

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-529**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

7/20/05



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

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**DATE:** July 20, 2005

**TO:** Daniel Shames, M.D., Director  
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(DRUDP), HFD-580

**FROM:** Mark Avigan, MD, CM, Director  
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**DRUG:** Implanon™ (Etonogestrel Subdermal Implant)

**NDA:** 21-529

**SPONSOR:** Organon USA, Inc.

**SUBJECT:** Review of Risk Management Proposals

**PID:** D050312

**1 EXECUTIVE SUMMARY**

This consult is in response to a request from the Division of Reproductive and Urological Drug Products (DRUDP) to review and comment on the proposed risk management measures and to advise the review division on how best to collect data on adverse events associated with the insertion and removal of the device.

Implanon™ is an etonogestrel-containing single rod implant for subdermal use. The implant is 4 cm in length with a diameter of 2 mm. The proposed indication is in women for the prevention of pregnancy. Implanon™ is a long-acting (up to 3 years), reversible contraceptive method and must be removed by the end of the third year. The primary risk management concern of Implanon is the insertion and removal related events (IRRE) that were noted from foreign

postmarketing experience. Failure to appropriately insert or remove the implant can result in inadequate contraception and was considered the major factor that contributed to unintended pregnancies<sup>1</sup>.

Organon, Inc is proposing a program to train Health Care Providers (HCP) on proper technique for inserting or removing Implanon. Only those clinicians who complete the program will be able to order and insert Implanon. Patient labeling and informed consent are also patient education tools that Organon is planning to utilize to inform patients of the risks and benefits of Implanon. A separate consult from DSRCs<sup>2</sup> addresses patient comprehension issues regarding the proposed Patient Labeling and Consent Form.

Comments were provided to DRUDP on the risk minimization tools and Phase IV Commitments currently proposed by Organon and DRUDP on May 16, 2005 and are again provided in this review (pgs 4-6). Further comments are provided on additional options that may be considered to manage the risk of IRREs.

## **2 BACKGROUND**

### ***2.1 Introduction***

The Division of Reproductive and Urological Drug Products (DRUDP) asked the Divisions within the Office of Drug Safety to review and comment on the proposed risk management measures and to advise the review division on how best to collect data on adverse events associated with the insertion and removal of the device.

The DRUDP specifically asked the following with regard to their risk management proposal:

1. Do you have any suggestions/recommendations regarding the proposed training program and method by which the Applicant proposes to distribute the product?
2. To determine if the training program appears to be successful, the Division intends to ask the Applicant to collect data on insertion/removal adverse events beyond that which would be reported to AERS. The Division seeks suggestions from DDRE as to mechanisms by which such data could be reliably collected. Ideally, the mechanism should be relatively simple to facilitate compliance by healthcare providers.
3. Does DSRCs believe that the voluntary mechanism by which patients will likely receive an information sheet/pamphlet and be asked to sign an informed consent form is adequate? The Division believes that (1) Implanon will be available mainly through family planning clinics and (2) standard operating procedures in these facilities will most likely include distribution of the information sheet/pamphlet and mandatory signing of the patient informed consent.

### ***2.2 Product Information and Regulatory History***

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<sup>1</sup> Barbara Weasley, M.D., M.P.H. Clinical Review, NDA 21-529 Implanon: etonogestrol implant; June 14, 2005: pg 39.

<sup>2</sup> Jeanine Best, M.S.N., R.N., P.N.P. DSRCs Review #2 of Patient Labeling for Implanon (etonogestrol subdermal implant), NDA 21-529.

Implanon™ (etonogestrel implant) is an etonogestrel-containing single rod implant for subdermal use. The implant is 4 cm in length with a diameter of 2 mm. The proposed indication is in women for the prevention of pregnancy. Implanon™ is a long-acting (up to 3 years), reversible contraceptive method and must be removed by the end of the third year.

