Procedural Haemorrhage, Premature Baby, Premature Separation Of Placenta, Product Quality Issue, Rash, Skin Discolouration, Systemic Lupus Erythematosus, Thrombophlebitis, Transient Ischaemic Attack, Transplant Rejection, Treatment Noncompliance, Unevaluable Event, Unwanted Pregnancy, Uterine Leiomyoma, Vision Blurred

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	SUPPL-7	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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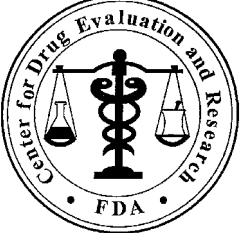
/s/

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MARK S MILLER  
05/20/2010

ADRIENNE M ROTHSTEIN  
05/20/2010

ROBERT M BOUCHER  
05/21/2010

	<p><b>Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology</b></p>
Date:	May 19, 2010
To:	<p>Scott Monroe, MD, Director Division of Reproductive and Urologic (DRUP) Office of New Drugs (OND), CDER</p> <p>Audrey Gassman, MD, Deputy Director of Safety Division of Reproductive and Urologic Products (DRUP) Office of New Drugs (OND), CDER</p>
Through:	<p>Robert M. Boucher, MD, MPH, FACS, Director Division of Pharmacovigilance II (DPV II) Office of Surveillance and Epidemiology (OSE), CDER</p> <p>Adrienne Rothstein, PharmD, Team Leader Division of Pharmacovigilance II (DPV II) Office of Surveillance and Epidemiology (OSE), CDER</p>
From:	<p>Mark Miller, PharmD, Safety Evaluator Division of Pharmacovigilance II (DPV II) Office of Surveillance and Epidemiology (OSE), CDER</p>
Subject:	Postmarketing review of seizure related activity in association with Implanon (etonogestrel implant)
Drug Name(s):	Implanon (etonogestrel implant)
Application Type/Number:	21-529
Applicant/sponsor:	ORGANON USA INC
OSE RCM #:	2010-832

# CONTENTS

EXECUTIVE SUMMARY .....	1
1 INTRODUCTION .....	1
1.1 Background .....	1
1.2 Regulatory history .....	1
2 METHODS AND MATERIALS.....	1
2.1 AERS Search and Selection of Cases .....	1
3 RESULTS .....	2
4 DISCUSSION.....	3
5 CONCLUSION.....	3
6 RECOMMENDATIONS.....	3
7 REFERENCES .....	4
8 APPENDIX.....	5

## EXECUTIVE SUMMARY

This review evaluates AERS postmarketing cases of seizure related activity in conjunction with Implanon (etonogestrel implant) use and provides recommendations to the Division of Reproductive and Urologic Products (DRUP) from the Division of Pharmacovigilance II (DPV II) concerning this *serious, unlabeled* adverse event.

DPV II recommends the sponsor update the Implanon label to include “convulsions” in the **Postmarketing** section.

DPV II's assessment and recommendations are based on review of FDA's Adverse Event Reporting System (AERS). DPV II identified 28 AERS cases (21 domestic, 7 foreign; average patient age of 25 years, range 17-40 years) of seizure related activity in association with Implanon use. An evaluation of the AERS cases has determined that Implanon may be associated with the initiation or exacerbation of seizures.

## 1 INTRODUCTION

### 1.1 BACKGROUND

This review evaluates AERS cases of seizure related activity in the Adverse Event Reporting System (AERS) with Implanon (etonogestrel implant). In March 2010, the Division of Reproductive and Urologic Products (DRUP) requested that Division of Pharmacovigilance II (DPV II) analyze and assess insertion and removal related events (IRRE) in association with Implanon use. Upon reviewing Implanon IRRE's, DPV II identified seizure related activity, a *serious, unlabeled* adverse event as a potential safety signal for further evaluation.

### 1.2 REGULATORY HISTORY

**Progestin-only implants for the prevention of pregnancy:** The original Norplant, a set of six small silicone capsules, each filled with 36mg of levonorgestrel, was FDA approved in 1990 and discontinued in 2002. Norplant II, a set of two small silicone rods each containing 75mg of levonorgestrel in a polymer matrix was originally FDA approved in 1996 as being effective for three years. Subsequently, Norplant II was FDA approved on 2002 as being effective for five years yet has not been marketed in the United States. Implanon, a reversible contraceptive method and single rod subdermal implant containing 68 mg of etonogestrel, was FDA approved on July 17, 2006 as being effective up to 3 years. Implanon is a progestin-only contraceptive and does not contain estrogen.<sup>1,2</sup>

## 2 METHODS AND MATERIALS

### 2.1 AERS SEARCH STRATEGY AND SELECTION OF CASES

AERS was searched on April 9, 2010 using the product name Implanon (etonogestrel implant) and the Standardized MedDRA Query (SMQ) Convulsions BROAD and NARROW.

The AERS search retrieved 33 reports of which 28 cases were relevant for DPV's analysis. Reports were excluded (N=5) for duplicate reports (2), unrelated adverse events (1), brain tumor present (1), and medication withdrawal (1).

### 3 RESULTS

DPV II identified 28 AERS cases (21 domestic, 7 foreign; average patient age of 25 years, range 17-40 years) of seizure related activity in association with Implanon use.

See the Appendix for a brief summary of the 28 AERS cases. Case characteristics are summarized in **Table 1** below.

<b>Table 1: Case characteristics of seizure related activity in association with Implanon use since market approval</b>	
<b>Number of Cases</b>	N=28
<b>Age of females (N=22)</b>	Average: 25 years Range: 17-40 years
<b>Country of Origin</b>	United States: 21 cases United Kingdom: 4 cases Australia: 2 cases France: 1 cases
<b>Type of Report</b>	Expedited (15-day report): 26 cases Direct reports: 2 cases
<b>Reporting year</b>	2010: 5 cases 2009: 14 cases 2008: 5 cases 2002-2007: 4 cases
<b>Reported Outcome</b>	Hospitalization: 8 cases Life Threatening: 1 cases Other Serious Outcome: 19 cases
<b>History of Seizures?</b>	Yes: 8 cases No: 12 cases Unknown: 8 cases
<b>Concomitant Anticonvulsants?</b>	Yes: 8 cases No: 9 cases Unknown: 11 cases
<b>Time-to-Onset of Event in Days following implant insertion</b>	All cases (N=19): average: 25; range: 1-669
	Cases with no seizure history (N=12): average: 39; range: 1-280
	Cases with seizure history (N=8): average: 25; range: 10-669

## 4 DISCUSSION

DPV II found 28 AERS cases (21 domestic, 7 foreign; average patient age of 25 years, range 17-40 years) of seizure related activity in association with Implanon use. The reviewer finds that the AERS case series suggests a causal association between Implanon and seizure related activity in some cases. The reviewer cannot ascertain whether the seizure activity is related to the device-like properties of Implanon (insertion related events) or to exposure to the active substance (etonogestrel).

An causal association between Implanon and seizure related activity is suggested based on the following information reviewed from postmarketing adverse event cases:

- 1) A temporal relationship exists between Implanon insertion and the onset of seizures. In three cases, seizures occurred immediately or within 24 hours of implantation. The first case (ISR#6476666) describes a female of unknown age with no seizure history who experienced an epileptic fit within 24 hours of Implanon insertion. In the second case (ISR#6179141), a 27-year-old female with no seizure history experienced a seizure five minutes after Implanon insertion (concomitant medication use was unknown). The third case (ISR#5678773) describes a female of unknown age experiencing seizures lasting 3-5 seconds five minutes after Implanon insertion.
- 2) Seven cases of patients experiencing seizure related activity leading to serious outcomes with no seizure history and concomitant anticonvulsant use
- 3) Confounding by concomitant medications was minimal with only two cases reporting concomitant medications other than Implanon and anticonvulsant therapy (for example, Adderall, Effexor, Paxil).

An evaluation of a possible drug interaction between Implanon and anticonvulsants resulting in increased seizure activity is unlikely. In eight cases, the reviewer found patients experiencing seizure related activity in conjunction with Implanon use while taking concomitant anticonvulsant medications such as carbamazepine, lamotrigine, phenytoin, phenobarbital, and topiramate. Although the patient's baseline seizure activity was unknown in all of the cases, five cases report possible exacerbations of seizure activity in conjunction with Implanon use. In one case (ISR#6084848), a 40-year-old female patient experienced an aggravation of childhood seizures without current anticonvulsant therapy. In another case (ISR#5566292), a 36-year-old female patient experienced a seizure 10 days after Implanon insertion and the Dilantin blood level was found to be subtherapeutic (Dilantin level=9.4; no baseline Dilantin or albumin blood level reported). In the label, Implanon is not recommended for women who require chronic use of drugs that are potent inducers of hepatic enzymes because Implanon is likely to be less effective for these women. Because anticonvulsants typically are inducers of hepatic enzymes and etonogestrel is metabolized in hepatic enzymes, the anticonvulsants cause, or would be expected to cause, decreased levels of etonogestrel.<sup>1,3</sup> Furthermore, based on this known mechanism, a drug interaction between Implanon and anticonvulsants resulting in lower anticonvulsant blood levels or lower seizure threshold is unlikely.

