# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-529**

## MEDICAL REVIEW(S)

# DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)
# DIVISION DIRECTOR MEMORANDUM

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| **NDA** | NDA 21-529 |
| **Type of Application** | Complete Response to Approvable Action |
| **Applicant** | Organon USA, Inc.<br>West Orange, New Jersey |
| **Proprietary Drug Name** | Implanon™ |
| **Established Drug Name** | Etonogestrel implant |
| **Drug Class** | Contraceptive/non-oral |
| **Indication** | Prevention of pregnancy in women |
| **Route of administration** | Subdermal |
| **Dosage Form** | Subdermal implant (non-biodegradable) |
| **Dosage Strength** | 68 mg of etonogestrel per implant |
| **Dosing Regimen** | A single implant to be replaced or removed at or before 36 months after insertion |
| **CDER Receipt Date** | January 17, 2006 |
| **PDUFA Goal Date** | July 17, 2006 |
| **Date of Memorandum** | July 17, 2006 |
| **Reviewer** | Scott E. Monroe, MD<br>Acting Division Director, DRUP |

## 1. RECOMMENDATIONS

### 1.1 Recommendation regarding Approvability

I concur with the recommendations of the primary Medical Reviewer (Lesley Furlong, MD) and clinical Team Leader (Lisa Soule, MD) that Implanon™ (etonogestrel implant) be approved for the indication of prevention of pregnancy in women. A single implant may be used continuously for up to 3 years.

### 1.2 Basis for Recommendation regarding Approvability

The present submission contains clinical trial data of acceptable quality from the equivalent of more than 24,000 x 28-day treatment cycles from 942 women who used Implanon™ for prevention of pregnancy for up to 3 years. The exposure to Implanon™ (hereinafter referred to as Implanon) expressed as 28-day cycle equivalents was 11,066 (Year 1), 8,768 (Year 2), and 3,652 (Year 3).

The clinical trial data demonstrate that Implanon is a highly effective contraceptive. Among women aged 18-35 years of age at entry, 6 pregnancies were reported. Two pregnancies occurred in each of Years 1, 2, and 3. Each conception was likely to have occurred shortly before removal or within 2 weeks after removal of Implanon. With these 6 pregnancies, the cumulative Pearl Index was 0.38 pregnancies per 100 women-years of use.

The safety profile for Implanon, based on the clinical trial data in the present and prior 2 submissions, is acceptable for a highly effective contraceptive. The safety profile is similar to that of other hormonal contraceptive products, particularly low dose progestin-only contraceptives. Irregular bleeding was the most common adverse event leading to discontinuation of use in 11% of subjects. Among the 942 women who provided the primary safety data, there were no deaths or thromboembolic adverse events, although one subject reported a transient ischemic attack, which spontaneously resolved. As a device implanted for up to 3 years, the efficacy of Implanon is not affected by patient compliance, a common shortcoming of other contraceptive methods. However, potential insertion and removal problems are an issue with Implanon (see Risk Management Steps (Section 1.3.1 below).

## 1.3 Recommendation on Risk Management Steps and/or Post Approval Studies

### 1.3.1 Risk Management Steps

**Training Program for Healthcare Providers**

Since the insertion/removal of Implanon has continued to be problematic to a varying degree in markets where the product is presently approved, an effective training program for healthcare providers is important to maximize the safe use of the drug product. The Applicant has proposed a training program for healthcare providers that will include training on implant insertion/removal techniques using model arms, information on implant localization techniques, and patient counseling. Only healthcare providers who complete the training program will be able to order Implanon. Ordering will be accomplished by means of an Organon-maintained database listing trained providers. A single distributor will verify that a provider ordering Implanon is in this database. The training program is described in detail in the clinical Team Leader Review.

**Assessment of Effectiveness of Training Program and Insertion/Removal-Related Events**

The Applicant will conduct a monitoring program for insertion/removal-related events (IRREs) that includes both a spontaneous reporting component (Pharmacovigilence Plan) and an active monitoring component (Active Monitoring Program). The objectives of the monitoring program include both evaluation of the effectiveness of the training program and obtaining information about the occurrence of IRREs. All spontaneous reports of IRREs will be evaluated by Organon using processes and procedures that have been developed in conjunction with European regulators and have been in place for several years. A listing of these IRREs as well as analyses of these events will be provided to the Division on a quarterly basis. To supplement the information obtained through spontaneous reporting, Organon will conduct an Active Monitoring Program for IRREs. This program will enroll 20-40 academic, private, or clinic-based centers to obtain data on at least 10,000 insertions in the first year of marketing. Data on all insertions/removals over a 3 year period will be collected from these centers to obtain a more complete picture of IRREs associated with the use of Implanon and a meaningful estimate of their incidence.

**Division Director's Comment**

- *Based on the review and recommendations of the Office of Surveillance and Epidemiology (OSE) during the prior review cycle, the assessments of the primary Medical Reviewers and clinical Team Leaders during the primary and current review cycles, and my own review, I believe that the overall risk management program (training and surveillance components) that will be conducted by Organon is adequate and acceptable. The program will be monitored on a quarterly basis and revised as warranted.*

### 1.3.2 Post Approval Studies

The Applicant has agreed to conduct the Active Monitoring Program as a formal Phase 4 commitment. I concur with both the primary Medical Officer and the clinical Team Leader that no additional Phase 4 study commitments are required.

Although not a formal Phase 4 commitment, the Applicant should continue development of a radio-opaque version of Implanon to facilitate localization of the implant.

## 2. BACKGROUND

### 2.1 Description of Drug Product

Implanon (etonogestrel implant) is a progestin-only contraceptive subdermal implant. The non-biodegradable implant is a co-axial rod with a length of 4 cm and a diameter of 2 mm. The core contains 68 mg of etonogestrel dispersed in a polymeric matrix of ethylene vinyl acetate copolymer that is surrounded by a 60 μm skin of ethylene vinyl acetate copolymer.

Etonogestrel, which is a derivative of 19-nortestosterone, is the biologically active metabolite of desogestrel, the progestin component of several combination oral contraceptives (COCs) approved for marketing in the U.S. Additionally, one product containing etonogestrel is approved and marketed in the U.S. for the prevention of pregnancy - NuvaRing® (Organon USA). NuvaRing is a combination contraceptive vaginal ring containing etonogestrel and ethinyl estradiol.

Implanon is supplied in a ready-for-use disposable applicator and is inserted subdermally in the inner side of the upper arm. After insertion, etonogestrel is released from the implant at rates that are effective for the prevention of pregnancy for at least 3 years.

### 2.2 Regulatory History and Prior Approvability Issues

The regulatory history of Implanon is described in detail in the clinical Team Leader Reviews of the first Complete Response (review dated June 14, 2005) and the present submission (review dated July 17, 2006).

**Original NDA Submission**. The original NDA submission of September 2003 included 6 clinical trials described by the Applicant as "adequate and well controlled." Following audits by the Applicant of several clinical trials sites, the Applicant withdrew from the NDA all data from 2 of the 6 clinical trials (both trials had been conducted in Indonesia and enrolled a total of 649 subjects) because of significant Good Clinical Practice (GCP) violations. The revised NDA provided data from approximately 1,117 subjects in the 4 remaining studies (See Table 1).

**Table 1 Principal Safety and Efficacy Studies in Revised Original NDA Submission**

| Study Number | Region | Description of Study |
|---|---|---|
| 069001 | United States | 330 women, age 18-40, treated for up to 2 years |
| 34505 | Thailand | 100 women, age 18-39, treated for up to 2 to 4 years |
| 34507 | Europe & Chile | 635 women, age 18-40, treated for up to 2 to 3 years |
| 34507-CDN | Canada | 52 women, age 18-40, treated for up to 2 years |

Source: Original NDA submission, 30 September 2003.

During the original review cycle, the FDA's Division of Scientific Investigation (DSI) inspected 3 of the sites that participated in U.S. Study 069001 and the 2 large non-U.S. sites from Study 34507 that had treated subjects for up to 3 years. Although citations were issued to all but one of the U.S. investigators, DSI concluded that the data submitted by these 5 investigators was "adequate in support of the relevant submission."

Late in the original review cycle, the Division learned that the European Regulatory Authorities, represented by the Dutch Medicines Evaluation Board (DMEB) conducted additional inspections of several clinical trial sites that had participated in Study 34507 or Study 34507-CDN. (Both of the studies in Indonesia and Study 34507 had provided much of the data supporting the safety and efficacy of Implanon, resulting in the approval of Implanon for marketing in Europe). These inspections by the DMEB revealed that GCP standards had not been met and that the reliability of the data from the inspected sites could not be assured. The DMEB inspections resulted in revised European labeling for Implanon, although the DMEB concluded that there were "no reasons to doubt the efficacy and safety of the product provided it is inserted in the proper manner."

Due to concerns about the quality of the clinical trial data and the adequacy of the clinical trial safety database, the initial application received an Approvable Action by the Division. The action letter, dated October 29, 2004, noted that the Applicant needed to:

- Address concerns about quality of data from Studies 34507 and 34507-CDN and provide a justification of why these studies are adequate and well-controlled trials able to provide sufficient data to demonstrate safety and efficacy of Implanon and to support accurate product labeling. As an alternative, the Applicant could conduct a new clinical trial to provide sufficient acceptable data to support efficacy and safety of the product.

**Complete Response No. 1.** The Applicant submitted a Complete Response to the Approvable action on December 14, 2004. In lieu of conducting an additional clinical trial, the Applicant opted to provide justification for the adequacy of Studies 34507 and 34507-CDN to provide data demonstrating safety and efficacy of Implanon and to support accurate labeling. The Division concluded, after reviewing the Applicant's Complete Response, that adequate justification to discount the concerns raised by the DMEB inspections had not been provided.

Based on these findings, the Division determined that only the data from Studies 069001 (U.S.) and 34505 (Thailand, pending FDA inspection) and from two sites in Study 34507 (Chile and Hungry) that had been inspected by DSI were acceptable. This reduced the number of subjects evaluated over the first year of treatment to 648 and the evaluable 28-day cycles to 7,520. This was less than the 10,000 x 28-day cycles in the first year of treatment generally required by the Division for evaluation of a new hormonal contraceptive product.

The Complete Response received an Approvable action. The action letter, dated June 14, 2005, noted that the justification provided by the Applicant attesting to the reliability of data from Study 34507 (with the exception of the 2 sites inspected by DSI) and Study 34507-CDN was inadequate. The Applicant was asked to provide "new clinical trial data, from a trial(s) conducted under GCP, sufficient to provide data for the first year of treatment from at least 10,000 28-day cycle equivalents."

### 2.2.1 Resolution of Issues Pertaining to Adequacy of Clinical Trial Database

An End of Review Meeting was held on August 11, 2005, at which the Applicant proposed to conduct additional audits of sites in Study 34507 that had not been audited by either the FDA or the DMEB as well as sites in clinical pharmacology studies. If these sites passed the audit, the Applicant proposed to submit data from these site/studies to supplement the data accepted previously by the Division, in order to provide data from at least 10,000 first-year treatment cycles. The Division concurred with the audit plan, but cautioned the Applicant that the Division would need to confirm the auditor's conclusions, and that adequacy of the data to support the application would be determined only following the Division's review of the clinical data.

**Complete Response No. 2.** The Applicant identified 26 potential study sites from which additional first-year cycles might be obtained. These sites were selected on the basis of their not having previously been audited by either the FDA or the DMEB, available number of Year 1 cycles, and geographic location (to facilitate audit conduct). Audits were conducted on-site and included identification of source documents for each subject, as well as in-depth review of source data for a sample of subjects. The following components were assessed: (1) reporting of adverse events and serious adverse events (SAEs); (2) source documentation, including patient diaries/bleeding cards; and (3) GCP compliance (acknowledging that strict GCP compliance was unlikely as many of the studies had been conducted prior to the adoption of formalized GCP rules and guidelines). Twenty-five sites were audited, and one was eliminated before an audit was conducted.

Reports were prepared for all audited study sites, and the Applicant decided that 14 of the 25 study sites were acceptable. An outside (third party) consulting group reviewed the audit findings and concurred with inclusion of 13 of the 14 sites. The consulting group also concurred with all decisions about which sites should be excluded from submission following internal audits. Reasons for such exclusion primarily concerned availability of and discrepancies in source data, underreporting of adverse events and use of data recording tools other than those specified in the protocol, leading to transcription errors and underreporting of adverse events.

On January 16, 2006, the Applicant submitted a second Complete Response. In addition to the safety and efficacy data from the equivalent of 7,520 x 28-day cycles of treatment in Year 1 previously accepted by the Division, the submission included data from an additional 3,347 x 28-day cycles in Year 1. These additional cycles of data were based on the Applicant's recently completed audits that had concluded that these data would meet the Division's criteria for adequate documentation to support their accuracy and reliability.

Based on her review of the audit information provided by the Applicant, the primary Medical Reviewer (Dr. Furlong) made the following statement in her review:

- "I have read a sampling of audits from non-accepted sites and all the audit reports from accepted sites, and the decisions made to accept or not accept the sites are reasonable." b(4)

The clinical Team Leader (Dr. Soule) made the following statements in her review:

- "The audits and outside review of audit findings did not find any evidence of fraudulent data. Issues leading to elimination of sites and studies from the safety and efficacy summaries involved procedural inadequacies or mistakes. There was no evidence that sites or studies were excluded from this submission due to unacceptable numbers of pregnancies or adverse events."
- "The number of 28-day equivalent cycles in the first year of treatment is sufficient to meet DRUP's general requirement for a new contraceptive product. The number of cycles in the third year is sufficient to allow evaluation of efficacy and safety when Implanon is used up to three years."
- "The studies submitted appear adequate and of sufficient reliability to support determination of safety and efficacy for Implanon for up to three years."