Organon Inc. submitted NDA 21-529 for Implanon on September 30, 2003. During the first review cycle, Implanon received an approvable action in October 2004 because of issues related to Good Clinical Practices (GCP) in some of the studies that were identified late in the review cycle<sup>3</sup>. The specific deficiencies are outlined in Clinical Review<sup>4</sup>. Organon submitted a Complete Response on December 12, 2004. On June 14, 2005, Implanon received another approvable action because the GCP issues outlined in the first letter did not appear to be adequately addressed. Implanon™ was introduced into the European market in 1998, and is currently approved for marketing in approximately 57 countries worldwide, with registration pending in approximately 20 other countries.

### 3 SAFETY CONCERNS

#### 3.1 *Synopsis of Medical Officer's Safety Summary*<sup>5</sup>

According to the medical officer's clinical review, the most frequently reported clinical trial adverse event is bleeding irregularities (occurring in more than 85% of subjects) and was the most common reason for discontinuing Implanon (13%- U. S. Study; 16%- non U. S. Studies). There were no deaths or serious adverse events such as thromboembolic events, (including pulmonary embolus, strokes, myocardial infarctions etc.) submitted in either the original submission or the complete response. In the clinical trials and there were no significant problems related to insertion/removal of the implant.

Postmarketing safety data since the start of marketing of Implanon in 1998 through 1 March 2005 included reports of four deaths (3 deaths due to pulmonary embolus; one death due to bacterial infection). Serious thrombotic/ thromboembolic cardiovascular adverse events have consisted of 13 reports of pulmonary emboli, 18 reports of CVAs, and 18 reports of DVTs. Implanon has not been withdrawn from any market because of safety issues.

#### 3.2 *Safety Issue Necessitating Risk Management*

During review of the original NDA submission, DRUDP noted that there appeared to be a significant number of postmarketing safety reports concerning complications related to insertion/removal of the implant. The insertion removal related events (IRRE) are defined as<sup>6</sup>:

<sup>3</sup> See Approvable Letter, NDA 21-529, dated October 29, 2004.

<sup>4</sup> Barbara Weasley, M.D., M.P.H. Clinical Review, NDA 21-529 Implanon: etonogestrol implant; June 14, 2005: pgs 6-7.

<sup>5</sup> Barbara Weasley, M.D., M.P.H. Clinical Review, NDA 21-529 Implanon: etonogestrol implant; June 14, 2005: pgs 8-9.

<sup>6</sup> Barbara Weasley, M.D., M.P.H. Clinical Review, NDA 21-529 Implanon: etonogestrol implant; June 14, 2005: pg 39.

- Any event that is related to the insertion and/ or removal of Implanon but cannot be classified as being an Adverse Event or Serious Adverse Event according to the definition for an AE or SAE.
- Any event for which it is clear or becomes clear at a stage later than the actual insertion procedure that the patient had accidentally not received Implanon due to an insertion failure.
- Any unintended pregnancy for which it is clear or becomes clear at a stage later than the actual insertion procedure that the patient had accidentally not received Implanon due to an insertion failure.

Insertion failures include (but are not limited to) “deep insertion”, “difficult to insert”, “no rod”, and “broken or cut”. Failure to appropriately insert the implant can result in inadequate contraception and was considered the major factor that contributed to unintended pregnancies<sup>1</sup>. Of 1814 medically confirmed reports of IRREs to Organon, 561 reported an unintended pregnancy. Removal failures include (but are not limited to) “rod not found”, “migration”, “no rod”, “surgical removal general anesthesia”, and “removal problem”. Since similar problems were not reported in the clinical trials, DRUDP felt that it was possible that these complications were related to inadequate training of healthcare providers regarding proper insertion/removal of the implant since insertion/removal of Implanon has continued to be problematic in markets where the product is presently marketed.