## 5 CONCLUSION

An evaluation of AERS postmarketing adverse event cases has determined that Implanon may be causally associated with the initiation or exacerbation of seizures in some cases.

Eight cases suggested the possibility of a drug interaction between Implanon and anticonvulsant medications resulting in increased seizure activity.

## 6 RECOMMENDATIONS

DPV II recommends the Sponsor update the Implanon label to include "convulsions" in the **Postmarketing** section; DPV II will continue pharmacovigilance activities concerning Implanon.

## **7 REFERENCES**

1. Accessed Implanon (etonogestrel implant) label information. NDA 21-529. Label approved on 02/19/2009. ORGANON, Inc.
2. Accessed Norplant and Norplant II (levonorgestrel implant) approval history, label information, and related documents. NDA 19-897 and NDA 20-544. Norplant II Label approved on 11/22/2002, Population Council (company).
3. Accessed anticonvulsant label information for the following drugs:  
Tegretol (carbamazepine, NDA 16-608, label approved 04/23/2009)  
Lamictal (lamotrigine, NDA 20-241, label approved 05/08/2009)  
Dilantin (phenytoin, ANDA 84-349, label approved 05/06/2009)  
Topamax (topiramate. NDA 20-505, label approved 12/22/2009)

## 8 APPENDIX

Brief summary of cases of seizure related activity associated with Implanon, etonogestrel implant (N=28)

ISR Number	Manufacturer Number	Country	Initial FDA Received Date	Age	Reported Adverse Events	History of Seizures?	Concomitant Anticonvulsant?	Reported Outcome
4015767	PHNR2002AU00457	AU	11/20/2002	30	aggravated convulsions	Y	Y carbamazepine	HO
5078269	AU-JNJFOC-20060802496	AU	8/11/2006	U	convulsion	U	Y carbamazepine	HO
5566292	2007-168830-NL	US	12/14/2007	36	seizure	Y	Y dilantin	OT
5567982	2007-168879-NL	US	12/18/2007	17	possible seizure	N	U	OT
5606783	2008-170547-NL	US	1/25/2008	30	seizure	N	N	HO
5678773	2008-173647-NL	US	3/21/2008	U	seizure	U	U	OT
5819970	2008-174077-NL	US	4/2/2008	19	seizure	N	U	OT
5883319 <i>Direct Report</i>	CTU 349300	US	9/11/2008	28	seizure	N	N	HO

ISR Number	Manufacturer Number	Country	Initial FDA Received Date	Age	Reported Adverse Events	History of Seizures?	Concomitant Anticonvulsant?	Reported Outcome
6016384	2008-188321-NL	US	12/18/2008	23	seizure	Y	N	OT
6055119	2009-189558-NL	US	1/22/2009	18	seizure	N	N Effexor, Adderall	HO
6055267	2009-189490-NL	US	1/23/2009	25	epileptic reaction	N	N	OT
6084848	2009-191112-NL	US	2/18/2009	40	seizure	Y	N	HO
6109507	2009-189433-NL	US	1/22/2009	22	seizure	N	N	OT
6156304	2009-194218-NL	US	4/13/2009	32	probable seizure	U	U	OT
6160290	2009-193254-NL	US	3/27/2009	U	seizure	Y	U	OT

ISR Number	Manufacturer Number	Country	Initial FDA Received Date	Age	Reported Adverse Events	History of Seizures?	Concomitant Anticonvulsant?	Reported Outcome
6179141	2009-194753-NL	US	4/21/2009	27	seizure	N	U	OT
6237765	2009-198262-NL	US	6/18/2009	28	seizure	N	N	LT
6253532 <i>Direct Report</i>	CTU 383073	US	6/29/2009	22	seizure	U	U	HO
6278722	2009-200344-NL	US	7/21/2009	U	seizure	U	U	OT
6287492	2009-200450-NL	US	7/27/2009	22	seizure	U	U	HO
6475610	2009SP016820	US	11/19/2009	20	possible seizure	N	Y topiramate for migraines	OT
6476666	2009SP017744	GB	11/19/2009	U	epileptic fit	N	N	OT

ISR Number	Manufacturer Number	Country	Initial FDA Received Date	Age	Reported Adverse Events	History of Seizures?	Concomitant Anticonvulsant?	Reported Outcome
6536763	2009SP031285	GB	11/19/2009	28	epileptic fit	Y	Y topiramate	OT
6540425	2009SP036672	US	1/13/2010	19	seizure	N	U	OT
6615749	2010SP009567	FR	2/26/2010	34	exacerbation of seizures	Y	Y carbamazepine, phenobarbital (Gardenal), Paxil	OT
6639192	2010SP013656	GB	3/12/2010	U	seizure	U	Y anticonvulsant drug unknown	OT
6645850	2010SP013720	US	3/18/2010	18	seizure	U	U	OT
6651564	B0640532A	GB	3/25/2010	20	epileptic fit	Y	Y lamotrigine	OT

**Reporting Country:** US=United States; GB=United Kingdom; AU=Australia; FR=France

**Reported Outcome:** LT=life threatening; HO=hospitalization; OT=other serious outcome

**All categories:** U=Unknown

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	ORIG-1	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG
SAFETY-936	ORIG-1	FOOD AND DRUG ADMINISTRATION	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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/s/

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MARK S MILLER  
05/19/2010

ADRIENNE M ROTHSTEIN  
05/19/2010

ROBERT M BOUCHER  
05/21/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: April 27, 2010

To: Scott Monroe, M.D. Director  
Division of Reproductive and Urologic Products (DRUP)

Through: Mary Willy, PhD, Deputy Director  
Division of Risk Management (DRISK)

LaShawn Griffiths, RN, MSHS-PH, BSN  
Patient Labeling Reviewer, Acting Team Leader  
Division of Risk Management

From: Barbara Fuller, RN, MSN, CWOCN  
Patient Labeling Reviewer  
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): (b) (4) (etonogestrel implant) 68 mg

Application Type/Number: NDA 21-529

Submission Number: S-007

Applicant/sponsor: Organon Schering-Plough, Inc.

OSE RCM #: 2009-2188

## 1 INTRODUCTION

On July 29, 2009 Organon Schering-Plough, Inc submitted a Prior Approval Supplement New Drug Application for (b) (4) (etonogestrel implant) 68 mg. The original NDA was approved on July 17, 2006. The Prior Approval Supplement provides for a new radiopaque version of the implant rod and a Next Generation Implanon Applicator.

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for (b) (4) (etonogestrel implant) 68 mg. Please let us know if DRUP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

## 2 MATERIAL REVIEWED

- Draft (b) (4) (etonogestrel implant) 68 mg Prescribing Information (PI) submitted on July 29, 2009, revised by the Review Division throughout the current review cycle and received by DRISK on April 13, 2010.
- Draft (b) (4) (etonogestrel implant) 68 mg Patient Package Insert (PPI) submitted on July 29, 2009, and received by DRISK on April 13, 2010.
- Guidance for Industry: Labeling for Combined Oral Contraceptives dated September 2007.

## 3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- rearranged information due to conversion of the PI to PLR format
- removed unnecessary or redundant information
- ensured that the PPI meets the Regulations as specified in 21 CFR 208.20
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	SUPPL-7	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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/s/

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BARBARA A FULLER  
04/27/2010

MARY E WILLY  
04/27/2010  
I concur

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

**\*\*\*PRE-DECISIONAL AGENCY MEMO\*\*\***

---

Date: April 6, 2010

To: Charlene Williamson  
Regulatory Project Manager  
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A.  
Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Carrie Newcomer, Pharm.D.  
Regulatory Review Officer  
DDMAC

Re: **NDA 21-529**  
DDMAC labeling comments for [REDACTED] (b) (4)  
[REDACTED] 68 mg

---

**Background**

DDMAC has reviewed the following label materials for [REDACTED] (b) (4)  
[REDACTED] 68 mg, submitted to DRUP on September 1, 2009:

Healthcare Provider Directed:

- Prescribing Information (PI)

Consumer Directed:

- Patient Product Information (PPI)

Please note that our comments are based on the substantially complete version of the draft label sent to DDMAC on March 30, 2010. In addition, we have considered the Implanon™ PI (approved February 2009) in our review of the draft [REDACTED] (b) (4) PI.