**Division Director's Comments**

- *I support the Division's earlier decision to allow the previously accepted Implanon database to be augmented by data from Phase 3 clinical trial sites with acceptable audit reports as well as by data from clinical pharmacology trials in order to obtain a total of the equivalent of 10,000 x 28-day treatment cycles in Year 1. My decision regarding inclusion of data from the clinical pharmacology trials is based on a number of considerations including the following:*
  - *Subjects in the clinical pharmacology studies were at risk for pregnancy and their overall demographic characteristics were comparable to those in the non-US Phase 3 clinical trials.*
  - *The clinical pharmacology protocols required that subjects be treated for up to 2 years, similar to the U.S. Phase 3 clinical trial.*
  - *Monitoring for safety and efficacy in the clinical pharmacology studies was comparable to that of the Phase 3 clinical trials.*
  - *Increased monitoring for collection of additional pharmacology data in the clinical pharmacology studies would have no impact of the effectiveness of Implanon. Once implanted, the effectiveness of Implanon does not depend on subject compliance.*
- *Based on my independent review of the audit information submitted by the Applicant, I concur with both the primary Medical Reviewer and the clinical Team Leader as to the acceptability of the processes used to assess data quality and with the clinical Team Leader that the submitted data appear adequate and of sufficient reliability to support determination of safety and efficacy for Implanon for up to 3 years.*

- *The reliability of the data are further supported by the FDA's inspection of 5 clinical sites during the first review cycle and by the FDA's inspection of 3 additional non-U.S. sites during the present review cycle. All sites contributing data involving the treatment of subjects for up to 3 years have been inspected by the FDA with the recommendation that the data appear to be acceptable to support the indication.*

## 3. EFFICACY OF IMPLANON

The efficacy clinical trial dataset provided data from 923 women and included the equivalent of slightly more than 24,100 x 28-day cycles of exposure over 3 years. Of these cycles of exposure, 10,867 occurred during Year 1 of treatment. The primary endpoint was pregnancy rate. Subjects were assessed for pregnancy every 3 months. The studies were open-label and used historical controls as is often the case for hormonal contraceptive products. The Applicant reported that there were no on-treatment pregnancies. The Applicant reported 50 pregnancies with estimated dates of conception following implant removal.

Contraceptive effectiveness is generally assessed primarily in women 35 years of age or younger at entry. Contraceptive effectiveness is generally expressed as the pregnancy rate per 100 women years of use (i.e., the Pearl Index). The effectiveness of Implanon based on the Applicant's determination of no on-treatment pregnancies is shown in Table 2.

**Table 2 Effectiveness of Implanon (Pearl Index) Assuming No On-Treatment Pregnancies**

| Treatment Period | N | Number of On-Treatment Pregnancies | Number of Cycles | Pearl Index (Pregnancies per 100 Women-Years) | 95% Confidence Interval* |
|---|---|---|---|---|---|
| Year 1 (Day 1 – 365) | 833 | 0 | 9816 | 0 | (0, 0.49) |
| Year 2 (Day 366 – 750) | 671 | 0 | 7766 | 0 | (0, 0.62) |
| Year 3 (Day 731 – 1095) | 482 | 0 | 3066 | 0 | (0, 1.57) |
| **Cumulative 3 Year (Day 1 – 1095)** | **833** | **0** | **20648** | **0** | **(0, 0.23)** |

Does not exclude cycles where use of other contraception (e.g., condoms) may have been used.
Source: Statistical Review, Table 3.1, dated June 15, 2006.

Among the post-treatment pregnancies, the estimated conception dates for 6 were reported to have been within 14 days of implant removal. Because of uncertainty as to the actual date of conception for these 6 subjects, the Applicant was asked to provide revised Pearl Index values based on the assumption that these 6 pregnancies may have been conceived just prior to implant removal. The effectiveness of Implanon assuming that these 6 pregnancies were on-treatment pregnancies is shown in Table 3.

**Table 3 Effectiveness of Implanon (Pearl Index) Assuming 6 On-Treatment Pregnancies**

| Treatment Period | N | Number of On-Treatment Pregnancies | Number of Cycles | Pearl Index (Pregnancies per 100 Women-Years) | 95% Confidence Interval* |
|---|---|---|---|---|---|
| Year 1 (Day 1 – 365) | 833 | 2 | 9816 | 0.27 | (0.03, 0.96) |
| Year 2 (Day 366 – 750) | 671 | 2 | 7766 | 0.34 | (0.04, 1.21) |
| Year 3 (Day 731 – 1095) | 482 | 2 | 3066 | 0.85 | (0.10, 3.07) |
| **Cumulative 3 Year (Day 1 – 1095)** | **833** | **6** | **20648** | **0.38** | **(0.14, 0.82)** |

Does not exclude cycles where use of other contraception (e.g., condoms) may have been used.
Source: Statistical Review, Table 3.2, dated June 15, 2006.

## Division Director's Comments

***Effectiveness***

- *Whether based on the observation of no on-treatment pregnancies, or more conservatively, considering that the 6 pregnancies with conception dates within 2 weeks after implant removal may have occurred on-treatment, the Pearl Index calculations indicate that Implanon is highly effective for up to 3 years of use.*
- *Data on 482 women, that include the equivalent of over 3,000 x 28-day cycles in Year 3, demonstrate acceptable efficacy when Implanon remains in place for 3 years. The 6 possibly on-treatment pregnancies were distributed evenly across 3 years, and not clustered during the third year of use. Based on a conservative estimate of effectiveness, in which the 6 pregnancies are considered to be on-treatment pregnancies (i.e., a method failure), the Pearl Index for Year 3 is 0.85 (95% confidence interval: 0.10, 3.07). The cumulative 3-year Pearl index is 0.38 (95% confidence interval: 0.14, 0.82).*
- *Both the primary Medical Reviewer and the clinical Team Leader have concluded that (1) Implanon is a highly effective contraceptive and (2) a single implant may be used continuously for up to 3 years. I concur with their conclusions.*

***Factors that may affect the effectiveness of Implanon***

- *The population studied included generally healthy women who were not extremely obese (entry criteria excluded women who weighted more than 130% of their ideal body weight) and for the most part were not taking concomitant medications that induce liver enzymes that would increase the metabolism of etonogestrel. Since both extreme obesity and increased metabolism of etonogestrel could reduce effectiveness of Implanon, both of these possibilities are addressed in labeling. In particular, product labeling includes a Precaution that chronic users of drugs that induce hepatic enzymes not use Implanon and recommends that short-term users of such drugs use a back-up nonhormonal method of contraception.*

- *The primary Medical Reviewer states in her review that in spontaneous postmarketing safety reports, the single most common reason identified as a cause of product failure (i.e., pregnancy) is "missing implant" (N=392), a problem that is largely avoidable by the simple expedient of palpating for the presence of the Implanon rod after insertion. Product labeling for Implanon in the U.S. includes the following Bolded Warning:*

  ***"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....Undetected failure to insert IMPLANON™ may lead to an unintended pregnancy."***

## 4. SAFETY PROFILE OF IMPLANON

### 4.1 Overall Assessment of Safety

The safety profile of Implanon has been well described in the primary Medical Review (by Dr. Wesley, dated October 28, 2004) and the clinical Team Leader Memorandum (by Dr. Monroe, dated October 29, 2004) for the original NDA submission and in the primary Medical Review (by Dr. Furlong) and the clinical Team Leader Memorandum (by Dr. Soule) of the present submission. I concur with these other reviewers that the overall safety profile for Implanon is acceptable for a highly effective contraceptive product.

#### Division Director's Comments

- *Based on my assessment of both the clinical trial and post-marketing safety data submitted by the Applicant, there are no safety signals that preclude approval of Implanon for prevention of pregnancy as long as (1) Implanon is properly labeled as to expected adverse events and (2) healthcare providers are adequately trained in Implanon insertion and removal techniques.*
- *Approved drug labeling for Implanon clearly describes the most significant adverse events that users of Implanon are likely to experience as well as those that are most likely to affect patient acceptability of the product.*
- *To minimize problems associated with insertion or removal of Implanon, the Applicant will require all healthcare providers who prescribe the product to undergo Company-sponsored training. Only those healthcare providers who complete the training program will be able to order Implanon (see Section 1.3.1 under Risk Management). The Applicant also will conduct a monitoring program for insertion/removal-related events that will include both a spontaneous reporting component (Pharmacovigilence Plan) and an active monitoring component (Active Monitoring Program).*

### 4.2 Adequacy of Revised Clinical Trial Safety Database

In the present submission, clinical trial safety data from 942 women treated for up to 3 years encompassing the equivalent of 24,679 x 28-day cycles of use (1,892 women-years) has been provided.

According to the primary Medical Reviewer, exposure to Implanon by year of use was:

- Year 1: 11,066 cycles, or 851 women-years
- Year 2: 8,768 cycles, or 674 women-years
- Year 3: 3,652 cycles, or 281 women-years
- More than 3 years: 1,193 cycles, or 92 women-years

**Division Director's Comments**

- *The submitted safety database meets the Division's general requirement that a new hormonal contraceptive product should include safety data from (1) the equivalent of 10,000 x 28-day treatment cycles in Year 1 of treatment and (2) 200 women treated for at least 1 year.*
- *In contrast to most NDAs for a new contraceptive product, which often do not include safety data beyond 1 year of treatment, the present Application also includes safety data from the equivalent of more than 10,000 x 28-day cycles in Years 2 and 3 of use combined.*

### 4.3 Safety Issues of Particular Importance or Interest

Because the safety profile of Implanon has been well described in other reviews of this NDA by the primary Medical Reviewers (Drs. Wesley and Furlong) and clinical Team Leaders (Drs. Monroe and Soule), my comments regarding safety findings will focus on those areas of particular importance to users of hormonal contraceptive in general and users of Implanon in particular.

#### 4.3.1 Deaths and Thrombotic Adverse Events

No deaths have been reported in any of the Applicant's clinical trials of Implanon.

According to the primary Medical Reviewer, there have been no reports of thrombotic adverse events (known risks of both hormonal contraception and pregnancy) in Implanon clinical trials with the exception of a single report of a deep vein thrombosis after 4 months of therapy. Another subject in a clinical trial was reported to have experienced a transient ischemic attack, which might have been secondary to an embolic event.

**Division Director's Comment**

- *A single documented case of a thromboembolic event (a deep vein thrombosis) does not raise concern about an increased thrombogenic risk associated with the use of Implanon beyond that known to be associated with the use of hormonal contraception as well as with pregnancy.*

#### 4.3.2 Premature Discontinuations

The major categories responsible for subject premature discontinuation of treatment and the percentages of subjects in each category for the U.S. and non-U.S. studies are listed in Table 4. Overall, 35% of subjects discontinued trial participation prematurely; this rate differed between U.S. and non-U.S. studies, with the U.S. subjects discontinuing more frequently (48.8%) versus 27.6% for non-U.S. subjects. Adverse events were the cause of premature discontinuation for 36.1% (U.S. study) and 18.6% (non-U.S. studies) of subjects, respectively. The most common single cause of premature discontinuations was irregular bleeding/amenorrhea (13.0% of U.S.

subjects and 10.1% of non-U.S. subjects). Other adverse events associated with premature discontinuations that were reported in a higher percentage of U.S. subjects included emotional lability (6.1% vs. 0.3%), depression (2.4% vs. 0.2%), and weight increase (3.3% vs. 1.8%).

**Table 4 Reasons and Percentages for Premature Discontinuation of Treatment**

| Reason for Discontinuation | U. S. Study 069001 N=330 | | Non-U.S. Studies N=612 | |
|---|---|---|---|---|
| | N | % | N | % |
| All Reasons | 161 | 48.8% | 169 | 27.6% |
| Adverse Events | 119 | 36.1% | 114 | 18.6% |
| Irregular bleeding/Amenorrhea | 43 | 13.0% | 62 | 10.1% |
| Other | 76 | 23.1% | 52 | 8.5% |
| Other (includes lost to follow-up) | 29 | 8.8% | 55 | 9.0% |
| Unwilling to continue | 8 | 2.4% | Not included as reason for withdrawal | |
| Protocol violation | 4 | 1.2% | | |
| Intercurrent illness | 1 | 0.3% | | |

Source: Table 6 of Clinical Team Leader Memorandum, July 17, 2006.

### Division Director's Comments

- *It is not clear why subjects in the U.S. trial were more likely to discontinue treatment prematurely than those in the non-U.S. trial. Some of the reasons may be cultural since slightly more than 50% of the subjects in the non-U.S. dataset were from Southeast Asia or South America.*
- *Irregular bleeding was the most common single reason for women to discontinue treatment. Since it cannot be determined in advance which women will have "acceptable" bleeding patterns while using Implanon, labeling (both physician and patient) fully describes the types of bleeding patterns that a woman might expect to help her decide if Implanon is likely to be an acceptable method of contraception for her.*
- *Overall, the profile of adverse events leading to premature discontinuation of Implanon is similar to what is to be expected for a progestin-only contraceptive. In her review, the primary Medical Reviewer states "in a recent FDA review of a new formulation of depot medroxyprogesterone acetate (one-year studies, coded with a different dictionary), the most frequently reported AEs leading to dropout were weight gain, bleeding problems, decreased libido, mood disorders, and acne."*

### Alterations in Menstrual (Vaginal) Bleeding Patterns

Virtually all women who use Implanon have altered menstrual (vaginal) bleeding. Bleeding patterns may range from no bleeding (amenorrhea), to irregular, unpredictable bleeding ranging in intensity from light to heavy. Bleeding complaints, as stated above, were the most common cause of premature terminations in the Implanon clinical trials.

**Division Director's Comments**

- *Since it is not possible to predict in advance the on-treatment bleeding pattern for a specific woman, it is important that both the healthcare provider and the woman be informed of the range of bleeding patterns.*
- *If regular cyclic vaginal bleeding is important to a woman, she would not be a good candidate for Implanon unless the need for highly effective contraception that is not dependent on patient compliance is the overriding consideration.*
- *See Section 6 (Labeling) for a description of the bleeding patterns observed in the Implanon clinical trials.*
- *In her primary Medical Review (dated October 28, 2004) of the Applicant's original submission, Dr. Wesley made the following statements regarding the clinical significance of the altered bleeding patterns in women using Implanon:*
  - *"The mean hemoglobin in the U.S. study was 8.43 mmol/L (13.9g/dL) at baseline and 8.38 mmol/L (13.8g/dL) at the last measurement, which is essentially unchanged."*
  - *"None of the 327 U.S. subjects had clinically significant low hemoglobin and 1 of 108 subjects in the Europe/Thailand group had a clinically significantly low hemoglobin. Overall, this comprised 0.2%, 1 of the 435 subjects, and is not a safety concern."*
- *I concur with Dr. Wesley's assessment.*

### 4.3.3 Insertion and Removal Related Adverse Events

In the clinical trials, the most common insertion-related complaint was pain, which affected 3% of subjects. Less than 1% of subjects reported redness, swelling, or hematoma at the site; none experienced expulsion of the implant. Procedural complications occurred in 1% of subjects with insertion and 1.7% with removal of the implant.