## 4 RISK MANAGEMENT

### 4.1 Sponsor’s Risk Management Proposal

#### 4.1.1 Training Program for Healthcare Providers

To address the concerns regarding removal and insertion of the implant, the Organon, Inc is proposing a program to train HCPs on the proper technique for inserting or removing Implanon. The Healthcare Provider Training: each training session will be a 3-hour program divided into 4 sections:

1. Implanon clinical information and data
2. Insertion/Removal/Localization procedures
3. Hands-on training of Insertion and Removal techniques using specially designed model arms
4. Patient Counseling, Ordering, Billing, and Coding information.

Only those healthcare providers who complete the program will be able to order and insert Implanon. An “Organon Clinical Contact Specialist” will meet with the clinicians on a regular basis beginning within 1 week after the training to review the procedures using the model arm, and other relevant information. Radiologists will receive information on the localization of Implanon with ultrasound and MRI via published journal articles, CD- ROMs, and the Implanon web site.

The effectiveness of the training programs will be monitored in the following ways:

- Evaluation forms and surveys

- The Clinical Contact Specialists to review the skills of clinicians
- The Steering Committee to review issues that have arisen and the progress of the training programs, surveys and evaluations

#### **4.1.2 Patient Education**

Patient labeling and informed consent are also patient education tools that Organon is planning to utilize to inform patients of the risks and benefits of Implanon. A separate consult from DSRCS<sup>7</sup> addresses patient comprehension issues regarding the proposed Patient Labeling and Consent Form.

#### **4.1.3 DRUDP Phase IV Proposals—Surveillance/Pharmacovigilance**

DRUDP would ideally like the sponsor to collect data on insertion and removal adverse events by methods beyond that which would be reported to by standard postmarketing surveillance. DRUDP seeks suggestions from DDRE as to mechanisms by which such data could be reliably collected as well as procedures to link implant lot number to patients in the event of a specific lot recall.

### **4.2 Comments on Risk Management Proposals**

#### **4.2.1 Training Program for Healthcare Providers**

- Patient Counseling is listed as one of the sections of the training program. To help ensure the distribution of the Patient Labeling (patient package insert or PPI), this training should include instructions to: (1) provide a copy of the PPI to the patient prior to Implanon insertion (2) use the PPI as a counseling tool by reviewing it with the patient prior to Implanon insertion
- To enhance surveillance, include a section in the training program to encourage providers to report any insertion and/or removal related events (IRRE) to the sponsor. Include a 1-800 number in the training materials for reporting of IRRE or other types of adverse events.
- Consider including questions about experience with insertion/removal problems or adverse events in the planned evaluation forms and surveys designed to evaluate effectiveness of the training programs.

#### **4.2.2 Patient Labeling and Informed Consent**

- A separate consult from DSRCS (5-13-05) addresses patient comprehension issues regarding the proposed Patient Labeling and Consent Form.
- Implanon will be distributed directly from the sponsor only to those clinicians who have completed the training program. Since this means that the product is unlikely to be dispensed by retail pharmacists, we recommend inclusion of training for distribution of the PPI as described under "Training Program" comments. There can be no assurance, however, that

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<sup>7</sup> Jeanine Best, M.S.N., R.N., P.N.P. DSRCS Review #2 of Patient Labeling for Implanon (etonogestrol subdermal implant), NDA 21-529.

the patient will receive this information, since distribution of the PPI (and completion of the consent form) is not mandatory for Implanon.