We offer the following comments:

**PI & PPI**

Please see our attached comments.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)  
(301) 796-3821, or [janice.maniwang@fda.hhs.gov](mailto:janice.maniwang@fda.hhs.gov)
- Carrie Newcomer (Consumer directed materials)  
(301) 796-1233, or [carrie.newcomer@fda.hhs.gov](mailto:carrie.newcomer@fda.hhs.gov)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	SUPPL-7	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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/s/

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JANICE L MANIWANG  
04/06/2010

**MEMORANDUM**

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

---

DATE: March 30, 2010

TO: Scott E. Monroe, M.D.  
Director  
Division of Reproductive and Urologic Products (DRUP)

FROM: Michael F. Skelly, Ph.D.  
Pharmacologist  
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. \_\_\_\_\_  
Acting Team Leader (Bioequivalence)  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-529, Implanon®  
(Etonogestrel Implants), sponsored by Organon USA Inc.

At the request of the Division of Reproductive and Urologic Products (DRUP), the Division of Scientific Investigations (DSI) conducted audits of clinical and analytical portions of the following bioequivalence study:

**Study #34528:**

**Title:** "A randomized, double-blind, parallel group, bioequivalence study of Implanon® and Radiopaque Implanon"

The clinical portions of the study were conducted at nine sites, and the analytical portion of the study was conducted at N.V. Organon (later Schering-Plough, and currently MSD or Merck Sharp Dohme). DSI conducted an audit of clinical portions of study #34528 at Dinox B.V. in Groningen, The Netherlands, and analytical portions of the study at MSD in Oss, The Netherlands. Following the inspections (February 22-26, 2010 at Dinox, and March 1-5, 2010 at MSD), Form FDA 483 was issued at each site. DSI received responses to the Form FDA 483 observations from Dinox on March 3, and from MSD on March 26. Our evaluation of the Form FDA 483 observations and the firms' responses follows:

**Dinox B.V., Groningen**

- 1. The firm did not retain reserve samples for the study (No. 34528). The study drug products were provided in three shipments as follows. One shipment of four units was designated as back-up supplies and was returned to the sponsor. The other two shipments provided by the sponsor consisted of 24 units and eight units, 32 units in total, and were used for subject dosing with none remaining.**

In addition, the sponsor's representative collected the sealed blinding codes for the subject-treatment randomizations from Dinox. Therefore, the inspection could not confirm the product or its shipment, administered to individual subjects, through reserves (required by 21 CFR 320.38) or through verifiable dosing records. However, the inspection confirmed that the Dinox-affiliated radiology unit maintained x-ray records independently of the sponsor's control. These records reveal whether the individual implants were electron-dense (i.e., the barium-containing test formulation), as described accurately in the study report. DSI recommends using the x-ray data as supportive evidence.

DSI notes that manufacturing reserves maintained by the sponsor cannot be substituted for this purpose. The clinical investigator at Dinox concurred with the observation and stated in the response to Form FDA 483 that Dinox will maintain reserves in future bioequivalence studies.

- 2. Administration of informed consent to the first 12 subjects utilized a consent form version (15 March 2005) that had not been approved by the reviewing ethics committee. The approved version (8 April 2005) was administered to the subjects at a subsequent visit. The approved version included changes to information on study risks and information on subject confidentiality.**

The Dinox response agrees with the observation, and emphasizes that these subjects later executed the correct consent. Dinox believes, and DSI agrees, that both consents provided subject safety and protections. Nevertheless, future Dinox studies will assure that consent forms are reviewed in proper and timely fashion.

MSD, Oss

- 1. Stability during long-term frozen storage was not validated pre-study for the same assay procedure used in study 34528 (b)(4) solid phase extraction with radioimmunoassay). Study samples were stored as long as 650 days (mean 231 days) before assay. However, within the study, stability of QCs was demonstrated for 105 days.**

The quality control (QC) program during the study measured the concentration of QC samples stored for as long as 105 days of age, against freshly-prepared calibrators. These QC data established quantitative accuracy (stability for 105 days, including extraction recovery, measurement, and interferences) with the identical method used in the study.

The response to Form FDA 483 includes recent data on reassay of selected samples from study #34528, in order to extend the stability and accuracy of these samples from the time of their original (at less than 105 days in storage) to the present. The reassays used freshly-prepared calibrators. Storage stability for more than two years results from combining QC and reassay data. DSI recommends using this as evidence of stability during storage.

MSD's response re-introduces the validation report on long-term stability from (b)(4). This validation (also submitted to the NDA) used the same radioimmunoassay for quantitation, but (b)(4) for the first stages of the procedure. DSI believes that the (b)(4) stability data are not interchangeable with solid phase extraction on (b)(4) stationary phase.

- 2. Run acceptance/rejection decisions were made inappropriately, by averaging replicate determinations of QC sample concentrations. When QC data were calculated in the same way as study sample data, the originally-failed run 27 would pass, and the passed runs 14 and 36 would fail.**

During the study, four replicate QC values (two solid phase extractions, then duplicate radioimmunoassay of each extract) at each concentration were averaged to a single value, and used for run acceptance/rejection. Study samples were assayed as duplicate radioimmunoassays of a single extract. Thus, the QCs

were treated differently from study samples. When QCs were calculated in the same way as study sample data, one of the originally-failed runs (#27) would pass, and two of the passed runs (#14 and 36) would fail.

MSD responds that the concentration data in runs #27 and its repeated run #31 are similar. Their revised study report combines data from both of these runs. The revised report excludes data from runs #14 and #36. See Attachments. DSI recommends that this response is reasonable.

**3. Five serum samples (subjects (b) (6), (b) (6), (b) (6), (b) (6), and (b) (6)) with insufficient volume to confirm measurable pre-dose ENG concentrations were listed as "not reportable." However, other measurable pre-dose ENG concentrations were confirmed to be accurate.**

The five subjects with pre-dose ENG concentrations unconfirmed by duplicate reassay are likely to have had true presence of drug, as was the case with several subjects with confirmed pre-dose concentrations from pre-study use of oral contraceptives. Note that pre-dose samples from subjects (b) (6) and (b) (6) were reassayed only in singlet, confirming the original assay, but were nevertheless listed as "not reportable." MSD agreed with the observation. The data from all of these assays are incorporated into MSD's revised study report, provided in their response to Form FDA 483. DSI recommends using all of the data.

**4. Failure to evaluate incurred sample reproducibility (ISR). Although 44 study samples in analytical run 27 were reassayed in run 31, because of the inappropriate process cited in observation #2, these 44 reassayed samples represent only about 2% of total study samples.**

Incurred sample reproducibility (ISR) was not evaluated in this study. The 44 study samples in analytical run 27 were reassayed in run 31, because of the inappropriate process cited in the observation above. These 44 reassayed samples represent only about 2% of total study samples, fewer than the 10% recommended by DSI. In response to the Form FDA 483 observation, MSD reassayed another 156 samples to meet the 10% recommendation. The combined data are provided in the attachment. The ISR results meet the acceptance criteria recommended by DSI. DSI recommends using these data to evaluate ISR for this study.

**Conclusions:**

Following the above inspections, the Division of Scientific Investigations recommends the following:

- Although Dinox and possibly other clinical sites for this study failed to retain reserve samples, there is partial confirmatory data in the independently-maintained x-rays. Despite this violation of the regulations, DSI recommends that the biopharmaceutics review consider the weight-of-evidence.
- Deficiencies in informed consent had little or no consequence to subject protection and bioequivalence.
- Deficiencies in method validation (stability assessments) and study conduct (run acceptance/rejection, pre-study concentrations, ISR) were corrected in post-study experiments and report amendments.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

---

Michael F. Skelly, Ph.D.

Attachments: Two pdf files

**Final Classifications:**

VAI - Dinox B.V., Groningen, The Netherlands  
FEI 30074557406  
VAI - MSD, Oss, The Netherlands  
FEI 3007113245

CC:  
DSI/GLPBB/Yau/Rivera-Lopez/CF  
OCP/HFD-880/Bashaw/Kim  
OND/DRUP/Williamson  
HFR-PA2535/Hall  
Draft: MFS 3/29/10  
Edit: MKY  
DSI: 6005  
O:\BIOEQUIV\EIRCOVER\21529org.eto.doc  
FACTS: 1109554

Email:  
CDER DSI PM TRACK

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	SUPPL-7	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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/s/

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MICHAEL F SKELLY  
03/30/2010

MARTIN K YAU  
03/30/2010

## **DSI CONSULT**

### **Request for Biopharmaceutical Inspections**

**DATE:** September 18, 2009

**TO:** Associate Director for Bioequivalence  
Division of Scientific Investigations, HFD-48

**THROUGH:** E. Dennis Bashaw, Pharm.D.  
Director, Division of Clinical Pharmacology III  
Office of Clinical Pharmacology

**FROM:** Charlene Williamson, Regulatory Health Project Manager  
Division of Reproductive and Urologic Products

**SUBJECT:** Request for Biopharmaceutical Inspections  
NDA 21-529  
Implanon (Etonogestrel Implants)

#### **Study/Site Identification:**

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
FOR01C	Dinox BV, Hanzeplein 1, entrance 53, 9713 GZ Groningen, Netherlands  Principal Investigator Name: Tjeerd Korver Address: NV Organon, PO Box20, 5340 BH Oss, Netherlands Phone: 31-412-661840	Schering-Plough, Molenstraat 110, 5342 CC Oss, Netherlands  Bioanalyst Name: W. Koslowksy Address: NV Organon, PO Box 20, 5340 BH Oss, Netherlands

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **March 30, 2010**. We intend to issue an action letter on this application by **May 30, 2010**.