**Division Director's Comments**

- *Postmarketing reports from non-U.S. markets of incorrect insertions and difficult removals continue to be submitted to the Applicant, supporting the need for an effective training program for U.S. healthcare providers.*
- *The Applicant has proposed a training program that will include modules on proper insertion and removal techniques, and a distribution program that will attempt to limit Implanon distribution only to healthcare providers who have been trained by the Applicant's program (see Section 1.3.1, Risk Management Steps). The utility of the training program will be specifically assessed in the proposed Active Monitoring program, which will collect data on 10,000 insertions and removals performed by trained healthcare providers. The Applicant has agreed to the Active Monitoring Program as a Phase 4 commitment.*
- *Labeling includes a detailed description of the steps to be taken for insertion and removal of Implanon, in an attempt to minimize IRREs attributable to operator errors. The need to palpate the implant following insertion is particularly emphasized in the label instructions as well as with a bolded warning statement.*

- *Both the primary Medical Reviewer and the clinical Team Leader recommend that the Applicant be encouraged to continue development of a radio-opaque version of Implanon. The ability to visualize a nonpalpable radio-opaque implant will assist greatly with removal, particularly in clinics that may not have easy access to MRI facilities. I concur with this recommendation.*

## 5. RECOMMENDATIONS OF OTHER DISCIPLINES AND CONSULTATIONS

There are no unresolved toxicology, chemistry-manufacturing-controls (CMC), microbiology, or clinical pharmacology issues.

All recommendations from the Office of Surveillance and Epidemiology (OSE) have been addressed. A few outstanding issues concerning the Active Monitoring Program will be resolved during review of the final study protocol that is to be submitted within 45 days of approval as part of a Phase 4 commitment.

DMETS recommended that the implants to be used for training not contain active drug. The Division does not agree with this recommendation since (1) use of a training implant containing active drug does not pose a safety concern and (2) a training implant that does not contain active drug may not have the same physical characteristics as the to-be-marketed implant, and thus might be a less effective training tool.

## 6. LABELING

All labeling issues have been satisfactorily resolved. Labeling submitted by the Applicant on July 17, 2006 is acceptable.

Items of note in the Package Insert (PI) or Patient Labeling (PL) include the following.

- *The primary Medical Reviewer recommended that the PI contain a Boxed Warning regarding the need to check by palpation immediately after insertion that Implanon was properly placed under the skin. Although this is an important step in ensuring proper placement of the implant, neither the clinical Team Leader nor I believe that this direction should be a boxed warning. However, the final approved PI contains the following Bolded Warning as the first warning:*

    1. **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. See INSTRUCTIONS FOR INSERTION AND REMOVAL.**

    *The following statement is included in PL in the section* **What is the most important information I should know about IMPLANON™?**

    "If IMPLANON™ is not placed properly, it may not prevent pregnancy, or it may be difficult or impossible to remove. After you receive IMPLANON™, check

that it is in place by pressing your fingertips over the skin in your arm where IMPLANON™ was placed. You should be able to feel the IMPLANON™ rod."

- *Virtually all women who use Implanon with have altered menstrual (vaginal) bleeding. Bleeding patterns may range from no bleeding (amenorrhea), to irregular, unpredictable bleeding ranging in intensity from light to heavy. Bleeding complaints were the most common cause of premature terminations in the Implanon clinical trials. The Warnings Section of the PI contains the following information regarding bleeding irregularities.*

  "Patients who use IMPLANON™ are likely to have changes in their vaginal bleeding patterns, which are often unpredictable. These may include changes in bleeding frequency or duration, or amenorrhea. Patients should be counseled regarding unpredictable bleeding irregularities so that they know what to expect. Abnormal bleeding should be evaluated as needed to exclude pathologic conditions or pregnancy.

  In clinical trials, bleeding changes were the single most common reason for stopping treatment with IMPLANON™ (11.1%, or 105 of 942 patients using IMPLANON™). Most patients stopped treatment with IMPLANON™ because of irregular bleeding (10.8%), but some stopped because of amenorrhea (0.3%). In these studies, patients using IMPLANON™ had an average of 17.7 days of bleeding or spotting every 90 days (based on 3315 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 IMPLANON™ is shown in the following table."

**Percentages of Patients with 0, 1-7, 8-21, or >21 Days of Spotting or Bleeding over a 90-Day Interval while using IMPLANON**

| Total Days of Spotting or Bleeding | Percentage of Patients | | |
|---|---|---|---|
| | Treatment Days 91-180 (N=566) | Treatment Days 270-360 (N=554) | Treatment Days 640-730 (N=547) |
| 0 days | 19% | 24% | 17% |
| 1-7 days | 15% | 13% | 12% |
| 8 to 21 days | 30% | 30% | 37% |
| >21 days | 36% | 33% | 35% |

*Patient labeling contains the following statement in the section* **What is the most important information I should know about IMPLANON™?**

"The most common side effect of IMPLANON™ is a change in your menstrual periods. Expect your menstrual period to be irregular and unpredictable throughout the time you are using IMPLANON™. You may have more bleeding, less bleeding, or no bleeding. The time between periods may vary, and in between periods you may have spotting."

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/s/
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Scott Monroe
7/17/2006 05:44:21 PM
MEDICAL OFFICER

# DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)
# CLINICAL TEAM LEADER MEMORANDUM

| | |
|---|---|
| **NDA** | 21-529 |
| **Type of Application** | Complete Response to Approvable Action |
| **Applicant** | Organon USA, Inc |
| **Proprietary Drug Name** | Implanon™ |
| **Established Drug Name** | Etonogestrel implant |
| **Drug Class** | Contraceptive/Non-oral |
| **Indications** | Prevention of pregnancy in women |
| **Route of Administration** | Subdermal |
| **Dosage Form** | Subdermal implant |
| **Dosage Strength** | 68 mg etonogestrel per implant |
| **Dosing Regimen** | One implant every three years |
| **CDER Receipt Date** | January 17, 2006 |
| **PDUFA Goal Date** | July 17, 2006 |
| **Date of Memorandum** | July 14, 2006 |
| **Reviewer** | Lisa M. Soule, M.D.<br>Clinical Team Leader, DRUP |

## 1 RECOMMENDATIONS

### 1.1 RECOMMENDATION REGARDING APPROVABILITY

I recommend that NDA 21-529, Implanon™, be approved for the indication of prevention of pregnancy in women. A single implant may be used continuously for up to three years.

#### 1.1.1 Basis for Recommendation regarding Approvability

The clinical trial data demonstrate that Implanon™ (hereinafter referred to as Implanon) is a highly effective contraceptive, with a cumulative Pearl Index of 0.38 over three years of use. The safety profile is similar to that seen with other progestin-based contraceptives, with irregular bleeding the most common adverse event leading to discontinuation of use. As an implant inserted for up to three years, the efficacy of Implanon is not affected by patient compliance, a common short-coming of other contraceptive methods. However, potential insertion and removal problems are an important issue with Implanon. These will be addressed in labeling, training of healthcare providers and a monitoring program to assess the frequency of such complications and to evaluate the effectiveness of the training program.

In two previous review cycles, Implanon received Approvable actions due to concerns about the quality of data from several sites that participated in pivotal trial 34507 and 34507-CDN (see Section 2.2). The Applicant was asked to provide data sufficient to evaluate the efficacy and

safety of Implanon for at least 10,000 28-day cycle equivalents in the first year of use, and to ensure that such data were of acceptable quality and reliability. The Applicant conducted an internal audit program of 24 study sites to examine the reliability of data from these sites (see Section 3.1) and the extent to which studies were conducted in accord with Good Clinical Practice (GCP) standards. The audit reports (plus earlier audit results on an additional site) were reviewed by an outside consultant.

In the current review cycle, the Executive Summary of the overall audit program, the third party review memorandum, and the individual audit reports from all sites for which the Applicant submitted data in support of the application were reviewed by the DRUP review team. In addition, the Division of Scientific Investigation (DSI) inspected three study sites that participated in five different studies and concluded that the data appeared acceptable to support the indication. Based upon the findings of the Applicant's audits and the DSI inspections, I conclude that the Applicant has met the Division's request for data representing a sufficient number of treatment cycles in the first year of use, and that the data provided are adequate and reliable.

## 1.2 RECOMMENDATION ON RISK MANAGEMENT STEPS AND/OR PHASE 4 STUDIES

### 1.2.1 Risk Management Steps

The Applicant's proposed risk management plan consists of:

- a training program that healthcare providers will be required to undergo before being allowed to order and insert Implanon
- a monitoring program for insertion and removal related events (IRREs)

The training program and distribution plan were reviewed in the second cycle review and further discussed with the Division in a teleconference held on May 6, 2005. Submission of an acceptable monitoring plan to detect IRREs was one of the requirements for the Complete Response to the second Approvable action in June 2005.

The training program proposed in the current submission is to be a three-hour program that will include hands-on training using a model arm to develop insertion and removal techniques, and instruction in confirmation of location and placement, localization techniques and patient counseling. Only those healthcare providers who complete the training program will be allowed to order Implanon, and labeling will specify that only such trained providers should insert Implanon. The restriction on ordering will be accomplished by means of an Organon-maintained database listing trained providers, and restriction of supply to a single distributor who will verify that a provider ordering Implanon is in this database prior to shipping Implanon.

Team Leader Comment

- ***While the restricted distribution plan will not preclude a single trained clinician ordering for his/her entire practice, this scenario will be addressed in the training program with cautions against a trained provider attempting to train his/her colleagues outside of the Organon program.***
- ***Recognizing that the restricted distribution plan is not a complete barrier to use by untrained providers, I believe that the Applicant has made an acceptable effort to ensure that providers are appropriately trained prior to ordering and using Implanon in a clinical setting.***

Periodic review of the training material by an Organon representative meeting with healthcare providers is planned. The faculty for the training program, practicing academicians, residency program directors and clinicians, will be trained themselves in a full-day program. A "Faculty Playbook" to guide the training faculty is included in the submission and covers a number of "key

clinical and procedural points" including the unpredictable bleeding profile expected; risk of pregnancy in cases such as incorrect insertions, use of hepatic enzyme inducing agents, and use in obese women; and the importance of palpating the arm to confirm appropriate placement of Implanon.

**Team Leader Comment**

- ***The Faculty Playbook has been revised to include specific instruction to encourage providers (both trainees and faculty members) to report IRREs to Organon. A toll-free number for such reports will be provided.***
- ***The Key Points document provided to trainees has been revised to include instruction to provide the Patient Package Insert (PPI) to the patient and review it with her prior to insertion. This document now also includes specific instruction to providers to report IRREs to Organon and provides a toll-free number for making such reports.***

The monitoring program proposed in this submission includes both spontaneous reporting (Pharmacovigilance Plan) and active monitoring of IRREs, regardless of whether the event qualifies as a serious adverse event (SAE). The objectives of the monitoring program include both provision of information about the occurrence of IRREs and evaluation of the utility of the training program.

The Pharmacovigilance Plan will cover IRREs communicated to the Applicant by any route (including provider, third party or patient reports). The Organon website will provide a toll-free number for reporting of adverse events or IRREs. An IRRE addendum will be used in conjunction with a standard adverse event reporting form; this will be provided to healthcare providers who report IRREs. In the case of a patient report, the addendum questions will be read to the reporter by an Organon Drug Safety Coordinator. The literature will be reviewed weekly for additional case reports of IRREs, and authors will be contacted for additional information. IRREs occurring in ongoing clinical trials will be reported in the usual manner used for SAE reports. IRREs originating from the Active Monitoring program (see below) will be documented on a form completed after every insertion/removal. Reports from all of the above sources will be entered into the global safety database.

The Active Monitoring program will focus on 20-40 academic, private and clinic-based centers to obtain data on at least 10,000 insertions in the first year of marketing. A three-year follow-up will capture data on removals. Sites will be selected to obtain a representative mix of clinicians, reflecting the general pool of trained providers. The only additional training provided will be instruction in reporting of SAEs and IRREs. Data for this component of the monitoring program will be collected on an Insertion and Removal Evaluation form to be completed after every insertion and removal; these forms will be collected monthly. Active Monitoring participants who report an IRRE will receive the IRRE Addendum in order to obtain all necessary details.

Data from the Insertion and Removal Evaluation forms will be analyzed monthly using a database that will allow queries to determine the nature, frequency and specific reporting patterns of IRREs. This database will capture reports from the Active Monitoring program, spontaneous reports from the U.S. (Pharmacovigilance Program) and abroad, and will contain input from the healthcare provider training database and the implant distribution database. The inclusion of the latter two sources will allow queries about IRRE incidence as a function of Implanon distribution and as a function of a particular training program. The analytic reports will be considered internally and presented to an outside expert panel, to determine modifications needed to the training program or to labeling instructions.

IRRE information will be reported to FDA in accordance with regulations for reporting of SAEs. Additionally, quarterly IRRE reports will be provided for the first four years following NDA

approval, and then annually thereafter, as part of the Periodic Safety Update Reports. These reports will include sections on the Active Monitoring program, the Pharmacovigilance Program and queries, evaluations and actions undertaken by the Applicant.

Representatives of the Office of Surveillance and Epidemiology (OSE, formerly the Office of Drug Safety) provided a consult to the Division on July 20, 2005 regarding the adequacy of the training and monitoring programs. The Applicant has responded to the majority of the recommendations made by DRUP and by OSE. Although OSE had recommended that placebo be used in the training implant, DRUP agrees with the Applicant that active drug may be used in the training system to ensure that the physical characteristics of the training implant are not altered due to a change in composition of the rod, as well as to minimize the risk of a patient accidentally receiving an inactive implant should a training kit be mistakenly used for insertion.

**Team Leader Comment**

- ***The primary limitation to the monitoring program relates to the fact that there is no assurance that patients will return to the same provider or center for removal of their implant. Thus, linkage of insertion and removal events may be problematic. However, even data on unlinked insertions and removals will be of considerable value.***
- ***The Applicant has agreed to conduct the Active Monitoring program as a formal phase 4 commitment.***

### 1.2.2 Phase 4 Studies

I do not recommend any required phase 4 study commitments beyond that of the Active Monitoring program described above. I concur with the primary Medical Officer that the Applicant should attempt to minimize the difficulty in locating nonpalpable implants by pursuing development of a radiopaque version. Study 34528, a bioequivalence study of the current version of Implanon™ with a radiopaque version is ongoing.

I concur with the primary Medical Officer that a study of the effectiveness of Implanon in obese women (e.g., > 120 - 130% of ideal body weight or with a BMI > 30 kg/m$^2$) would be of value to provide more accurate labeling information.

## 2 BACKGROUND

### 2.1 DESCRIPTION OF PRODUCT

Implanon (etonogestrel implant) is a progestin-only contraceptive to be implanted subdermally. The non-biodegradable implant is a co-axial rod with a length of 4 cm and a diameter of 2 mm. The core contains 68 mg of etonogestrel (ENG) dispersed in a polymeric matrix of ethylene vinyl acetate copolymer that is surrounded by a 60 μm skin of ethylene vinyl acetate copolymer.