#### 4.2.3 DRUDP Phase IV Proposals—Surveillance/Pharmacovigilance

- Short of an active surveillance effort, it is not likely that the sponsor will be able to reliably track and link insertion and removal related events. Two of the most significant limitations are that patients are not obligated to use the same health care provider for insertion and removal of the product, and there is no guarantee that the health care provider that removes the product will have either been trained or will be aware of the sponsor's interest in tracking adverse events related to insertion and removal.
- One possibility is a two-part form for identifying IRREs - one part would be completed and returned to the sponsor at insertion, and the second part at the time of removal. The form could contain information on lot number, insertion date, expected and actual removal dates, and summary or coded information concerning adverse insertion or removal events. The patient could be identified by a unique ID number to maintain confidentiality. Of course, the success of this type of program would depend on both health care provider compliance and significant numbers of patients returning to the same provider for insertion and removal.
- With regard to the IRRE EVENTS:
  - It would be helpful to have sponsor summarize insertion and removal related events reported for US patients as a separate section in their US Periodic Report/Periodic Safety Update Report, with the following emphasis: a) provide summary data on reasons for early removal – safety vs. efficacy; b) sponsor should present a summary of IRREs with associated AEs to evaluate which types (with appropriate accompanying characterization) and how many IRRE lead to serious outcomes; c) provide more summary data on how many IRRE related pregnancies are due to operator error; and d) summary section describing outcomes on pregnancies and all patients with a “lost” implant.
  - If possible, attempt to identify (via IRRE reports and surveys) implanters/clinic sites with a relatively high number of IRRE and provide targeted training to them.
  - IRRE reporting should be strongly encouraged for the “Organon faculty”/“Local Implanon Expert”, since difficult cases from the community may be referred to them.
  - The Implanon website should facilitate reporting of adverse events and IRRE events by consumers and HCPs. Perhaps the website would allow direct emailing of adverse events or IRRE events and/or the phone number for reporting these events should be noted in a visible location to facilitate adverse event and IRRE reporting.

#### 4.2.4 Other Issues

- With regard the Sponsor’s Distribution Program—Consider changing the chart sticker at the time of implant to include lot number, location of implant, date of implant, **AND prompt for the physician to record how implantation was confirmed** - 1) palpation, 2) ultrasound, or 3) MRI. Hopefully this prompt will facilitate compliance with insertion instructions.
- DMETS has concerns with including the active drug substance in the Implanon Training and Demonstration Device.

- Typically, training devices contain no drug product. Practitioners in the U.S. are accustomed to the use of training devices without active ingredient. If training is to be conducted on mannequins, why is there a need for active ingredients in this device? This is contradictory to current medical practice and may create confusion. Additionally, using active ingredient in this packaging configuration will set precedence for future products.
- DMETS questions the need for specific training and demonstration packaging containing active ingredient since the other packaging configurations (clinic package and stock) provides identical instructions for insertion/use, as well as package contents. However, if the sponsor insists on having the training and demonstration packaging, we recommend that the active ingredient be replaced with placebo.

## 5 DISCUSSION/CONCLUSIONS

DRUDP is concerned that the absence of adequate training of healthcare providers will lead to multiple complaints of improper insertion and removal of Implanon, ultimately leading to unintended pregnancies or requirement for more invasive procedures to remove the device.

The sponsor has proposed HCP training on the insertion and removal of the implant. Only those HCPs who complete the program will be able to order and insert Implanon. While we believe HCP training to be reasonable, DRUDP should understand that it is voluntary and can be terminated by the sponsor at any time. It is also possible that one practitioner within a practice can receive training and order implants for the entire practice. The sponsor has also proposed patient education in the form of a patient labeling and informed consent. Again, these are voluntary and at the discretion of the HCP and there does not appear to be any measures in place to determine whether patients are indeed receiving, reading, or comprehending the patient educational materials, or whether they are signing the informed consent.

DRUDP would ideally like the sponsor to collect data on insertion and removal adverse events by methods beyond that which would be reported to by standard postmarketing surveillance. Short of an active surveillance effort, it is not likely that the sponsor will be able to reliably track and link insertion and removal events. Two of the most significant limitations are that patients are not obligated to use the same health care provider for insertion and removal of the product, and there is no guarantee that the health care provider that removes the product will have either been trained or will be aware of the sponsor's interest in tracking adverse events related to insertion and removal.

While we acknowledge the above limitations, we recognize that insertion and removal difficulties have not led to life-threatening outcomes to date. Given the above caveats and limitations, the ODS Divisions have provided comments (pgs 5-7) on the risk minimization tools proposed by Organon and DRUDP.

**Implanon RiskMAP Review Team**

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