Should you require any additional information, please contact Charlene Williamson.

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/s/  
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ZETA-MAE C WILLIAMSON  
09/22/2009

EDWARD D BASHAW  
09/23/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021529Orig1s007**

**PROPRIETARY NAME REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: April 22, 2011

Application Type/Number: NDA 021529

Through: Carlos Mena-Grillasca Rph, Team Leader  
Kellie Taylor, PharmD, Associate Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Lissa C. Owens , Pharm.D, Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Proprietary Name Review

Drug Name(s) & Strength(s): Nexplanon (Etonogestrel) Implant 68 mg

Applicant: Merck & Co. Inc.

OSE RCM #: 2011-1282

**\*\*\* Note: This review contains proprietary and confidential information that should not be released to the public.\*\*\***

## **1 INTRODUCTION**

This re-assessment of the proprietary name responds to a notification from the Division of Reproductive and Urology Products that NDA 021529 may be approved within 90 days. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Nexplanon, acceptable in OSE Review #2010-2415, dated January 31, 2011.

## **2 METHODS AND RESULTS**

For the proposed proprietary name, DMEPA staff searched a standard set of databases and information sources (see section 4) to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name review. We used the same search criteria that was used in OSE Review #2010-2415 for the proposed proprietary name, Nexplanon. Since none of the proposed product characteristics were altered we did not re-evaluate previous names of concern. Additionally, DMEPA searched the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates.

The searches of the databases yielded no new names thought to look similar to Nexplanon and represent a potential source of drug name confusion. DMEPA staff also did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name Nexplanon, as of April 20, 2011.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

The Proprietary Name Risk Assessment findings indicate that the proposed name, Nexplanon, is not vulnerable to name confusion that could lead to medication errors nor is the name considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Nexplanon, for this product at this time.

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Reproductive and Urology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

## 4 REFERENCES

1. **OSE review #2010-2415 Proprietary Name Review of Nexplanon; Fava, Walter.**
2. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)  
Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.
3. ***USAN Stems*** (<http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml>)  
USAN Stems List contains all the recognized USAN stems.
4. ***Division of Medication Error Prevention and Analysis proprietary name 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.

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/s/  
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CARLOS M MENA-GRILLASCA on behalf of LISSA C OWENS  
04/22/2011

CARLOS M MENA-GRILLASCA  
04/22/2011

KELLIE A TAYLOR  
04/25/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: January 31, 2011

Application Type/Number: NDA 021529/S-007

Through: Carlos M Mena-Grillasca RPh, Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Walter Fava, RPh, MSed, Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Proprietary Name Review

Drug Name(s): Nexplanon (Etonogestrel) Implant 68 mg

Applicant/sponsor: Merck & Co. Inc.

OSE RCM #: 2010-2415

**\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\***

## CONTENTS

EXECUTIVE SUMMARY .....	3
1 BACKGROUND.....	3
1.1 Introduction.....	3
1.2 Regulatory History .....	3
1.3 Product Information .....	3
2 METHODS AND MATERIALS .....	3
2.1 Search Criteria.....	4
2.2 Prescription Analysis Studies.....	4
3 RESULTS.....	5
3.1 Data base and Information Sources.....	5
3.2 Expert Panel Discussion.....	5
3.3 Prescription Analysis Studies.....	5
3.4 Comments from the Division of Reproductive and Urologic Products (DRUP) .....	6
3.5 Safety Evaluator Risk Assessment.....	6
4 DISCUSSION .....	6
4.1 Promotional Assessment .....	6
4.2 Safety Assessment.....	6
5 CONCLUSIONS .....	7
5.1 Comments to the Applicant.....	7
6 REFERENCES .....	8
APPENDICES.....	9

## **EXECUTIVE SUMMARY**

This review summarizes the Division of Medication Error Prevention and Analysis' evaluation for the proposed proprietary name, Nexplanon, for Etonogestrel Implant. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name, Nexplanon, acceptable for this product.

We consider this a final review of the proposed proprietary name, Nexplanon. However, if the action on this Supplemental NDA is delayed 90 days beyond the date of this review, the proposed proprietary name, Nexplanon, must be re-reviewed.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review responds to a request from Merck & Co. Inc. dated November 12, 2010, for an assessment of the proposed proprietary name, Nexplanon, regarding potential name confusion with other proprietary or established drug names in the usual practice settings as well as a promotional assessment of the name.

### **1.2 REGULATORY HISTORY**

The Applicant submitted the proposed proprietary name (b) (4) for review on September 23, 2009. DMEPA objected to the proposed name in OSE review # 2009-1753, dated December 23, 2009. On March 1, 2010 the Applicant submitted a reconsideration request. However, DMEPA maintained its objection in OSE review # 2010-498, dated May 21, 2010.

On July 6, 2010 the Applicant submitted a formal Dispute Resolution at the Office level (OSE), which was denied on August 5, 2010. Subsequently, the Applicant submitted a formal Dispute Resolution at the Center level (CDER) on August 9, 2010, which was denied on September 21, 2010. Thus, the Applicant is currently seeking approval of the proposed proprietary name Nexplanon.

### **1.3 PRODUCT INFORMATION**

Nexplanon is a line extension of the existing Implanon product. Nexplanon (etonogestrel) implant, 68 mg, is a subdermal long-acting hormonal contraceptive that provides prevention of pregnancy for up to three years. Each implant is supplied in the needle of a disposable applicator which is packaged in a blister. The new product differs from the currently marketed product in two ways: (1) it contains radiopaque coating (15 mg barium sulfate) to allow visualization of the implant by means of X-rays or CT scans, and (2) the applicator has been modified to facilitate the insertion of the implant. The Applicant will phase out the currently marketed Implanon product after the introduction of the new one. However, both products will coexist in the market for at least three years.

## **2 METHODS AND MATERIALS**

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment

for all proprietary names. Sections 2.1, 2.2, and 2.3 identify specific information associated with the methodology for the proposed proprietary name, Nexplanon.

## **2.1 SEARCH CRITERIA**

For this review, particular consideration was given to drug names beginning with the letter ‘N’ when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.<sup>1,2</sup>

To identify drug names that may look similar to Nexplanon, the DMEPA safety evaluators also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (nine letters), upstrokes (two, capital letter ‘N’ and lower case ‘l’), down strokes (one, lower case ‘p’), cross strokes (one, lower case ‘x’) and dotted (none). Additionally, several letters in Nexplanon may be vulnerable to ambiguity when scripted (See Appendix B). As a result, the DMEPA safety evaluator also considers these alternate appearances when identifying drug names that may look similar to Nexplanon.

When searching to identify potential names that may sound similar to Nexplanon, the safety evaluators search for names with similar number of syllables (three), stresses (NEX-pla-non, nex-PLA-non, and nex-pla-NON), and placement of vowel and consonant sounds. The Applicant’s intended pronunciation (NEX-plah-non) was also taken into consideration, as it was included in the External Proprietary Risk Assessment. However, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered. (See Appendix B)

## **2.2 PRESCRIPTION ANALYSIS STUDIES**

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient medication order, outpatient and verbal prescription was communicated during the FDA prescription studies. (See Appendix C for samples and results)

## **2.3 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT**

For this product, the Applicant submitted an external evaluation of the proposed proprietary name, Nexplanon, conducted by (b) (4). The Division of Medication Error Prevention and Analysis conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in DMEPA’s database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator’s Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

---

<sup>1</sup> Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

<sup>2</sup> Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

After the Safety Evaluator has determined the overall risk associated with proposed name, the Safety Evaluator compares the findings of his/her overall risk assessment with the findings of the proprietary name risk assessment submitted by the Sponsor. The Safety Evaluator then determines whether the Division's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, the Division of Medication Error Prevention and Analysis provides a detailed explanation of these differences.

### **3 RESULTS**

The following sections describe the findings from our database searches, expert panel discussion, prescription analysis studies and safety evaluator risk assessment.

#### **3.1 DATA BASE AND INFORMATION SOURCES**

The DMEPA safety evaluator searches yielded a total of 19 names as having some similarity to the name Nexplanon.