Etonogestrel, which is a derivative of 19-nortestosterone, is the biologically active metabolite of desogestrel, the progestin component of several combination oral contraceptives (COCs) approved for marketing in the U.S. Additionally, one product containing etonogestrel is approved and marketed in the U.S. for the prevention of pregnancy: NuvaRing® (Organon USA) is a combination contraceptive vaginal ring containing etonogestrel and ethinyl estradiol (EE) designed to release on average 0.120 mg/day of etonogestrel and 0.015 mg/day of EE over a 3-week period.

Implanon is supplied in a ready-for-use disposable applicator and is inserted subdermally in the inner side of the upper arm. After insertion, etonogestrel is released through the rate-controlling skin of the implant for up to 3 years.

## 2.2 REGULATORY HISTORY AND APPROVABILITY ISSUES

The original NDA for Implanon was submitted on September 30, 2003, and included six studies containing a total of 1763 subjects and 21,281 28-day treatment cycles in the first year of treatment, with smaller numbers of subjects treated for between two and five years. During the course of that review, the Applicant conducted internal audits in preparation for upcoming FDA inspections that revealed significant Good Clinical Practice (GCP) violations in two of the studies (34506 and 34520), sufficient to compromise the integrity and reliability of data from those trials. The Applicant withdrew these two studies from the submission, resulting in an application (revision submitted on May 3, 2004) that contained data on 1117 women, treated over 12,887 28-day cycles in the first year of treatment (see Table 1).

**Table 1 Principal Safety and Efficacy Studies in Revised Original Submission**

| Study Number | Region | Description of Study |
|---|---|---|
| 069001 | United States | 330 women, age 18-40, treated for up to 2 years |
| 34505 | Thailand | 100 women, age 18-39, treated for up to 2 to 4 years |
| 34507 | Europe & Chile | 635 women, age 18-40, treated for up to 2 to 3 years |
| 34507-CDN | Canada | 52 women, age 18-40, treated for up to 2 years |

Source: Team Leader Memorandum dated June 14, 2005, Table 1, p 3; from Original NDA submission, 30 September 2003.

During this review cycle, the Division of Scientific Investigation (DSI) inspected three U.S. sites (Study 069001) and two non-U.S. sites (Study 34507). Although citations were issued to all but one of the U.S. investigators, DSI concluded that the data submitted by these five investigators was "adequate in support of the relevant submission."

Later in the review cycle, the European Regulatory Authorities, represented by the Dutch Medicines Evaluation Board (DMEB), conducted further inspections of several European sites that had participated in Studies 34507 and 34507-CDN, which revealed that GCP standards had not been met and that the reliability of the data from these sites could not be assured. The DMEB inspections resulted in revised European labeling for Implanon, although the DMEB concluded that there were "no reasons to doubt the efficacy and safety of the product provided it is inserted in the proper manner."

Due to these concerns about the quality of clinical trial data as well as about the adequacy of the remaining data, the initial application received an Approvable action. The action letter, dated October 29, 2004, noted that the Applicant needed to:

- Address concerns about quality of data from Studies 34507 and 34507-CDN and provide a justification of why these studies are adequate and well-controlled trials able to provide sufficient data to demonstrate safety and efficacy of Implanon and to support accurate product labeling. As an alternative, the Applicant could conduct a new clinical trial to provide sufficient acceptable data to support efficacy and safety of the product.
- Provide final labeling
- Obtain satisfactory inspection of a sterilization factory

A Complete Response to the Approvable action was submitted on December 14, 2004. In lieu of conducting an additional clinical trial, the Applicant opted to provide justification of the adequacy of Studies 34507 and 34507-CDN to provide sufficient data demonstrating safety and efficacy and to support appropriate labeling. Consideration of the integrated inspection report by the Netherlands Inspectorate of Health Care (IGZ) highlighted significant concerns about the reliability of the data from these two studies, and the Division concluded that the Applicant had not provided adequate justification to discount the IGZ findings.

Based on these findings, the Division determined that only the data from Studies 069001 and 34505 and from two sites in Study 34507 that had been inspected by DSI were acceptable. This reduced the number of subjects evaluated over the first year of treatment to 648 and the evaluable 28-day cycles to 7,520, below the 10,000 in the first year of treatment generally required by FDA for evaluation of a new hormonal contraceptive product. If the Division further limited the data under consideration to that obtained only at sites inspected by DSI, then only 6,279 28-day cycles in Year 1 of treatment were available for evaluation (see Table 2).

**Table 2 Numbers of Subjects and 28-day Cycle Equivalents by Study Year in Clinical Trials considered to be "Adequate and Well Controlled" by Applicant or FDA Clinical Reviewers**

| "Adequate and Well Controlled" Trials | Year 1 | | Year 2 | | Year 3 | |
|---|---|---|---|---|---|---|
| | N | # of Cycles [E] | N | # of Cycles | N | # of Cycles |
| Original Submission (9/30/03)[A] (Data from 6 principal studies) | 1,763 | 21,281 | 1,495 | 18,114 | 1,094 | 9,619 |
| Revised Original Submission (5/3/04)[B] (Data from 4 of 6 original principal studies) | 1,114 | 12,887 | 862 | 10,158 | 597 | 2,989 |
| Data Assessed as likely to be reliable [C] (Data from 2 principal studies plus 2 additional sites from another study) | 648 | 7,520 | 505 | 5,931 | 369 | 2,737 |
| Data from FDA Inspected Studies or Sites [D] (Data from one principal study plus 2 additional sites from another study) | 548 | 6,279 | 415 | 4,813 | 292 | 1,911 |

Source: Team Leader Memorandum dated June 14, 2005, Table 2, p 6

A: Studies 069001 (U.S.), 34505 (Thailand), 34506 (Indonesia), 34507 (Europe/Chile), 34507-CDN (Canada), and 34520 (Indonesia).

B: Studies 069001 (U.S.), 34505 (Thailand), 34507 (Europe/Chile), and 34507-CDN (Canada).

C: Studies 069001 (U.S.), 34505 (Thailand), and 34507 (only sites of Drs. Urbancsek [Budapest] and Croxatto [Santiago]).

D: Studies 069001 (U.S.) and 34507 (only sites of Drs. Urbancsek and Croxatto).

E. Values are approximate and based on the equivalent of a 28-day treatment cycle.

The second cycle submission again received an Approvable action. The action letter, dated June 14, 2005, noted that the justification provided by the Applicant of the reliability of Studies 34507 and 34507-CDN was inadequate, and that, in the absence of data from these trials, insufficient total exposure in the first year of treatment had been obtained. The Applicant was asked to provide:

- New clinical trial data, from a trial(s) conducted under GCP, sufficient to provide data for the first year of treatment from at least 10,000 28-day cycle equivalents
- An acceptable plan for a post-marketing monitoring program of insertion and removal-related adverse events
- Acceptable labeling.

An End of Review meeting was held on August 11, 2005, at which the Applicant proposed to conduct additional audits of sites in Study 34507 that had not been audited by either the FDA or the EMEA, as well as from clinical pharmacology studies (34501, 34508, 34509, 34510, 34511, 34515 and 34522). If these sites passed the audit, the Applicant proposed to submit data from these studies to supplement the date accepted previously by the Division, in order to provide data from at least 10,000 first year treatment cycles. The Division concurred with the audit plan, but

cautioned the Applicant that the Division would need to confirm the auditor's conclusions, and that adequacy of the data to support the application would be determined only following the Division's review of the clinical data. In addition, a successful inspection by DSI of the Thailand site (Study 34505) would be necessary. If additional clinical pharmacology studies were submitted in support of safety and efficacy, they would need to have acceptable entry criteria for a contraceptive efficacy study, and subjects would need regular evaluations for pregnancy and an end-of-treatment pregnancy test.

### 2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary Medical Officer concluded in her review dated July 14, 2006:

> *From a clinical perspective, I recommend approval of the subdermal implant, Implanon, for the indication prevention of pregnancy. A single Implanon implant may be used continuously for up to three years.*

**Team Leader Comment**

- ***I concur with Dr. Furlong's recommendation that Implanon be approved for prevention of pregnancy.***

## 3 EFFICACY OF IMPLANON

### 3.1 OVERVIEW OF CLINICAL PROGRAM

A total of 27 studies have been conducted in the Implanon clinical development program. They are listed in Table 3, along with comments about why they were or were not accepted in support of safety and efficacy of this product.

**Table 3 List of Studies in Implanon Clinical Development Program**

| Study # | Design/Objective | Location | N | # 28-day Cycle Equivalents | Duration | Comments about Acceptability |
|---|---|---|---|---|---|---|
| **069001** | Open label, noncomparative, multicenter (16), safety & efficacy | U.S. | 330 | 6,198 | 2 years | **Accepted by FDA** as pivotal in 2nd cycle review; inspected by DSI in 2004 |
| **34502** | Open label, noncomparative, single center PK/PD | Thailand | 15 | 755 | 2 years, extended to 5 years | **Acceptable** per internal audit & 3rd party review; DSI inspection 5/06 |
| 34503 | Open label, noncomparative, single center PK/PD | Indonesia | 15 | 816 | 2 years, extended to 5 years | **Excluded** in 5/04 – GCP, serious misconduct |
| 34504 | Open label, noncomparative, single center PK/PD | UK | 15 | 306 | 1 year, extended to 4 years | **Excluded** due to use of "Leached implant" w/daily release rate of 40 µg ENG |
| **34505** | Open label, noncomparative, single center, safety & efficacy | Thailand | 100 | 3,863 | 2 years, extended to 4 years | **Accepted by DRUP** as "likely to be reliable" in 2nd cycle review; DSI inspection 5/06 |
| 34506 | Open label, noncomparative, single center, safety & efficacy | Indonesia | 200 | 8,589 | 2 years, extended to 4 years | **Excluded** in 5/04 – GCP, serious misconduct |
| **34507** | Open label, noncomparative, multicenter (22) | Germany, Hungary, Netherlands | 635 | 15,653 | 2 years, extended to 3 | 2 sites in Chile & Hungary **accepted by FDA** as pivotal in 2nd |

| Study # | Design/Objective | Location | N | # 28-day Cycle Equivalents | Duration | Comments about Acceptability |
|---|---|---|---|---|---|---|
| | safety & efficacy | Sweden, France, Austria, UK, Belgium & Chile | | | years in Chile & Hungary | cycle review; inspected by DSI in 2004 –<br>3 sites **acceptable** per internal audit & 3rd party review;<br>7 sites **excluded** per internal audit & 3rd party review primarily due to source record problems;<br>3 sites not selected for audit;<br>5 sites **excluded** per 2004 EMEA audit;<br>2 sites **excluded** prior to original NDA submission; |
| 34507-CDN | Open label, noncomparative, single center safety & efficacy | Canada | 52 | 1,085 | 2 years | **Excluded** per 2004 EMEA audit |
| 34508 | Open label, randomized, comparative (Norplant) two center, PK/PD | Finland, Sweden | 16 | 420 | 2 years, extended to 3 years in Finland | 1 site **excluded** per internal audit & 3rd party review;<br>1 site not selected for audit |
| 34509 | Open label, randomized, comparative (Norplant), multicenter (4) safety & efficacy | Finland, Sweden | 43 | 789 | 2 years | 1 site not audited due to missing master subject log;<br>1 site acceptable per initial internal audit but **excluded** after further audit requested following 3rd party review<br>2 sites not selected for audit |
| **34510** | Open label, randomized, comparative (Norplant), two center lipid study | Thailand, Indonesia | 15 | 358 | 2 years | **1 site acceptable** per internal audit & 3rd party review;<br>1 site **excluded** in 5/04 – GCP, serious misconduct |
| **34511** | Open label, randomized, comparative (Norplant) single center laboratory parameter safety study | Singapore | 40 | 1028 | 2 years | **Acceptable** per internal audit & 3rd party review; DSI inspection 5/06 |
| **34512** | Open label, randomized, comparative (Norplant) two center lipid study | Finland | 40 | 728 | 2 years | **1 site acceptable** per internal audit & 3rd party review;<br>1 site **excluded** per internal audit & 3rd party review |
| 34513 | Open label, randomized, comparative (IUD) single center lactation study | Indonesia | 0 | 0 | N/A | Study cancelled due to recruitment problems |
| | | | | | | |

| Study # | Design/Objective | Location | N | # 28-day Cycle Equivalents | Duration | Comments about Acceptability |
|---|---|---|---|---|---|---|
| 34514 | Open label, randomized, comparative (Norplant) two center endometrial safety study | Indonesia, UK | 30 | 904 | 2 years, extended to 3 years | 1 site **excluded** in 5/04 – GCP, serious misconduct;<br>1 site not selected for audit |
| **34515** | Open label single center absolute BA study | Singapore | 10 | 253 | 2 years | **Acceptable** per internal audit & 3rd party review; DSI inspection 5/06 |
| 34520 | Open label, comparative (Norplant), multicenter (9), safety, efficacy & acceptability | Indonesia | 449 | 16,244 | 2 years, extended to 3 years | **Excluded** in 5/04 – GCP, serious misconduct |
| **34522** | Open label, nonrandomized, comparative (IUD), three center bone density study | Chile, Finland, Netherlands | 46 | 1054 | 2 years | **Acceptable** per internal audit & 3rd party review |
| 34523 | Open label, nonrandomized, comparative (IUD), single center lactation study | Thailand | 42 | 1483 | 2.7 years | **Excluded** due to lactating subjects, not at equivalent risk of pregnancy |
| 34524 | Open label, noncomparative, nonrandomized, two center safety & efficacy | Mexico | 58 | 1223 | 2-3 years | Both sites **excluded** per internal audit & 3rd party review |
| **34525** | Open label, noncomparative, two center safety & efficacy | Russia | 60 | 774 | 1-3 years | **1 site acceptable** per internal audit & 3rd party review;<br>1 site **excluded** based on 2004 EMEA review of existing audit |
| 34528 | Double blind, parallel group, multicenter (9) BE study | Switzerland, Netherlands, France | 108 | Ongoing | 3 years planned | Ongoing |
| BKKBN | Open label, noncomparative, multicenter (8) postmarketing surveillance | Indonesia | 10,068 | N/A | 3 years | **Excluded** prior to original NDA submission – postmarketing surveillance study |

| Study # | Design/Objective | Location | N | # 28-day Cycle Equivalents | Duration | Comments about Acceptability |
|---|---|---|---|---|---|---|
| E-1729 | Open label, noncomparative, multicenter (12) safety & efficacy | Malaysia | 211 | Ongoing | 3 years planned | **1 site acceptable** per audit & 3rd party review; DSI inspection 5/06; 11 sites - data validation ongoing |
| L-1784 | Double blind, multicenter (32) safety study | France | 114 | Ongoing | 6 months | Ongoing |
| RM01 | Open label, noncomparative, single center PK/PD | China | 16 | 837 | 2 years, extended to 4.5 years | **Excluded** prior to original NDA submission – GCP noncompliance |
| RM02 | Open label, noncomparative, multicenter (4) safety & efficacy | China | 200 | 8669 | 2 years, extended to 4 years | **Excluded** prior to original NDA submission – GCP noncompliance |
| RM04 | Open label, randomized, comparative (Norplant) multicenter (4) safety & efficacy | China | 100 | 4456 | 2 years, extended to 4 years | **Excluded** prior to original NDA submission – GCP noncompliance |

Source: List of Studies & List of Investigators, January 2006 Update
PK = pharmacokinetics, PD = pharmacodynamics, BA = bioavailability, BE = bioequivalence
Shaded entries – considered for internal audit in order to be submitted in 2nd Complete Response
**Bolded studies** – included in 2nd Complete Response

The studies considered for submission in the second Complete Response are shaded in Table 3. The Applicant identified study sites for possible internal audit (so that they could be verified to provide reliable data for additional cycles of first year treatment data) based on the following criteria:

- Available number of first year cycles
- Geographic location (to facilitate audit conduct)

In addition to data from Studies 069001, 34505 and two sites from Study 34507 that had previously been accepted by FDA as likely reliable, a total of 26 sites (involving 12 studies) were considered for inclusion in the Complete Response submission. One site in Study 34509 was removed from the audit list after confirmation that the master subject log was unable to be located. Study E-1729 was not included in the internal audit, but had been previously audited by the Applicant in September 2004 and April 2005.