Eight of the names were thought to look like Nexplanon. These include: Nexium, Naltrexone, Naprelan, Mexiletine, Neoprofen, Norplant, Norpramin, and Nexphen. Six of the names, (b) (4), Nexavar, (b) (4), (b) (4), Exelon, and Mestinon, were thought to sound like Nexplanon. The remaining five names were thought to look and sound similar to Nexplanon: Implanon, Nexplanon, Nexiclon XR, (b) (4), and Nexterone.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of January 4, 2011.

#### **3.2 EXPERT PANEL DISCUSSION**

The Expert Panel reviewed the pool of names identified by DMEPA Safety Evaluators (See Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Nexplanon.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

#### **3.3 PRESCRIPTION ANALYSIS STUDIES**

A total of 37 practitioners responded to the study with no responses overlapping with an existing drug product name. Eleven of the participants interpreted the name correctly as "Nexplanon," predominantly in the inpatient and verbal studies. The remainder of the responses misinterpreted the drug name. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

#### **3.4 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT**

An external proprietary name analysis was conducted by (b) (4) on November 18, 2010, to evaluate the proprietary name Nexplanon. (b) (4) identified and evaluated a total of ten drug names thought to have some potential for confusion with the name Nexplanon (Exelon, Hexalen, Implanon, melphalon, naltrexone, Naprelan, Naproxen, Nexavar, Nexium, and Norplant).

Three of the ten names were not previously identified in the DMEPA Safety Evaluator searches, the Expert Panel Discussion, or FDA prescription studies. DMEPA included these names in our analysis of the proposed proprietary name.

(b) (4)'s analysis concluded that Nexplanon is an acceptable proprietary name for the radiopaque etonogestrel implant.

### **3.5 SAFETY EVALUATOR RISK ASSESSMENT**

Independent searches by the primary Safety Evaluator identified one additional name, Norplant II, which was thought to look similar to Nexplanon.

Thus, we identified a total of 23 names with some similarity to Nexplanon: 1 identified by the primary Safety Evaluator, 3 names identified in the External Study, and 19 names identified in section 3.1 above.

### **3.6 COMMENTS FROM THE DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)**

#### **3.6.1 Initial Phase of Review**

In response to the OSE December 1, 2010 e-mail, the Division of Reproductive and Urologic Products (DRUP), did not offer any comments relating to the proposed name.

#### **3.6.2 Midpoint of Review**

On January 11, 2011, DMEPA notified DRUP via e-mail that we found the proposed name, Nexplanon, acceptable. On January 14, 2011, DRUP responded “the name is acceptable” to them.

## **4 DISCUSSION**

The proposed name, Nexplanon, was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. Furthermore, input from pertinent disciplines involved with the review of this application was considered accordingly.

### **4.1 PROMOTIONAL ASSESSMENT**

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name. DMEPA and the Division of Reproductive and Urologic Products concurred with the findings of DDMAC’s promotional assessment of the proposed name.

### **4.2 SAFETY ASSESSMENT**

In this review we evaluated the proposed name, Nexplanon, from a look-alike/sound-alike perspective and considered other aspects of the name that might function as a source of error. We identified 23 names as having some similarity to the proposed name, Nexplanon. No other aspects of the name were found to be a source of error.

Four of the 23 names did not undergo Failure Mode and Effect Analysis (FMEA) for the following reasons: One name (Nexplanon) was identified as a trademark licensed to Merck & Co., likely for this product, one name ((b) (4)) was determined not to be a drug name, and two

names were determined to be discontinued products which have no generic equivalent available (see Appendix D).

Failure mode and effects analysis (FMEA) was applied to determine if the proposed proprietary name could potentially be confused with the remaining 21 names and lead to medication errors. This analysis determined that the name similarity between Nexplanon and all of these 21 identified names was unlikely to result in medication error for the reasons presented in Appendix E.

## **5 CONCLUSIONS**

The Proprietary Name Risk Assessment indicates that the proposed name, Nexplanon, is not vulnerable to name confusion that could lead to medication errors, nor is it considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Nexplanon, for this product at this time. The Applicant will be notified via letter from DMEPA.

We consider this a final review of the proposed proprietary name, Nexplanon. However, if the action on this supplemental NDA is delayed 90 days beyond the date of this review, the proposed proprietary name, Nexplanon, must be re-reviewed.

If you have further questions or need clarifications, please contact Maria Wasilik, project manager, at 301-796-0567.

### **5.1 COMMENTS TO THE APPLICANT**

We have completed our review of the proposed proprietary name, Nexplanon, and have concluded that the name is acceptable.

The proposed proprietary name, Nexplanon, will be re-reviewed 90 days prior to the approval of the Supplemental NDA. If we find the name unacceptable following the re-review, we will notify you.

## 6 REFERENCES

1. ***Micromedex Integrated Index*** (<http://csi.micromedex.com>)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO***  
(<http://factsandcomparisons.com>)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***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.

6. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

7. ***Electronic online version of the FDA Orange Book***  
(<http://www.fda.gov/cder/ob/default.htm>)

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. ***U.S. Patent and Trademark Office*** (<http://www.uspto.gov>)

USPTO provides information regarding patent and trademarks.

9. ***Clinical Pharmacology Online*** ([www.clinicalpharmacology-ip.com](http://www.clinicalpharmacology-ip.com))

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

**10. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at ([www.thomson-thomson.com](http://www.thomson-thomson.com))**

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

**11. Natural Medicines Comprehensive Databases ([www.naturaldatabase.com](http://www.naturaldatabase.com))**

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

**12. Stat!Ref ([www.statref.com](http://www.statref.com))**

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

**13. USAN Stems (<http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml>)**

USAN Stems List contains all the recognized USAN stems.

**14. Red Book Pharmacy's Fundamental Reference**

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

**15. Lexi-Comp ([www.lexi.com](http://www.lexi.com))**

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

**16. Medical Abbreviations Book**

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

## **APPENDICES**

### **Appendix A:**

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. 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.<sup>3</sup>

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies.

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<sup>3</sup> National Coordinating Council for Medication Error Reporting and Prevention.  
<http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.<sup>4</sup> DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.<sup>5</sup> DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in

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<sup>4</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

<sup>5</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

clinical settings. If provided, DMEPA will consider the Sponsor’s intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice.

**Table 1.** Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

<b>Type of similarity</b>	<b>Considerations when searching the databases</b>		
	<i>Potential causes of drug name similarity</i>	<i>Attributes examined to identify similar drug names</i>	<i>Potential Effects</i>
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication</li> <li>Names may look similar when scripted and lead to drug name confusion in written communication</li> </ul>
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may look similar when scripted, and lead to drug name confusion in written communication</li> </ul>
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may sound similar when pronounced and lead to drug name confusion in verbal communication</li> </ul>

Lastly, the DMEPA staff also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

## **1. Database and Information Sources**

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

## **2. CDER Expert Panel Discussion**

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

## **3. FDA Prescription Analysis Studies**

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 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 send their interpretations of the orders via e-mail to DMEPA.

## **4. Comments from the OND review Division or Generic drugs**

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division responsible for the application for their comments or concerns with the proposed proprietary name and 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 DDMAC's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND or 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 concur/not concur with DMEPA's final decision.

## **5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name**

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.<sup>6</sup> When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

***“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?”***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

***“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA

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<sup>6</sup> Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

- a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Sponsor. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name

changes, in the past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. (See Section 4 for limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

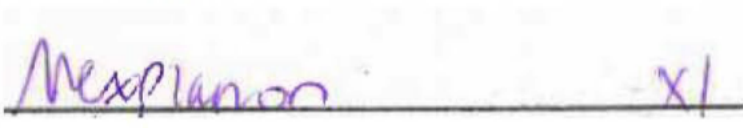
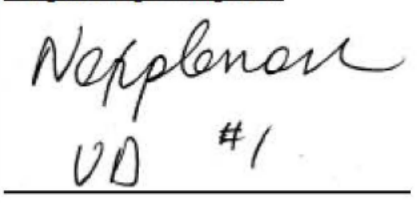
In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

**Appendix B:** Letters with possible orthographic or phonetic misinterpretation

Letters in Name, Nexplanon	Scripted may appear as	Spoken may be interpreted as
Upper case 'N'	'M', 'V', 'W', 'U'	Gn, Kn, Pn, M
lower case 'e'	a, i, l, p, o	Any vowel
lower case 'x'	a, d, f, k, n, p, r, t, v, y	ck, s, k
lower case 'p'	g, j, l, q, yn, ys, x	b
lower case 'l'	b, e, s, A, P, I	w
lower case 'a'	el, ci, cl, d, o, u	Any vowel
lower case 'n'	m, u, x, r, h, s	d, m
lower case 'o'	a, c, e, u	Any vowel

**Appendix C: Prescription study samples and results**

**Figure 1. Nexplanon Study (conducted on November 19, 2010)**

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Medication Order:</u></p>  <p><u>Outpatient prescription:</u></p> 	<p>Nexplanon Use as Directed #1</p>

**FDA Prescription Study Responses.**

<b>Inpatient Medication Order</b>	<b>Outpatient Prescription</b>	<b>Voice Prescription</b>
Mexplanon	Nexplenon	Nexplanon
Mexplanon	Nexplenon	Nexplanon
Nexplanon	Nexplenon	Nexplene
Nexplanon	Nexplenon	Nexplena
Nexplanin	Nexplanon	Nexplanon
Nexplanon	Nexplenon	Nexplanon
Mexplanon	Nexplenon	Nexplenade
Mexplanon	Nexplenon	Nesplenon
Nexplanon	Nexplenov	Nexplanon
Mexplanon	Nexplenon	Nexplanon
	Nexplenon	
	Nexplenon	
	Nexplenon	
	Nexplenerr	

**Appendix D:** Discontinued products with no generic therapeutic equivalent

<b>Product name with potential for confusion</b>	<b>Similarity to proposed proprietary name</b>	<b>Strength</b>	<b>Usual Dose</b>	<b>Marketing status</b>
Norplant (levonorgestrel) Norplant II (levonorgestrel)	Look	36 mg implant 75 mg implant	Two implants subdermally up to 5 years	Norplant and Norplant II are discontinued and no longer marketed with no generic equivalents available

**Appendix E:** Risk of name confusion minimized by preventions listed.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Failure Mode of name confusion prevented by the combination of stated product characteristics as well as orthographic and/or phonetic differences as described.
Nexplanon (Etonogestrel)		68 mg implant	One implant subdermally every 3 years	
Nexium (esomeprazole)	Look	20 mg and 40 mg tablets	20 mg to 40 mg once a day	<p><b>Orthographic difference:</b> Nexplanon includes the upstroke letter 'l' and the downstroke letter 'p', which help to differentiate it from Nexium when scripted. Nexplanon includes three additional letters (nine vs. six) providing additional length and shape when scripted.</p> <p><b>Strength:</b> Single (68 mg) vs Multiple (20 mg and 40 mg)</p> <p><b>Dosage Form:</b> Implant vs tablet</p> <p><b>Route of Administration:</b> Subdermal vs. oral</p> <p><b>Frequency of use:</b> One time every 3 years vs. daily</p>
Naltrexone	Look	25 mg, 50 mg, and 100 mg tablet	50 mg by mouth once a day	<p><b>Orthographic difference:</b> Nexplanon contains the downstroke letter 'p' and one upstroke letter 'l' which helps differentiate it when scripted from Naltrexone which has two upstroke letters, 'l' and 't'.</p> <p><b>Strength:</b> Single (68 mg) vs. Multiple (25 mg, 50 mg, and 100 mg)</p> <p><b>Dosage form:</b> implant vs. tablet</p> <p><b>Route of Administration:</b> Subdermal vs. oral</p> <p><b>Frequency of use:</b> One time every 3 years vs. daily</p>

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Failure Mode of name confusion prevented by the combination of stated product characteristics as well as orthographic and/or phonetic differences as described.
Nexplanon (Etonogestrel)		68 mg implant	One implant subdermally every 3 years	
Naprelan (naproxen)	Look	375 mg, 500 mg, and 750 mg controlled-release tablets	1000 mg by mouth once daily	<p><b>Orthographic difference:</b> Despite the overlapping downstroke and upstroke letters ‘p’ and ‘l’ in both names, they appear in different positions between the names which helps differentiate the names when scripted. The beginning letters, ‘Nex’ in Nexplanon appear different from the beginning letters, ‘Nap’ in Naprelan when scripted.</p> <p><b>Strength:</b> Single (68 mg) vs Multiple (375 mg, 500 mg, and 750 mg)</p> <p><b>Dosage form:</b> Implant vs. tablet</p> <p><b>Route of administration:</b> Subdermal vs. oral</p> <p><b>Frequency of use:</b> One time every 3 years vs. daily</p>
Naproxen	Look and Sound	250 mg and 500 mg tablet	One tablet by mouth twice a day	<p><b>Orthographic difference:</b> ‘Nex’ in Nexplanon appear different from the beginning letters, ‘Nap’ in Naprelan when scripted. Nexplanon also contains the upstroke letter ‘l’ which Naproxen does not have.</p> <p><b>Phonetic difference:</b> The beginning syllable ‘Nex’ in Nexplanon sounds different than the beginning syllable, ‘Nap’ in Naproxen. Additionally the ‘x’ sound in Nexplanon occurs in the first syllable whereas the ‘x’ sound in Naproxen occurs in the transition between the second and third syllables. Also, Naproxen has an ‘r’ which Nexplanon does not have.</p> <p><b>Strength:</b> Single (68 mg) vs Multiple (250 mg and 500 mg)</p> <p><b>Dosage form:</b> Implant vs. tablet</p> <p><b>Route of administration:</b> Subdermal vs. oral</p> <p><b>Frequency of use:</b> One time every 3 years vs. twice daily</p>

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Failure Mode of name confusion prevented by the combination of stated product characteristics as well as orthographic and/or phonetic differences as described.
Nexplanon (Etonogestrel)		68 mg implant	One implant subdermally every 3 years	
Melphalon	Look and Sound	2 mg tablet 50 mg injection	<p><b><u>Testicular cancer, non-Hodgkin's lymphoma, Osteogenic sarcoma, and breast cancer:</u></b></p> <p><i>Oral:</i> 150 mcg/kg/day for 7 days every 4 weeks</p> <p><b><u>Palliative treatment for multiple myeloma:</u></b></p> <p><i>Oral:</i> 6 mg by mouth every day for 2 to 3 weeks</p> <p><i>Intravenous:</i> 16 mg/m<sup>2</sup> over 15 to 20 minutes every 2 weeks x 4 doses</p> <p><b><u>Palliative treatment for non-resectable epithelial ovarian cancer:</u></b></p> <p><i>Oral:</i> 200 mcg/kg/day x 5 days</p> <p><b><u>Pediatric rhabdomyosarcoma:</u></b></p> <p><i>Intravenous:</i> 10 mg to 35 mg/m<sup>2</sup> every 21 to 28 days</p> <p><b><u>Stem cell procedures:</u></b></p> <p><i>Intravenous:</i> 140 mg/m<sup>2</sup> one day or over 2 days in divided doses prior to stem cell transplant</p> <p><b><u>Neuroblastoma:</u></b></p> <p><i>Intravenous:</i> 70 mg to 100 mg/m<sup>2</sup>/day on day 7 or 6 before bone marrow transplant</p> <p>140 mg to 220 mg/m<sup>2</sup> single dose before stem cell transplant</p> <p>50 mg/m<sup>2</sup> for 4 days</p> <p>70 mg/m<sup>2</sup> for 3 days</p> <p><b><u>Familial mediterranean fever:</u></b></p> <p><i>Intravenous:</i> 0.15 mg/kg once daily for 7 days every 6 weeks</p>	<p><b>Orthographic difference:</b> Nexplanon contains one upstroke letter, 'l' compared to two upstroke letters 'l' and one upstroke letter 'h' in Melphalon, which helps differentiate the names when scripted. Also, Nexplanon contains the cross-stroke letter, 'x' which Melphalon does not have.</p> <p><b>Phonetic difference:</b> The first two syllables, 'Nexpla' sound different from the corresponding first two syllables, 'Melpha' in Melphalon, due to the presence of the letter 'x' in the first syllable of Nexplanon compared to the corresponding letter 'l' in the first syllable of Melphalon.</p> <p><b>Strength:</b> Single (68 mg) vs Multiple (2 mg and 50 mg)</p> <p><b>Dosage form:</b> Implant vs. tablet and injection</p> <p><b>Route of administration:</b> Subdermal vs. oral and intravenous</p> <p><b>Frequency of use:</b> One time every 3 years vs. multiple frequencies depending on indication</p>