Audits were conducted on-site and included identification of source documents for each subject, as well as in-depth review of source data for a sample of subjects. The following components were assessed:

- Reporting of adverse events and serious adverse events (SAEs)
- Source documentation, including patient diaries/bleeding cards
- GCP compliance (acknowledging that strict GCP compliance was unlikely as many of the studies had been conducted prior to the adoption of formalized GCP rules and guidelines)

Of the 24 sites audited, 14 were considered by the Applicant to be acceptable for submission.

A third party review of all audit results was conducted by — , which concurred with all conclusions except in the case of the remaining site in Study 34509. noted that fewer subject records than planned had been reviewed; when the Applicant returned to audit additional records, discrepancies noted in adverse event reporting led to the site's exclusion. b(4)

concurred with all decisions about which sites should be excluded from submission following internal audits. Reasons for such exclusion primarily concerned availability of and discrepancies in source data, underreporting of adverse events and use of data recording tools other than those specified in the protocol, leading to transcription errors and underreporting of adverse events. -- conclusion upon review of the Implanon audit program was: b(4)

> *Based upon our review as described in this memorandum, we conclude that the Implanon™ audit program was conducted in accordance with the plan set out by Organon in its correspondence with the Agency [FDA]. For the reasons set out in greater detail below, we agree with the conclusions reached by Organon concerning the overall reliability of data from the study sites audited. We concur with the list of study sites that will be included in the clinical trial database as part of Organon's response to the Approvable letter.*

**Team Leader Comment**

- ***The audits and outside review of audit findings did not find any evidence of fraudulent data. Issues leading to elimination of sites and studies from the safety and efficacy summaries involved procedural inadequacies or mistakes. There was no evidence that sites or studies were excluded from this submission due to unacceptable numbers of pregnancies or adverse events.***

## 3.2 EXTENT OF EXPOSURE

Subsequent to the audit process, data from a total of 13 sites (9 studies) providing an additional 3,346 first year cycles and 7,158 total cycles were submitted, in addition to the 7,520 first year cycles and 16,188 total cycles previously accepted in the second cycle review. Table 4 shows the specific sites and studies contributing safety and efficacy data in the second Complete Response. The studies comprise phase 3 clinical trials (069001, 34505, 34507 and 34525), phase 2 clinical pharmacology studies (34502, 34510, 34511, 34512, 34515 and 34522) and a postmarketing study (E-1729). The Applicant justifies the inclusion of the non-phase 3 trials on the basis that:

- The duration of exposure was similar to that in the primary clinical trials (at least two years)
- The selection criteria for inclusion in the database was similar to that used for the clinical trials primarily focusing on safety and efficacy
- Visit frequency and nature of assessments were the same as those in the phase 3 trials (i.e., visits every three months including three months posttreatment, pregnancy testing if amenorrheic over 45 days)

**Table 4 Studies Included in Second Complete Response**

| Study | Site | Duration of treatment (Number of subjects, cycles of exposure) | | | | | | | | Total Extent of exposure |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Year 1 | | Year 2 | | Year 3 | | > 3 years | | |
| | | N | cycles | N | cycles | N | cycles | N | cycles | Cycles |
| U.S. study | | | | | | | | | | |
| 069001 | All | 327[a] | 3,584 | 226 | 2,522 | 136 | 80 | 0 | 0 | 6,186 |
| Non-U.S. studies | | | | | | | | | | |
| 34502 | T_001 (=all) | 15 | 196 | 15 | 195 | 13 | 147 | 10 | 217 | 755 |
| 34505 | T_001 (=all) | 100 | 1,241 | 90 | 1,118 | 77 | 826 | 57 | 678 | 3,863 |
| 34507 | A_004 | 8 | 95 | 7 | 81 | 3 | 2 | 0 | 0 | 177 |
| | H_003 | 114 | 1,376 | 95 | 1,113 | 75 | 863 | 58 | 51 | 3,406 |
| | D_019 | 19 | 213 | 15 | 175 | 10 | 8 | 0 | 0 | 395 |
| | D_021 | 19 | 221 | 16 | 183 | 9 | 10 | 0 | 0 | 414 |
| | RCH_001 | 107 | 1,317 | 94 | 1,178 | 81 | 968 | 54 | 24 | 3,487 |
| 34510 | T_002 | 15 | 187 | 14 | 171 | 5 | 0.4 | 0 | 0 | 358 |
| 34511 | SGP_001 (=all) | 40 | 515 | 39 | 489 | 35 | 24 | 0 | 0 | 1,028 |
| 34512 | SF_019 | 20 | 224 | 14 | 150 | 9 | 1.4 | 0 | 0 | 376 |
| 34515 | SGP_001 (=all) | 10 | 130 | 10 | 120 | 5 | 2.1 | 0 | 0 | 253 |
| 34522 | NL_027 | 16 | 196 | 13 | 145 | 10 | 2.8 | 0 | 0 | 344 |
| | RCH_001 | 15 | 196 | 14 | 176 | 13 | 7.0 | 0 | 0 | 378 |
| | SF_020 | 15 | 171 | 12 | 156 | 11 | 5.3 | 0 | 0 | 332 |
| 34525[b] | RU_003 | 28 | 337 | 22 | 19 | 0 | 0 | 0 | 0 | 356 |
| E1729[b] | MY_002 | 55 | 667 | 47 | 604 | 43 | 545 | 40 | 176 | 1,992 |
| Total Non-U.S. studies | | 596 | 7,282 | 517 | 6,073 | 399 | 3,412 | 219 | 1,146 | 17,913 |
| Total US and non-US | | 923 | 10,867 | 743 | 8,595 | 535 | 3,492 | 219 | 1,146 | 24,100 |

Source: Appendix A, Tables 2A and 2B

Year 1 = Day 1-365; Year 2 = Day 366-730; Year 3 = Day 731-1095; >3 years = Day >1095

[a] Three subjects, who had no post-baseline assessments, were not included in the calculation of extent of exposure.

[b] Excluding breastfeeding women (34525: n=2; E-1729: n=14)

Source: Table 1, p 17, Integrated Summary of Efficacy, January 2006 Update

In addition, DRUP had noted that entry criteria and assessment of pregnancy in the submitted studies would need to be comparable to the methodology used in the primary safety and efficacy studies.

**Team Leader Comment**

- ***The studies submitted appear adequate and of sufficient reliability to support determination of safety and efficacy for Implanon for up to three years.***
- ***The number of 28-day equivalent cycles in the first year of treatment is sufficient to meet DRUP's general requirement for a new contraceptive product. The number of cycles in the third year is sufficient to allow evaluation of efficacy and safety when Implanon is used up to three years.***

## 3.3 DEMOGRAPHICS AND DISPOSITION OF SUBJECTS

Subjects in all studies were to be healthy women, 18 to 40 years, sexually active and of childbearing potential (except in Study 34502, where an ovulatory cycle was documented at screening), with normal menstrual cycles, and body weight between 80-130% of ideal body weight. Demographic characteristics in the U.S. and non-U.S. studies are shown in Table 5.

**Table 5 Demographic Characteristics of Subjects**

| | U.S. Study | Non-U.S. Studies |
|---|---|---|
| N (All-Subjects Treated) | 330 | 596 |
| Mean age | 26.1 | 26.0 to 32.3 |
| Race (%) | | |
| • Caucasian | 71 | Not assessed |
| • Black | 12 | Not assessed |
| • Asian | 2 | Not assessed |
| • Other | 15 | Not assessed |
| Mean Body Mass Index (SD) | 23.6 (3.6) | 21.7 to 23.6 |
| Mean Weight (kg) | 63 | 51.2 to 63.5 |
| % Nulliparous | 36.7 | 0 to 100 |

Source: Primary medical review, dated July 14, 2006, based on Tables 5, 6 & 8, pp 33-4, 37-8, Integrated Summary of Efficacy, January 2006 Update

Overall, 35% of subjects discontinued trial participation prematurely; this rate differed between U.S. and non-U.S. studies, with the U.S. subjects discontinuing more frequently (48.8% versus 27.6%) . Reasons for discontinuation were categorized somewhat differently over the U.S. and non-U.S. studies. Table 6 compares reasons for withdrawal to the extent possible over the two locations. While the frequency of irregular bleeding as a cause for withdrawal was similar over study locations, the withdrawal rate due to other adverse events was higher in the U.S (36.1% versus 18.6%). This is discussed further in Section 4.1.2.

**Table 6 Reasons for Study Withdrawal**

| Reason for Discontinuation | U. S. Study 069001 N=330 | | Non-U.S. Studies N=612 | |
|---|---|---|---|---|
| | N | % | N | % |
| Adverse Events | 119 | 36.1 | 114 | 18.6 |
| • Irregular bleeding | 43 | 13.0 | 62 | 10.1 |
| • Other | 76 | 23.0 | 52 | 8.5 |
| Other (includes lost to follow-up) | 29 | 8.8 | 55 | 9.0 |
| Unwilling to continue | 8 | 2.4 | Not included as reason for withdrawal | |
| Protocol violation | 4 | 1.2 | | |
| Intercurrent illness | 1 | 0.3 | | |
| Total | 161 | 48.8 | 169 | 27.6 |

Source: Based on Tables 5 & 6, pp 33-4, Integrated Summary of Safety, January 2006 Update

## 3.4 EFFICACY FINDINGS

### 3.4.1 Assessment of Efficacy

All subjects who received Implanon, excluding lactating women, comprised the All-Subjects Treated Group (a total of 923 women). Of these, 833 women were between ages 18-35, the group typically used for assessment of contraceptive efficacy.

Assessment for pregnancy was done prior to implant insertion, and at each clinic visit (every three months). Pregnancy testing was done if no bleeding had occurred for at least 45 days. The use of condoms for STD protection was allowed, and was not recorded except in Study 34502.

The Applicant reported that no on-treatment pregnancies occurred. No pre-treatment pregnancies were detected. There were 50 post-treatment pregnancies recorded following implant removal. Based on ultrasound, date of last menstrual period (LMP) or gestational age estimation of the neonate, the estimated date of conception (EDC) of six of these pregnancies was likely within 14 days of implant removal:

- Subject #0327 (Study E-1729) – used Implanon 1082 days (36 months); EDC 13 days after removal (due to end of study) based on LMP
- Subject #0336 (Study E-1729) – used Implanon 1077 days (35 months); EDC 9 days after removal (due to end of study, planning pregnancy) based on LMP
- Subject #0345 (Study E-1729) – used Implanon 447 days (15 months); EDC 8 days after removal (due to planning pregnancy) based on delivery of term infant
- Subject #0024 (Study 34522) – used Implanon 634 days (21 months); EDC 3 days after removal (due to planning pregnancy) based on LMP and delivery of term infant
- Subject #05014 (Study 069001) – used Implanon 172 days (6 months); EDC 7 days after removal (due to severe moodiness) based on first trimester ultrasound
- Subject #10017 (Study 069001) – used Implanon 100 days (3 months); EDC 12 days after removal (due to planning pregnancy) based on second trimester ultrasound

The Applicant calculated the Pearl Index for each year of treatment and overall for the situation with no on-treatment pregnancies and more conservatively, assuming that the six pregnancies occurring within two weeks of implant removal were actually conceived on-treatment. The FDA Statistical Reviewer confirmed these calculations. They are shown below in Table 7 and Table 8, respectively.

**Table 7 Pearl Index – All Treated Subjects 18-35 Years, No On-Treatment Pregnancies**

| Treatment Period | N | Number of On-Treatment Pregnancies | Number of Cycles | Pearl Index (Pregnancies per 100 Women-Years) | 95% Confidence Interval* |
|---|---|---|---|---|---|
| Year 1 (Day 1 – 365) | 833 | 0 | 9816 | 0 | (0, 0.49) |
| Year 2 (Day 366 – 750) | 671 | 0 | 7766 | 0 | (0, 0.62) |
| Year 3 (Day 731 – 1095) | 482 | 0 | 3066 | 0 | (0, 1.57) |
| Cumulative 3 Year (Day 1 – 1095) | 833 | 0 | 20648 | 0 | (0, 0.23) |

Does not exclude cycles where use of other contraception was reported
Source: Statistical Review, Table 3.1, dated June 15, 2006

**Table 8 Pearl Index – All Treated Subjects 18-35 Years, Including Pregnancies within 14 Days of Implanon Removal**

| Treatment Period | N | Number of On-Treatment Pregnancies | Number of Cycles | Pearl Index | 95% Confidence Interval* |
|---|---|---|---|---|---|
| Year 1 (Day 1 – 365) | 833 | 2 | 9816 | 0.27 | (0.03, 0.96) |
| Year 2 (Day 366 – 750) | 671 | 2 | 7766 | 0.34 | (0.04, 1.21) |
| Year 3 (Day 731 – 1095) | 482 | 2 | 3066 | 0.85 | (0.10, 3.07) |
| Cumulative 3 Year (Day 1 – 1095) | 833 | 6 | 20648 | 0.38 | (0.14, 0.82) |

Does not exclude cycles where use of other contraception was reported
Source: Statistical Review, Table 3.2, dated June 15, 2006

**Team Leader Comment**

- ***Whether based on the observation of no on-treatment pregnancies, or more conservatively, considering that the six pregnancies within two weeks after implant removal may have occurred on-treatment, the Pearl Index calculations indicate that Implanon is highly effective for up to three years of use.***
- ***Data on 482 women, for over 3,000 cycles in Year 3, demonstrate acceptable efficacy when Implanon remains in place for three years. The six possibly on-treatment pregnancies were distributed evenly across three years, and not clustered during the third year of use.***

### 3.4.2 Postmarketing Reports of Pregnancy

The Applicant submitted a safety update with a cutoff date of March 1, 2006. It includes postmarketing data (medically confirmed and unconfirmed reports) as well as updated reports from three ongoing trials – E-1729, 34528 and L-1784. Pregnancy data from the ongoing trials is not reported except insofar as no study withdrawals due to pregnancy are reported in any of the trials.