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Failure Mode of name confusion prevented by the combination of stated product characteristics as well as orthographic and/or phonetic differences as described.
Nexplanon (Etonogestrel)		68 mg implant	One implant subdermally every 3 years	
Hexalen (altretamine)	Look and Sound	50 mg capsule	260 mg/m <sup>2</sup> /day by mouth four times a day for 14 or 21 days of a 28 day cycle	<p><b>Orthographic difference:</b> Nexplanon contains the downstroke letter 'p' which Hexalen does not have and will help differentiate the names when scripted. Nexplanon contains 9 letters compared to 7 letters in Hexalen and appears longer when scripted. The overlapping upstroke letter 'l' appears in different positions within the names and will also provide differentiation when the names are scripted.</p> <p><b>Phonetic difference:</b> Nexplanon has the letters 'pl' in the second syllable which makes it sound different from Hexalen when spoken.</p> <p><b>Dosage form:</b> Implant vs. capsule</p> <p><b>Route of administration:</b> Subdermal vs. oral</p> <p><b>Frequency of use:</b> One time every 3 years vs. four times a day</p>
Mexiletine	Look	150 mg, 200 mg, 250 mg capsule	200 mg to 300 mg by mouth every 8 hours	<p><b>Orthographic difference:</b> Nexplanon includes the downstroke letter 'p' which Mexiletine does not have and may help differentiate the names when scripted. Additionally, Nexplanon has one upstroke letter 'l' vs. two upstroke letters 'l' and 't' in Mexiletene. The ending letters, 'anon' in Nexplanon look different from the ending letters, 'tine' in Mexiletene.</p> <p><b>Strength:</b> Single (68 mg) vs. Multiple (150 mg, 200 mg, and 250 mg)</p> <p><b>Dosage Form:</b> Implant vs. capsule</p> <p><b>Route of Administration:</b> Subdermal vs. oral</p> <p><b>Frequency of use:</b> One time every 3 years vs. every 8 hours</p>

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Failure Mode of name confusion prevented by the combination of stated product characteristics as well as orthographic and/or phonetic differences as described.
Nexplanon (Etonogestrel)		68 mg implant	One implant subdermally every 3 years	
Neoprofen (ibuprofen lysine)	Look	10 mg/mL Injection	10 mg/kg intravenous infusion x1 dose followed by two doses of 5 mg/kg each after 24 and 48 hours for a total of three doses	<p><b>Orthographic difference:</b> Nexplanon contains the cross stroke letter 'x' in the beginning of the name which makes it look different from the corresponding letter 'o' in Neoprofen. Additionally, the upstroke letter 'f' in Neoprofen appears near the end of the name, which may also help differentiate it from Nexplanon which has the upstroke letter 'l' in the middle of the name, when scripted. The ending letters 'non' in Nexplanon also look different from the corresponding letters, 'fen' in Neoprofen.</p> <p><b>Strength:</b> 68 mg vs. 10 mg/mL</p> <p><b>Dosage Form:</b> Implant vs. injection</p> <p><b>Route of Administration:</b> Subdermal vs intravenous</p> <p><b>Frequency of use:</b> One time every 3 years vs. once a day for 3 days</p>

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Failure Mode of name confusion prevented by the combination of stated product characteristics as well as orthographic and/or phonetic differences as described.
Nexplanon (Etonogestrel)		68 mg implant	One implant subdermally every 3 years	
Norpramin (desipramine)	Look	10 mg, 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg tablets	<p><b>For the treatment of major depression (including patients with schizophrenia or psychosis):</b></p> <p>Initially, 50 mg to 75 mg/day by mouth in 1- 4 divided doses or once at bedtime to minimize daytime sedation. Titrate dose by 25 mg to 50 mg at weekly intervals up to 200 mg by mouth in single or divided doses.</p> <p><b>For the treatment of social phobia (social anxiety disorder) and panic disorder:</b></p> <p>10 mg by mouth at bedtime. May titrate by 10 mg every 2 to 4 days up to 100 mg to 200 mg per day.</p> <p><b>For the treatment of attention-deficit hyperactivity disorder (ADHD), bulimia nervosa, or other eating disorders:</b></p> <p>25 mg by mouth three times per day initially. May titrate the dose to 200 mg per day by increasing by 25 mg to 50 mg per day at weekly intervals.</p> <p><b>For the treatment of neuropathic pain and for postherpetic neuralgia (PHN):</b></p> <p>Initially, use doses of 10mg to 25 mg by mouth at bedtime, and titrate to pain relief up to a maximum of 167 mg per day.</p>	<p><b>Orthographic differences:</b> Nexplanon has an upstroke letter 'l' which Norpramin does not have and may help differentiate the names when scripted.</p> <p><b>Strengths:</b> Single (68 mg) vs. Multiple (10 mg, 25 mg, 50 mg, 75 mg, 100 mg and 150 mg)</p> <p><b>Dosage form:</b> Implant vs. tablet</p> <p><b>Route of administration:</b> Subdermal vs. oral</p> <p><b>Frequency of use:</b> One time every 3 years vs. daily up to four times a day</p>

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Failure Mode of name confusion prevented by the combination of stated product characteristics as well as orthographic and/or phonetic differences as described.
Nexplanon (Etonogestrel)		68 mg implant	One implant subdermally every 3 years	
Nexphen PD (guaifenesin and phenylephrine hydrochloride)	Look	200 mg/7.5 mg extended-release tablet	One to two tablets every 12 hours as needed	<p><b>Orthographic difference:</b> Nexplanon includes two additional letters (nine vs. seven) providing additional length and shape when scripted. The modifier 'PD' in Nexphen PD may also help differentiate the two names.</p> <p><b>Frequency of use:</b> One time every 3 years vs every 12 hours as needed.</p> <p><b>Dosage form:</b> Implant vs. extended-release tablet</p> <p><b>Route of Administration:</b> Subdermal vs. oral</p>
(b) (4)				
Nexavar (sorafenib)	Sound	200 mg tablet	400 mg by mouth twice a day	<p><b>Orthographic difference:</b> Nexplanon includes the downstroke letter 'p' and the upstroke letter 'l' which Nexavar does not have and may help differentiate the names when scripted. Nexplanon includes two additional letters (nine vs. seven) providing additional length and shape when scripted.</p> <p><b>Phonetic difference:</b> The second and third syllables, 'planon' in Nexplanon sound different from the second and third syllables, 'avar' in Nexavar.</p> <p><b>Dose:</b> One 68 mg implant vs two 200 mg tablets</p> <p><b>Dosage Form:</b> Implant vs. tablet</p> <p><b>Route of Administration:</b> Subdermal vs. oral</p> <p><b>Frequency of Administration:</b> Every 3 years vs. twice a day</p>

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Failure Mode of name confusion prevented by the combination of stated product characteristics as well as orthographic and/or phonetic differences as described.
Nexplanon (Etonogestrel)		68 mg implant	One implant subdermally every 3 years	
(b) (4)				
Exelon (rivastigmine)	Sound	1.5 mg, 3 mg, 4.5 mg and 6 mg capsules	1.5 mg to 3 mg by mouth twice a day	<p><b>Phonetic difference:</b> The second syllable, 'pla' of Nexplanon sounds different when spoken from the second syllable, 'e' in Exelon.</p> <p><b>Strength:</b> Single (68 mg) vs Multiple (1.5 mg, 3 mg, 4.5 mg, and 6 mg)</p> <p><b>Dosage form:</b> Implant vs. capsules</p> <p><b>Route of administration:</b> Subdermal vs. oral</p> <p><b>Frequency of administration:</b> Every 3 years vs. twice a day</p>

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Failure Mode of name confusion prevented by the combination of stated product characteristics as well as orthographic and/or phonetic differences as described.
Nexplanon (Etonogestrel)		68 mg implant	One implant subdermally every 3 years	
Mestinon (pyridostigmine)	Sound	60 mg tablet 60 mg/5 mL syrup 180 mg extended-release tablet 5 mg/mL injection	<i>Syrup and tablets:</i> Average dose is ten 60 mg tablets or ten teaspoonsful by mouth daily in divided doses as needed. <i>Timespan tablets:</i> One to three 180 mg tablets by mouth once or twice a day. <i>Injection:</i> 1/30 <sup>th</sup> of the oral dose administered intramuscularly or by slow intravenous infusion	<b>Phonetic difference:</b> The transition letters between the first and second syllables of both names, ('sti' in Mestinon and 'xpl' in Nexplanon) sound different when spoken. <b>Strength:</b> Single (68 mg) vs Multiple (60 mg, 60 mg/5 mL, 180 mg, and 5 mg/mL) <b>Dosage Form:</b> Implant vs. tablet, syrup, or extended-release tablet, or injection <b>Route of administration:</b> Sudermal vs. oral, intramuscular or intravenous <b>Frequency of administration:</b> Every 3 years vs. divided doses as needed throughout the day (oral)
Nexiclon XR***	Look and Sound	0.17 mg and 0.26 mg extended-release tablets 0.09 mg/mL oral suspension	0.17 mg to 0.52 mg by mouth once a day	<b>Orthographic difference:</b> Nexplanon contains the downstroke letter, 'p' which Nexiclon XR does not contain and may help to differentiate the names when scripted. The ending letters 'anon' in Nexplanon look different from the ending letters, 'lon' in Nexiclon. The modifier 'XR' may help to differentiate the name pair. If the modifier in Nexiclon XR is dropped, a pharmacist would need to contact the prescriber for clarification because there is no immediate release 'Nexiclon' on the market currently. <b>Strengths:</b> Single (68 mg) vs Multiple (0.17 mg, 0.26 mg and 0.09 mg/mL). <b>Dosage Forms:</b> Impant vs. extended-release tablet and oral suspension <b>Route of Administration:</b> Subdermal vs. oral <b>Frequency of Administration:</b> Every 3 years vs once daily