#### 3.4.2.1 Overall Number of Reported Pregnancies

A total of pregnancies medically confirmed) have been reported from market introduction of Implanon in August 1998 through March 1, 2006. Of these, 63 were ectopic and two were heterotopic. These are measured against a background of implants sold over that time period, resulting in a pregnancy rate per implant sold of 0.051. The Applicant did not estimate a Pearl Index for the postmarketing pregnancy reports, as the number of implants actually inserted and the duration of use are unknown. b(4)

The Applicant classified the medically confirmed pregnancies according to likely reason the pregnancy occurred. Table 9 displays the number of pregnancies in each group as categorized by the Applicant.

**Table 9 Pregnancies by Category**

| Likely Reason for Pregnancy Report | N |
|---|---|
| Presence of pregnancy not confirmed[1] | |
| No active implant present[2] | |
| Conception outside period of Implanon use[3] | |
| Contraceptive method failure[4] | |
| Reason for pregnancy cannot be determined[5] | |
| Improper use[6] | |
| **Total** | |

b(4)

[1] Conflicting pregnancy test results or report of spontaneous abortion without pregnancy confirmation by test or ultrasound
[2] ENG levels below level of quantification or placebo training rod or other non-active parts inserted in lieu of Implanon
[3] Pregnant prior to insertion , or after removal of Implanon
[4] Implanon placement confirmed by ENG level or implant removal; EDC >10 days after insertion and <10 days before removal
[5] Includes probably method failure – Implanon localized but not removed or ENG level not checked , reportedly already pregnant at insertion, but no dating conception within 10 days before to 10 days after insertion , conception within 10 days before to 10 days after removal doubt about presence of Implanon , insufficient data to determine timing of conception relative to insertion/removal and presence of Implanon not investigated
[6] Implanon in place > 3 years 37-48 months) or apparently only 1 cm of the rod inserted )

b(4)

Source: Tables 2-6, pp 12-19, Appendix E, Update of Safety Information, May 2006

Of note or 11% of pregnancies classed as contraceptive method failures were ectopic pregnancies. Within the category of "undetermined reason, or 5.7% were ectopic or heterotopic (one case). Also in this category, in cases (48%) where conception occurred around the time of Implanon insertion, the implant was placed outside the recommended timing in the woman's menstrual cycle.

**Team Leader Comment**

- ***The occurrence cases of "no active implant," accounting for 30% of pregnancies (and another cases where Implanon presence was doubtful), highlights the need for clear instructions on insertion and emphasis on confirming placement by palpation of the implant by the patient and provider.***
- ***The method failure classification is defined conservatively; it is likely that at least 55 of the cases from the "undetermined" category should be included. This would bring the proportion of all pregnancies due to method failure to 23%.*** b(4)
- ***The relatively high frequency of ectopic pregnancies occurring among method failures and likely method failures is consistent with an increased risk of ectopic pregnancy when pregnancy occurs on progestin-only contraception. This is addressed in the Warnings Section of the labeling.***

In 116 of the pregnancies, drug interactions (97) or possible drug interactions (19) occurred due to use of concomitant medications with Implanon. This was particularly notable in the method failure category, where drug interactions (29%) or possible interactions (4%) occurred. b(4)

**Team Leader Comment**

- ***The labeling includes a Precaution that chronic users of drugs that induce hepatic enzymes not use Implanon, and recommends that short-term users of such drugs use a back-up nonhormonal method of contraception.***

### 3.4.2.2 Pregnancies based on Time of Conception post Insertion of Implanon

Similar numbers of the pregnancies attributed to method failure occurred during Years 1, 2 and 3 respectively, with unknown); however, since the continuation of use in subsequent years is likely to be less than 100%, it is likely that the pregnancy rate increases slightly with duration of use. The Applicant also noted that the frequency of concomitant use of interacting drugs also increased with duration of use, which may further reduce the efficacy, particularly as the serum levels of ENG decrease with time. b(4)

### 3.4.3 Overall Assessment of Efficacy

**Team Leader Comment**

- ***Implanon is a highly effective contraceptive for up to three years of use, with a Pearl Index that compares favorably to other hormonal contraceptives. Very limited data on obese women suggests that efficacy may not experience the same degree of efficacy. I recommend that this be explored further in a phase 4 study. Factors that adversely affect efficacy – failed insertions and use of concomitant medications that induce hepatic enzymes – need to be clearly addressed in labeling. The Applicant has also developed training and monitoring programs focused on preventing and assessing insertion and removal problems (see Section 1.2.1).***

# 4 SAFETY FINDINGS

## 4.1 CLINICAL TRIAL FINDINGS

### 4.1.1 Extent of Exposure

The safety dataset contained 942 women, followed over 24,679 cycles (1,892 women-years) of treatment. Table 10 summarizes the extent of exposure in the safety database.

**Table 10 Extent of Exposure in Safety Database**

| | Implanon™ | | |
|---|---|---|---|
| | U.S.[a] (N=327) | Non-U.S.[b] (N=612) | All Studies (N=939) |
| Treatment duration (days) | | | |
| Mean ± SD | 529.7 ± 256.2 | 846.1 ± 390.7 | 735.9 ± 380.7 |
| Median | 721 | 754.5 | 736 |
| Total exposure | | | |
| Woman-years | 474.2 | 1417.7 | 1891.9 |
| Number of 28-day cycles | 6188.2 | 18493.1 | 24679.3 |
| Number of subjects exposed by duration | | | |
| < 1 year | 101 (30.9%) | 80 (13.1%) | 181 (19.3%) |
| 1 to < 2 years | 90 (27.5%) | 120 (19.6%) | 210 (22.4%) |
| 2 to < 3 years | 136 (41.6%) | 181 (29.6%) | 317 (33.8%) |
| 3 to < 4 years | | 184 (30.1%) | 184 (19.6%) |
| ≥ 4 years | | 47 (7.7%) | 47 (5.0%) |

Source: Appendix F, Table 7
< 1 year – 1-365 days, 1 to < 2 years – 366-730 days, 2 to < 3 years – 731-1095 days, 3 to < 4 years – 1096-1461 days, ≥ 4 years 1462 days
[a] Study 069001. Extent of exposure was calculated from 327 subjects in Study 069001 (three subjects had no postbaseline assessments).
[b] Studies 34502 (T 001), 34505 (T 001), 34507 (D 019, D 021, H 003, RCH 001, A 004), 34525 (RU 003), 34510 (T 002), 34511 (SGP 001),34512 (SF 019), 34515 (SGP 001), 34522 (NL 027, RCH 001, SF 020) E1729 (MY 002).

Source: Table 8, p 40, Integrated Summary of Safety, January 2006 Update

### 4.1.2 Deaths and Serious Adverse Events

There were no deaths in any of the trials. Fifty-six subjects (5.9%) in the safety database experienced 77 serious adverse events (SAEs). SAEs of greatest relevance included eight subjects with gall bladder disorders (cholecystitis, cholelithiasis and cholecystectomy), three breast malignancies, two non-dermoid ovarian cysts, and one case each of transient ischemic attack, acute exacerbation of depression and a suicide attempt. The most frequent SAEs involved the gastrointestinal system, with five cases of cholelithiasis and five of gastrointestinal disorder not otherwise specified (NOS). Five subjects had SAEs that remained ongoing at the end of the trial: three with breast malignancies, one with abdominal pain with unknown outcome and one with congenital heart disease.

A total of 25% of subjects discontinued trial participation due to adverse events, including bleeding irregularities. Table 11 displays the system-organ class leading to discontinuation due to adverse events. As noted previously, the discontinuation rate overall and due to adverse events was higher among U.S. subjects than non-U.S. subjects. The categories particularly higher among U.S. subjects included bleeding irregularity exclusive of amenorrhea (12% vs. 10%) and psychiatric disorders (9% vs. 1%).

**Team Leader Comment**

- ***It is unknown whether these differences in adverse events leading to premature withdrawal represent reporting disparities or true differences in the occurrence of these adverse events.***

**Table 11 Discontinuations due to Adverse Events (System Organ Class with ≥ 2 Events)**

| WHO system-organ class | Preferred term | U.S. (N=330) | | Non-U.S. (N=612) | | All Studies (N=942) | |
|---|---|---|---|---|---|---|---|
| | | n | (%) | n | (%) | n | (%) |
| Reproductive disorders, | | 51 | 15.4 | 65 | 10.6 | 116 | 12.3 |
| | Bleeding irregularity | 39 | 11.8 | 59 | 9.6 | 98 | 10.4 |
| | Amenorrhea | 4 | 1.2 | 3 | 0.5 | 7 | 0.7 |
| | Sexual function abnl. | 4 | 1.2 | 0 | | 4 | 0.4 |
| | Dysmenorrhea | 2 | 0.6 | 0 | | 2 | 0.2 |
| | Premenstrual tension | 2 | 0.6 | 0 | | 2 | 0.2 |
| | Breast pain female | 0 | | 3 | 0.5 | 3 | 0.3 |
| Psychiatric disorders | | 31 | 9.4 | 5 | 0.8 | 36 | 3.8 |
| | Emotional lability | 20 | 6.1 | 2 | 0.3 | 22 | 2.3 |
| | Depression | 8 | 2.4 | 1 | 0.2 | 9 | 1.0 |
| | Nervousness | 3 | 0.9 | 1 | 0.2 | 4 | 0.4 |
| | Anxiety | 2 | 0.6 | 1 | 0.2 | 3 | 0.3 |
| Metabolic and nutritional disorders | | 11 | 3.3 | 14 | 2.3 | 25 | 2.7 |
| | Weight increase | 11 | 3.3 | 11 | 1.8 | 22 | 2.3 |
| | Weight decrease | 0 | | 3 | 0.5 | 3 | 0.3 |
| Skin and appendages disorders | | 7 | 2.1 | 13 | 2.1 | 20 | 2.1 |
| | Acne | 5 | 1.5 | 7 | 1.1 | 12 | 1.3 |
| | Alopecia | 2 | 0.6 | 5 | 0.8 | 7 | 0.7 |
| Central and peripheral nervous system disorders | | 6 | 1.8 | 14 | 2.3 | 20 | 2.1 |
| | Headache | 4 | 1.2 | 11 | 1.8 | 15 | 1.6 |
| | Dizziness | 0 | | 3 | 0.5 | 3 | 0.3 |
| Body as a whole disorders | | 5 | 1.5 | 3 | 0.5 | 8 | 0.8 |
| | Fatigue | 2 | 0.6 | 1 | 0.2 | 3 | 0.3 |
| Application site disorders | | 3 | 0.9 | 1 | 0.2 | 4 | 0.4 |
| | Injection site pain | 3 | 0.9 | 0 | | 3 | 0.3 |
| Neoplasms | | 2 | 0.6 | 1 | 0.2 | 3 | 0.3 |
| | Breast neoplasm (malig.) | 1 | 0.3 | 1 | 0.2 | 2 | 0.2 |
| Vascular disorders | | 0 | | 2 | 0.3 | 2 | 0.2 |
| Cardiovascular disorders | | 0 | | 2 | 0.3 | 2 | 0.2 |
| | Hypertension | 0 | | 2 | 0.3 | 2 | 0.2 |

Source: Based on Table 13, pp 59-60, Integrated Summary of Safety, and Tables 5 & 6, pp 33-4, Integrated Summary of Efficacy, January 2006 Update

**Team Leader Comment**

- ***Although bleeding disorders are considered by the Applicant in the efficacy section, and not as adverse events, they are included here, as they are side effects of treatment that adversely affect women's willingness to continue use of Implanon.***

Events considered drug-related by the Applicant that occurred in >5% of subjects included:

- Headache (15.3%)

- Weight increase (11.8%)
- Acne (11.4%)
- Breast pain (10.2%)
- Emotional lability (5.7%)
- Abdominal pain (5.2%)

**Team Leader Comment**

- ***The common, apparently drug-related adverse events are typical of those reported with progestin-based contraceptive products.***
- ***As noted above, the Applicant did not consider bleeding irregularities to be adverse events, and they are therefore not listed among the Applicant's drug-related adverse events. However, they were the most common reason for discontinuation, leading to discontinuation of treatment in 11 % of women, and, in women entering the trial with normal cycles, are likely to be drug-related. Thus, I would expect that drug-related bleeding irregularities also occurred in >5% of subjects.***

### 4.1.3 Other Adverse Events

Bleeding Irregularities

A common complaint with progestin contraceptives concerns irregular bleeding. This was among the most common reasons for study withdrawal. Bleeding data were characterized over 90-day "Reference Periods," the first of which began with the date of Implanon insertion. Up to two days of missing date per reference period were imputed from bordering days' data; Reference Periods with three or more days of missing data were considered non-evaluable. The Applicant excluded breastfeeding women from evaluation of bleeding irregularities; thus 926 subjects provided bleeding data, recorded on daily diary cards.

Table 12 shows the number of bleeding or spotting days for subjects who completed two years of treatment, those who discontinued due to bleeding complaints and all subjects. As Implanon is inserted during a menstrual period, it is expected that the first Reference Period will have more days of bleeding than subsequent Reference Periods.

**Table 12 Number of Bleeding or Spotting Days per 90-Day Reference Period – Completers, Subjects Who Discontinued Prematurely Because of Bleeding Complaints and All Subjects**

| Parameters | RP | Implanon™ | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Completers | | | | Discontinuers due to bleeding irregularities | | | | Total (Completers + Discontinuers for any cause)[a] | | | |
| | | N | Mean | SD | Median | N | Mean | SD | Median | N | Mean | SD | Median |
| Number of bleeding-spotting days | 1 | 555 | 26.39 | 20.24 | 22.00 | 78 | 51.77 | 21.24 | 54.00 | 802 | 29.10 | 21.90 | 24.00 |
| | 2 | 566 | 18.69 | 19.39 | 14.00 | 50 | 48.9 | 24.93 | 46.00 | 745 | 20.38 | 21.18 | 15.00 |
| | 3 | 559 | 14.92 | 15.90 | 11.00 | 37 | 45.05 | 24.34 | 41.00 | 690 | 16.83 | 18.05 | 13.00 |
| | 4 | 554 | 15.93 | 16.15 | 12.00 | 27 | 43.44 | 21.95 | 41.00 | 657 | 16.97 | 17.18 | 13.00 |
| | 5 | 547 | 16.13 | 14.89 | 13.00 | 16 | 43.44 | 22.35 | 42.00 | 620 | 16.71 | 15.71 | 14.00 |
| | 6 | 548 | 16.72 | 15.52 | 14.00 | 12 | 37.08 | 19.23 | 37.50 | 603 | 17.11 | 15.67 | 15.00 |
| | 7 | 547 | 16.45 | 15.17 | 13.00 | 4 | 50.00 | 22.65 | 53.50 | 569 | 16.51 | 15.38 | 14.00 |
| | 8 | 547 | 17.42 | 13.77 | 16.00 | 0 | 0 | 0 | 0 | 547 | 17.42 | 13.77 | 16.00 |

Source: Table 22, p 66, Integrated Summary of Efficacy, January 2006 Update

**Team Leader Comment**

- ***The mean number of bleeding-spotting days in the completers and all subjects is consistent with the number expected for a woman having normal menstrual cycles over a 90-day Reference Period (three menses, 4-7 days each).***

- ***Women who discontinued due to bleeding problems had markedly more days of bleeding (2-3 times that seen among completers), although there is a downward trend as length of time in study increases.***

Subjects also were categorized by bleeding pattern and these data are presented for subjects who completed two years of treatment, those who discontinued due to bleeding complaints and all subjects in Table 13. Among completers and all subjects, more than half of the 90-day reference periods were categorized as infrequent bleeding or amenorrhea, while among those who discontinued, almost 89% of the reference periods were categorized as frequent and/or prolonged bleeding.

**Table 13 Bleeding Patterns: Percentages of 90 Day Reference Periods with Amenorrhea, Infrequent Bleeding, Frequent Bleeding, or Prolonged Bleeding in Completers, Subjects Who Discontinued Prematurely Because of Bleeding Complaints and All Subjects**

| Bleeding pattern indices | Implanon™ | | | | | |
|---|---|---|---|---|---|---|
| | Completers | | Discontinuers due to bleeding irregularities | | Total (Completers + Discontinuers for *any* cause)[a] | |
| | N = 588 | | N = 55 | | N = 780 | |
| | Number of RP | % | Number of RP | % | Number of RP | % |
| Amenorrhea | 2774 | 23.1 | 142 | 0.7 | 3315 | 22.2 |
| Infrequent bleeding | 2774 | 33.2 | 142 | 37.3 | 3315 | 33.6 |
| Frequent bleeding | 2774 | 6.4 | 142 | 18.3 | 3315 | 6.7 |
| Prolonged bleeding | 2774 | 15.5 | 142 | 61.3 | 3315 | 17.7 |

Source: Appendix A, Table 21.
Studies 069001, 34502, 34505, 34507, 34510, 34511, 34512, 34515, 34522, and E-1729.
Reference periods 2-6. %=Percentage of pattern index occurrence. RP = 90-day reference period
N=number of subjects with bleeding-spotting parameters defined for at least one RP.
Completers: 2-year completers, i.e. subjects with treatment duration ≥720 days
[a] Note that "total" does not equal the sum of completers and discontinuers due to bleeding irregularities, because "total" also includes discontinuation due to other reasons.

Source: Table 21, p 65, Integrated Summary of Efficacy, January 2006 Update

**Team Leader Comment**

- ***Women who discontinued due to bleeding problems reported 2-4 times more 90-day reference periods with frequent and/or prolonged bleeding than completers or all subjects.***

The frequency distribution of bleeding or spotting days among completers, those who discontinued due to excessive bleeding and all subjects is shown in Table 14. It can be seen that fewer than 20% of women who discontinued due to frequent or prolonged bleeding experienced the equivalent number of bleeding days of normal menstrual cycles. Among completers and all subjects, about two-thirds had numbers of bleeding days equivalent to that expected with three normal menses after the first cycle. However, even in this group, 1-2% experienced >60 days of bleeding or spotting per Reference Period.

**Table 14 Distribution of Bleeding-Spotting Days in Completers, Subjects who Discontinued Prematurely Because of Bleeding Complaints and All Subjects**

| Reference period | Bleeding-Spotting Days | Completers | | Discontinuers due to excessive bleeding [a] | | Total (Completers + discontinuers for *any* reason) [b] | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| 1 | 0 | 8 | 1.4 | 0 | 0 | 12 | 1.5 |
| | 1-7 | 105 | 18.9 | 3 | 4.7 | 132 | 16.5 |
| | 8-21 | 161 | 29.0 | 6 | 9.4 | 225 | 28.1 |
| | 22-45 | 181 | 32.6 | 15 | 23.4 | 243 | 30.3 |
| | 46-60 | 56 | 10.1 | 19 | 29.7 | 99 | 12.3 |
| | >60 | 44 | 7.9 | 21 | 32.8 | 91 | 11.3 |
| 2 | 0 | 116 | 20.5 | 0 | 0 | 144 | 19.3 |
| | 1-7 | 85 | 15.0 | 1 | 2.7 | 112 | 15.0 |
| | 8-21 | 174 | 30.7 | 6 | 16.2 | 225 | 30.2 |
| | 22-45 | 136 | 24.0 | 11 | 29.7 | 169 | 22.7 |
| | 46-60 | 32 | 5.7 | 10 | 27.0 | 49 | 6.6 |
| | >60 | 23 | 4.1 | 9 | 24.3 | 46 | 6.2 |
| 3 | 0 | 152 | 27.2 | 0 | 0 | 177 | 25.7 |
| | 1-7 | 82 | 14.7 | 0 | 0 | 95 | 13.8 |
| | 8-21 | 170 | 30.4 | 4 | 13.8 | 202 | 29.3 |
| | 22-45 | 129 | 23.1 | 14 | 48.3 | 168 | 24.3 |
| | 46-60 | 16 | 2.9 | 3 | 10.3 | 23 | 3.3 |
| | >60 | 10 | 1.8 | 8 | 27.6 | 25 | 3.6 |
| 4 | 0 | 137 | 24.7 | 0 | 0 | 156 | 23.7 |
| | 1-7 | 74 | 13.4 | 0 | 0 | 84 | 12.8 |
| | 8-21 | 167 | 30.1 | 3 | 15.0 | 200 | 30.4 |
| | 22-45 | 147 | 26.5 | 10 | 50.0 | 170 | 25.9 |
| | 46-60 | 20 | 3.6 | 5 | 25.0 | 33 | 5.0 |
| | >60 | 9 | 1.6 | 2 | 10.0 | 14 | 2.1 |

**Table 9 (continued)**

| Reference period | Bleeding-Spotting days | Completers | | Discontinuers due to excessive bleeding [a] | | Total (Completers + discontinuers for any reason) [b] | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| 5 | 0 | 117 | 21.4 | 0 | 0 | 132 | 21.3 |
| | 1-7 | 76 | 13.9 | 0 | 0 | 82 | 13.2 |
| | 8-21 | 176 | 32.2 | 0 | 0 | 197 | 31.8 |
| | 22-45 | 155 | 28.3 | 7 | 58.3 | 178 | 28.7 |
| | 46-60 | 18 | 3.3 | 2 | 16.7 | 21 | 3.4 |
| | >60 | 5 | 0.9 | 3 | 25.0 | 10 | 1.6 |
| 6 | 0 | 120 | 21.9 | 0 | 0 | 127 | 21.1 |
| | 1-7 | 67 | 12.2 | 0 | 0 | 76 | 12.6 |
| | 8-21 | 175 | 31.9 | 0 | 0 | 191 | 31.7 |
| | 22-45 | 161 | 29.4 | 5 | 55.6 | 180 | 29.9 |
| | 46-60 | 15 | 2.7 | 2 | 22.2 | 17 | 2.8 |
| | >60 | 10 | 1.8 | 2 | 22.2 | 12 | 2.0 |
| 7 | 0 | 115 | 21.0 | 0 | 0 | 123 | 21.6 |
| | 1-7 | 60 | 11.0 | 0 | 0 | 61 | 10.7 |
| | 8-21 | 200 | 36.6 | 0 | 0 | 207 | 36.4 |
| | 22-45 | 144 | 26.3 | 0 | 0 | 147 | 25.8 |
| | 46-60 | 21 | 3.8 | 1 | 33.3 | 22 | 3.9 |
| | >60 | 7 | 1.3 | 2 | 66.7 | 9 | 1.6 |
| 8 | 0 | 91 | 16.6 | 0 | 0 | 91 | 16.6 |
| | 1-7 | 63 | 11.5 | 0 | 0 | 63 | 11.5 |
| | 8-21 | 203 | 37.1 | 0 | 0 | 203 | 37.1 |
| | 22-45 | 168 | 30.7 | 0 | 0 | 168 | 30.7 |
| | 46-60 | 21 | 3.8 | 0 | 0 | 21 | 3.8 |
| | >60 | 1 | 0.2 | 0 | 0 | 1 | 0.2 |

Source: Appendix A, Table 19.
Studies 069001, 34502, 34505, 34507, 34510, 34511, 34512, 34515, 34522, 34525, E-1729.
[a] Excessive bleeding is frequent and/or prolonged bleeding, not amenorrhea and infrequent bleeding.
[b] Note that "total" does not equal the sum of completers and discontinuers due to excessive bleeding, because "total" also includes discontinuation due to other reasons.

Source: Table 23, pp 67-8, Integrated Summary of Efficacy, January 2006 Update

**Team Leader Comment**

- ***While the majority of women who continued to use Implanon experienced bleeding similar to that expected of women having normal menstrual periods, 1-2% experienced >60 days of bleeding or spotting during a 90 day Reference Period.***

Venous thromboembolic events

No thromboembolic events were reported in the clinical trials, although one subject experienced a transient ischemic attack, which could be an embolic phenomenon.

Weight Gain

In the U.S. studies, 11 (3.3%) of subjects discontinued use of Implanon due to increase in weight. Among the non-U.S. studies, 12 (2.0%) of subjects did so. Over both U.S. and non-U.S. studies,

almost 20% of subjects experienced an increase of >10% in BMI. Table 15 displays change in weight from baseline; about 20% of subjects gained >5 kg (11 lbs) during Implanon use.

**Table 15 Weight Change by Category**

| Change in weight (Kg) | Number (%) of subjects with change from baseline to last measurement |
|---|---|
| <-5.0 | 40 (4.27%) |
| -5.0 to -2.5 | 81 (8.65%) |
| -2.4 to 0.0 | 173 (18.5%) |
| 0.1 to 2.5 | 233 (24.9%) |
| 2.6 to 5.0 | 224 (23.9%) |
| 5.1 to 7.5 | 86 (9.19%) |
| 7.6 to 10.0 | 43 (4.59%) |
| >10.0 | 56 (5.98%) |

Source: Table 17, p 69, Integrated Summary of Safety, January 2006 Update

Over all studies, the mean weight change by duration of use is shown in Table 16.

**Table 16 Weight Gain by Year**

| Statistic | End of Year 1 | End of Year 2 | End of Year 3 | End of Year 4 |
|---|---|---|---|---|
| Number of Subjects [n] | 723 | 584 | 243 | 51 |
| Mean of weight change | 2.6 | 4.1 | 6.5 | 5 |
| Standard error of mean wt. change[(b)] | 0.32 | 0.42 | 0.66 | 1.51 |
| Minimum of weight change | -42.5 | -38.5 | -16.5 | -17.6 |
| Maximum of weight change | 38.4 | 40.8 | 50.5 | 28.2 |

Weight change measured from baseline
Source: Primary medical review, dated July 14, 2006, based on data submitted by Applicant on March 14, 2006

Team Leader Comment

- ***The weight gain seen with Implanon use is characteristic of women who use hormonal contraceptives. The mean weight increase at one year (2.6 lbs) is less than that seen in women who use depot medroxyprogesterone acetate (5.7 lbs).***

### 4.1.4 Insertion and Removal Related Adverse Events

The most common insertion-related complaint was pain, which affected 3% of subjects. Less than 1% of subjects reported redness, swelling or hematoma at the site; none experienced expulsion of the implant. Procedural complications occurred in 1% of subjects with insertion and 1.7% with removal of the implant. Reported rates were slightly higher at U.S. as compared to non-U.S. sites (1.8% had insertion complications, 1.9% removal complications). Investigators' descriptions of insertion complications included:

- Implanon capsule did not disengage totally from applicator
- Insertion rod fell out onto floor
- Unable to verify placement by palpation
- Scant bleeding at placement site

- Implant stayed in the needle
- Small hematoma at implant site
- There was a little piece of plastic on the needle leading to difficult insertion and removal of the needle

Investigators' descriptions of removal complications included:

- Piece of rod broke off
- Difficult to palpate tips of implant
- Implant adherent to underlying tissue
- Device was deeply inserted
- Moderate difficulty with respect to adhesions to tissue
- Difficult to remove implant because of deep insertion
- Very flexible implant couldn't be removed at the insertion site
- Hard to find Implanon
- The implant was very deep
- Implant broke at removal
- Partially broken at extraction
- Significant fibrosis; terminal end of implant bent during removal
- Tip of implant broken at preparation of adhesions

Team Leader Comment

- ***With a previous six rod implantable contraceptive, Norplant, difficulties with removal were not uncommon. While the single rod used with Implanon will likely be less problematic, it is clear that insertion and removal related events remain a potential concern with all implantable products.***
- ***As noted in Section 3.4.2.1, although the number of reports of postmarketing pregnancies are low relative to the number of implants sold, from 30-43% of such pregnancies may have resulted from failed insertions (Implanon not present, or presence doubtful).***
- ***The Applicant has proposed a training program that will include modules on proper insertion and removal techniques, and a distribution program that will attempt to limit Implanon distribution to clinicians who have been trained by the Applicant's program. The utility of the training program will be specifically assessed in the proposed Active Monitoring program, which will collect data on 10,000 insertions and removals performed by trained clinicians. Conduct of the Active Monitoring program is requested as a phase 4 commitment.***
- ***In addition, surveillance of IRREs occurring in actual use will be attempted through both the Active Monitoring program and data collection from spontaneous reports. The Applicant has included discussion of the importance of reporting IRREs in the training program.***
- ***The label includes a detailed description of the steps to be taken in insertion and removal of Implanon, in an attempt to minimize IRREs attributable to operator errors. The need to palpate the implant following insertion is particularly emphasized in the label instructions as well as with a bolded warning statement.***
- ***The Applicant is strongly encouraged to continue development of a radiopaque version of Implanon. The ability to visualize a nonpalpable implant will assist greatly with removal, particularly in areas that may not have easy access to MRI facilities.***

## 4.2 SAFETY UPDATE

The Applicant submitted a Safety Update on May 23, 2006, which updated the Complete Response submission of January 16, 2006 to a safety closing date of March 1, 2006. Postmarketing data presented covered the period from August 28, 1998 to March 1, 2006.