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Failure Mode of name confusion prevented by the combination of stated product characteristics as well as orthographic and/or phonetic differences as described.
Nexplanon (Etonogestrel)		68 mg implant	One implant subdermally every 3 years	
Nexterone (amiodarone)	Look and Sound	50 mg/mL, 150 mg/100 mL, 360 mg/200 mL injection	<b>Loading Infusion:</b> 150 mg over the first 10 minutes by rapid intravenous infusion followed by 360 mg slow intravenous infusion (1mg/minute) over the next six hours  <b>Maintenance dose:</b> 540 mg intravenous infusion (0.5 mg/minute) over the remaining 18 hours, followed by 720 mg per 24 hours for subsequent infusions	<b>Orthographic difference:</b> Nexplanon includes the downstroke letter 'p' in the fourth position which corresponds to the upstroke letter 't' in Nexterone and may help differentiate the names when scripted.  <b>Phonetic difference:</b> The second and third syllables in each name (planon vs terone) sound different when spoken.  <b>Strength:</b> Single (68 mg) vs Multiple (50 mg/mL, 150 mg/100 mL, 360 mg/200 mL)  <b>Dosage form:</b> Implant vs. injection  <b>Route of administration:</b> Subdermal vs. Intravenous  <b>Frequency of administration:</b> Every 3 years vs. once daily
Implanon (etonogestrel)	Look and Sound	68 mg	One implant every 3 years	<b>Orthographic difference:</b> The first three letters, 'Nex' in Nexplanon look different from the first two letters, 'Im' in Implanon and may help minimize the potential for confusion between the two names.  <b>Phonetic difference:</b> The first syllable, 'Nex' in Nexplanon sounds different from the first syllable, 'Im' in Implanon.  <b>Additional rationale:</b> Implanon is the same product with the same active ingredient without the radiopaque coating and will be phased out within three years if Nexplanon is approved. Confusion between these two products is not likely to present additional health risks than those that currently exist for Implanon.

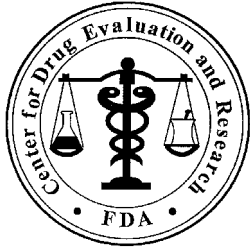
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WALTER L FAVA  
01/31/2011

CARLOS M MENA-GRILLASCA  
01/31/2011

CAROL A HOLQUIST  
01/31/2011



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: May 21, 2010

To: Scott Monroe, MD, Director  
Division of Reproductive and Urologic Products

Through: Carlos Mena-Grillasca, RPh, Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Judy Park, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Proprietary Name Reconsideration Request Review

Drug Name(s): (b) (4) (Etonogestrel Implant) 68 mg

Application Type/ Number: NDA 021529

Applicant/sponsor: Merck & Co., Inc.

OSE RCM #: 2010-498

## Contents

EXECUTIVE SUMMARY .....	2
1 BACKGROUND .....	2
1.1 Introduction.....	2
1.2 Regulatory history.....	2
2 MATERIAL REVIEWED.....	2
3 RESULTS' .....	2
4 DISCUSSION.....	3
5 CONCLUSIONS AND RECOMMENDATIONS .....	3
5.1 Comments to the Applicant.....	3
6 REFERENCE .....	3

**EXECUTIVE SUMMARY**

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA) evaluation of the request for reconsideration of the proposed proprietary name, (b) (4). DMEPA concluded in OSE Review # 2009-1753 dated December 23, 2009 that the name is unacceptable due to the absence of data to support that (b) (4) and not contribute to errors by misinterpretations. Based on our evaluation of data submitted in support of the reconsideration, we are not convinced that (b) (4) and will not function as a source of error. Thus, DMEPA continues to find the use of the proprietary name, (b) (4), unacceptable for the proposed product.

**1 BACKGROUND**

**1.1 INTRODUCTION**

This review responds to a March 1, 2010 request from Merck & Co., Inc. to reconsider the proposed proprietary name, (b) (4).

**1.2 REGULATORY HISTORY**

(b) (4) is a line extension of the currently marketed product, Implanon. The Application is currently under review by the Division of Reproductive and Urologic Products with a goal date of May 28, 2010. The Applicant submitted a request for reconsideration of the proposed proprietary name, (b) (4), on March 1, 2010.

**2 MATERIAL REVIEWED**

DMEPA reviewed Merck's request for reconsideration as well as our initial review of the proposed proprietary name, (b) (4), OSE review # 2009-2131 in which we expressed concerns for (b) (4).

The request for reconsideration includes responses from Merck regarding DMEPA's concerns with the proposed proprietary name, (b) (4), and an external study conducted by (b) (4) of (b) (4).

**3 RESULTS**

The external study conducted by (b) (4) assessed the meaning and acceptability of (b) (4). The study included an 'unaided' and 'aided' part. The 'unaided' part of the study did not give participants any product information and asked to determine what (b) (4) meant. 37% of healthcare professionals and 26% of consumers reported that (b) (4)

(b) (4)

Based on their study, (b) (4) acknowledged that (b) (4)

(b) (4)

(b) (4)  
to distinguish the proposed product when ordering since Implanon and the proposed product will overlap in distribution if approved.

#### 4 DISCUSSION

Based on the information provided, we agree (b) (4) would be helpful in differentiating the proposed device from the currently marketed device. However, we cannot agree that the data supports (b) (4). Only 1/3 of the participants in the study were able to correctly report (b) (4) during the 'unaided' part of the study and even when the product information was provided, only 52% suggested that the proposed name communicated (b) (4). Furthermore, the study of (b) (4) demonstrates confusion (b) (4). Thus, the potential for confusion already demonstrated in the study and lack of clear meaning raises concerns with (b) (4).

Overall, we do not concur with the results and conclusions contained in the Request for Reconsideration of Proprietary Name and maintain our objection to the proposed proprietary name (b) (4).

#### 5 CONCLUSIONS AND RECOMMENDATIONS

Our analysis of the data provided by Merck & Co., Inc. in support of the Request for Reconsideration of the proposed proprietary name, (b) (4), did not support that (b) (4) and will not be a source of error. Thus, DMEPA continues to find the use of the proprietary name, (b) (4), unacceptable for the proposed product. We communicated our decision to the Applicant in a Tcon held on April 27, 2010 and requested that they submit a new proposed proprietary name. As to this date we have not received a new proposed proprietary name for evaluation.

If you have any further questions or need clarification, please contact Maria Wasilik, OSE Project Manager, at 301-796-0567.

##### 5.1 COMMENTS TO THE APPLICANT

We have completed our review of the Request for Reconsideration of Proprietary Name and find the name, (b) (4) unacceptable for the proposed product. Based on our evaluation of data submitted in support of the reconsideration, we are not convinced that (b) (4) and will not contribute to errors by misinterpretations. Only 1/3 of the participants in the study were able to correctly report (b) (4) during the 'unaided' part of the study and even when the product information was provided, only 52% suggested that the proposed name communicated the (b) (4). Furthermore, the study of (b) (4) demonstrates confusion (b) (4).

Therefore, we do not concur with the results and conclusions contained in the Request for Reconsideration of Proprietary Name and maintain our objection to the proposed proprietary name (b) (4).

#### 6 REFERENCE

OSE review #2009-1753, Proprietary Name Review for (b) (4), Mena-Grillasca, C. December 23, 2009.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	SUPPL-7	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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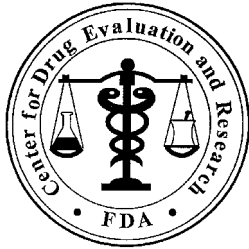
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/s/

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CARLOS M MENA-GRILLASCA  
05/21/2010

CAROL A HOLQUIST  
05/21/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: December 23, 2009

To: Scott Monroe, MD  
Director, Division of Reproductive and Urology Products

Through: Denise Toyer, PharmD, Deputy Director  
Division of Medication Error Prevention and Analysis

From: Carlos M Mena-Grillasca, RPh, Team Leader  
Division of Medication Error Prevention and Analysis

Subject: Proprietary Name Review

Drug Name: (b) (4) (Etonogestrel Implant)  
68 mg

Application Type/Number: NDA 021529

Sponsor: Schering-Plough Corporation

OSE RCM #: 2009-1753

**\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\***

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21529	SUPPL-7	ORGANON USA INC	IMPLANON (ETONOGESTREL IMPLANT) 68MG

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/s/

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CARLOS M MENA-GRILLASCA  
12/23/2009

DENISE P TOYER  
12/23/2009