### 4.2.1 Ongoing Clinical Trials

Interim reports from three ongoing trials (Protocols 34528, E-1279 and L-1784) were presented in the Safety Update. Protocol 34528 is a randomized, double-blind multicenter trial (N=108) evaluating the bioequivalence of Implanon and a radiopaque implant of identical composition except for addition of barium sulfate. Protocol E-1729 is an open label multicenter safety and efficacy trial (N=211). Data from one site were presented in the second Complete Response submission; data from 11 ongoing sites (N=142) were presented in the safety update. Protocol L-1784 is an open label study evaluating the effect of mefenamic acid vs. placebo on bleeding irregularities (N=114) in Implanon users; draft data listings were presented in the safety update.

#### 4.2.1.1 Deaths and Serious Adverse Events

No deaths occurred in any of the trials. A total of 16 SAEs occurred in 10 subjects:

- 2 in two subjects in Trial 34528 (one DVT, one intervertebral disc protrusion)
- 13 in seven subjects in Trial E-1729 (including two reports of depression, ovarian cyst torsion, and other events unlikely to be drug-related)
- 1 in one subject in Trial L-1784 (acute pelvic pain, diagnosed by hysteroscopic resection as adenomyosis)

The DVT occurred in a subject after 123 days of Implanon use. She had a history of Protein C deficiency and a family history of thrombosis.

#### 4.2.1.2 Other Adverse Events

Discontinuation due to adverse events occurred in 3% of Study 34528 subjects, In Study E-1729, 16% discontinued due to adverse events (other than vaginal bleeding) and 16% discontinued due to unacceptable vaginal bleeding. In Study L-1784, <2% of subjects discontinued due to adverse events, but 22% discontinued due to bleeding irregularities. No subjects are reported as having discontinued due to pregnancy in the ongoing trials.

The most common adverse events in Study 34528 were vaginal hemorrhage and metrorrhagia (10-13%), events included under the system-organ class "Infections and Infestations" and fatigue and hangover. In Study E-1729, the most common adverse events were "Infections and Infestations," breast tenderness and breast pain (9-11%) and headache. In Study L-1784, most adverse events occurred only in single subjects, with the system-organ class categories of "General Disorders and Administration Site Conditions," "Reproductive System and Breast Disorders," and "Infections and Infestations" and "Gastrointestinal Disorders" comprising the greatest numbers of adverse events.

Data on IRREs for the three ongoing studies were not yet reported.

### 4.2.2 Postmarketing Data

Postmarketing data note that implants have been sold worldwide since Implanon's initial launch in 1998. Over half of these sales have been in Europe. The total exposure to Implanon in that time period is estimated by the Applicant to be 5, 017,850 woman-years. A total of 17,677 adverse events have been reported spontaneously since that time. In addition, 8,723 IRRE reports that do not meet criteria for an SAE have been received. b(4)

#### 4.2.2.1 Deaths and Serious Adverse Events

Seven deaths have been reported as of the safety update. They include:

- Three cases of pulmonary emboli, at 19 months, 22 months and unspecified time following insertion
- A suicide, five months after Implanon insertion and two weeks following removal
- A fatal tetanus infection, with death 3-4 days following Implanon insertion
- A neonatal death from sepsis after a 27 week delivery of twins following a pregnancy complicated by twin-twin transfusion syndrome and hydramnios
- A fetal death in utero at 21 weeks of gestation, fetus with malformations and intrauterine growth restriction, following exposure to Implanon from conception to week 7

Based on estimated exposure to Implanon, the reporting rate of deaths is 0.14 per 100,000 woman-years.

Of 1,261 SAE reports received, 522 concerned unlisted events. Events of concern include arterial and venous thromboembolic events and malignancies. Fifty-eight thromboembolic events were reported, including 20 pulmonary emboli and 15 DVTs. The reporting rate for these two venous thromboembolic events is 0.7 per 100,000 woman-years. Three myocardial infarctions have been reported, for a reporting rate of 0.06 per 100,000 woman-years. Twenty-five serous reports of cerebrovascular events have also been received, for a reporting rate of 0.5 per 100,000 woman-years. Twenty-nine cases of breast cancer have been reported; 19 of these occurred within two years of insertion. In addition, two cases of uterine cancer and four of ovarian cancer have been reported.

**Team Leader Comment**

- ***The reporting rates for deaths, venous thromboembolic events, myocardial infarctions and serious cerebrovascular events have not changed significantly since the prior review cycles.***
- ***Although underreporting of postmarketing adverse events is to be expected, these rates, relative to other approved hormonal contraceptive products, do not raise concerns.***

### 4.2.2.2 Other Adverse Events

The system organ classes with the greatest numbers of adverse event reports are:

- Reproductive system and breast disorders (8,276)
- Skin and subcutaneous tissue disorders (1,705)
- Pregnancy, Puerperium and perinatal conditions (1,392)
- General disorders and administration site conditions (1,294)
- Investigations (1,096)
- Psychiatric disorders (997)

The most commonly reported events involved changes in vaginal bleeding patterns (7,464 events), pregnancies (1385 including 65 ectopic or heterotopic pregnancies), weight gain (915 events), local reactions at implant site (739 events), acne (718 events), headache (474 events), breast pain (305 events) and depression (280 events).

**Team Leader Comment**

- ***The adverse events commonly reported in the postmarketing period are similar to those reported in the clinical trial experience.***

### 4.2.2.3 Insertion and Removal Related Adverse Events

Of the IRREs reported, 6,924 were not associated with pregnancies. Those associated with pregnancy are discussed in Section 3.4.2.1. Of the former reports, 1,234 (18%) are described as insertion-related events, with the greatest number of these "deep insertions." Localization-related

events comprise 3502 reports (51%), the majority involving nonpalpable implants. Removal-related events account for 1393 reports (20%), which included 282 reports of cases where the ENG level was detectable, but the rod could not be found. The remaining reports involved implants that could not be localized, but the method of localization used was unspecified, and "other," which included expulsions.

### 4.3 OVERALL ASSESSMENT OF SAFETY FINDINGS

**Team Leader Comment**

- ***As noted in the previous review cycles, the safety profile of Implanon is acceptable for a highly effective contraceptive. The additional safety data provided in this Complete Response and the current Safety Update do not raise any new safety concerns.***
- ***Adverse events relating to insertion and removal problems are of particular concern. They will be addressed in labeling and through the Applicant's training and monitoring programs. In addition, the Applicant is encouraged to pursue development of a radiopaque implant to minimize the issue of implants that cannot be localized.***
- ***Bleeding irregularities, while not a safety issue per se, caused a high proportion of study withdrawals, and may affect women's willingness to continue use of Implanon. This adverse effect of Implanon is adequately described in both the Package Insert and the Patient Package Insert.***

## 5 LABELING ISSUES

I do not concur with the Primary Medical Officer's recommendation that a boxed warning be included to highlight the importance of subdermal placement of the implant, and the importance of checking for a palpable implant after insertion. While I agree with the importance of these points, I believe they are adequately addressed in the Warnings Section of the label, where they are listed in bold font, as the first item.

Labeling negotiations with the Applicant were concluded satisfactorily.

## 6 RECOMMENDATIONS OF OTHER DISCIPLINES AND DIVISIONS

### 6.1 TOXICOLOGY AND PRECLINICAL PHARMACOLOGY

The primary Toxicology Reviewer (Krishan Raheja, D.V.M., Ph.D.) made the following recommendations in his memorandum dated March 22, 2006:

> ***Recommendations on labeling:*** *Pharmacology/Toxicology section of the labeling adequately represents the preclinical findings with regard to carcinogenesis, mutagenesis and impairment of fertility as were reviewed under original NDA submission 9-30-03. No new pharmacology/toxicology study reports were submitted after the original NDA submission. Pharmacology considers the labeling adequate*

### 6.2 CMC AND PRODUCT MICROBIOLOGY

The primary Chemistry Reviewer (Amit Mitra, Ph.D.) made the following recommendations in his review of July 13, 2006:

> *From Chemistry, Manufacturing and Controls point of view, NDA 21-529 may be approved.*

Inspections of two facilities (drug substance manufacturer and drug substance quality control sites) were acceptable. The sterilization facility cited in the Approvable letter of October 29, 2004 was judged to be acceptable upon its inspection.

Labeling recommendations made by the Chemistry Reviewer were adopted by the Sponsor.

## 6.3 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The primary Clinical Pharmacology and Biopharmaceutics Reviewer (Myong-Jin Kim, Pharm.D.) stated the following in the addendum to her original review, dated June, 16, 2006:

> *The overall Human Pharmacokinetic Section of NDA 21-529 submitted on September 30, 2003 is acceptable to the Office of Clinical Pharmacology/Division of Clinical Pharmacology III. Labeling comments outlined in this addendum should be conveyed to the Sponsor as appropriate.*

Labeling recommendations made by the Clinical Pharmacology and Biopharmaceutics Reviewer were adopted by the Sponsor.

## 6.4 STATISTICS

The Statistical Reviewer (Sonia Castillo, Ph.D.) stated the following in the "Conclusions" of her review dated June 15, 2006:

> *From a statistical standpoint, the Sponsor has provided several adequate clinical studies that resulted in a cumulative 3-year Pearl Index of 0.38 (95% C.I. from 0.14 to 0.82) for Implanon contraceptive implant for use in the prevention of pregnancy.*

## 6.5 DIVISION OF SCIENTIFIC INVESTIGATION

The Division of Scientific Investigation (DSI) inspected three study sites for this NDA:

- Protocol E-1729 – Malaysia
- Protocols 34502 and 34505 – Thailand
- Protocols 34511 and 34515 – Singapore

Roy Blay, Ph.D. from DSI made the following overall assessment and general recommendations in his review dated July 13, 2006 of the three Establishment Inspection Reports:

> *The inspections of Drs. Tambi, Koetsewant/Kiriwat and Viegas/Biswas did not identify any significant regulatory violations. Overall the data appear acceptable in support of the respective indication.*

## 6.6 OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

### 6.6.1 Division of Medication Errors and Technical Support

Loretta Holmes, Pharm.D. of the Division of Medication Errors and Technical Support (DMETS) made several recommendations concerning carton and container labeling and the Package Insert and the Patient Package Insert in her review dated May 16, 2006. These recommendations were considered by DRUP and those judged to have a significant impact on appropriate use of the product were conveyed to the Applicant. The Applicant accepted all the recommendations.

DMETS noted in the current review that they had not objected to the name Implanon in its previous reviews (most recent prior review dated March 20, 2005). At this time, one product under review is noted to have a name (Indiplon) that could cause potential confusion with Implanon; however, DMETS concludes that this was unlikely to occur due to multiple differences between the products.

### 6.6.2 Division of Surveillance, Research and Communication Support

Jeanine Best, M.S.N., R.N., P.N.P. of the Division of Surveillance, Research and Communication Support (DSRCS) made numerous comments and recommendations in her review dated May 25, 2006. Among these were steps that would lower the reading grade and reading ease levels from grade 10.4 and 49.4% respectively in the Patient Package Insert submitted by the Applicant. These goals are consistent with the improvement in reading grade and ease achieved in the revisions made by the primary medical reviewer.

## 6.7 DIVISION OF DRUG MARKETING, ADVERTISING AND COMMUNICATIONS

The Division of Drug Marketing, Advertising and Communications (DDMAC) made a number of recommendations about the Package Insert. These recommendations were considered by DRUP and those judged to have a significant impact on appropriate use of the product were conveyed to the Applicant. These recommendations were adopted by the Applicant.

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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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Lisa Soule
7/17/2006 12:18:34 PM
MEDICAL OFFICER

Scott Monroe
7/17/2006 12:35:46 PM
MEDICAL OFFICER
I concur with Dr. Soule's recommendation that Implanon (etonogestrel implant) be approved for prevention of pregnancy in women and that a single implant may be used continuously for up to three years.

# DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
## DEPUTY DIVISION DIRECTOR MEMORANDUM

| | |
|---|---|
| **NDA** | NDA 21-529 |
| **Type of Application** | Complete Response to Approvable Action |
| **Applicant** | Organon USA, Inc.<br>West Orange, New Jersey |
| **Proprietary Drug Name** | Implanon™ |
| **Established Drug Name** | Etonogestrel implant |
| **Indication** | Prevention of pregnancy in women |
| **Route of administration** | Subdermal |
| **Dosage Form** | Subdermal implant (non-biodegradable) |
| **Dosage Strength** | 68 mg of etonogestrel per implant |
| **Dosing Regimen** | A single implant to be replaced or removed at or before 36 months after insertion |
| **CDER Receipt Date** | December 14, 2004 |
| **PDUFA Goal Date** | June 14, 2005 |
| **Date of Memorandum** | June 14, 2005 |
| **Reviewer** | Donna Griebel, MD<br>Deputy Division Director, DRUDP |

## 1. RECOMMENDATIONS

### 1.1 Recommendation Regarding Approvability

I concur with the recommendations of both the primary medical reviewer Dr. Barbara Wesley, MD and the medical team leader Dr. Scott Monroe, MD that this NDA for Implanon™ (etonogestrel implant) for the prevention of pregnancy in women should receive an Approvable Action. Approval for marketing is contingent upon the submission of additional clinical trial data from a clinical trial(s) that has been conducted in accordance with Good Clinical Practices. The new clinical trial data should include a sufficient number of subjects to establish a clinical trial database containing the equivalent of at least 10,000 28-day cycles obtained during the first year of treatment for assessment of the safety and efficacy of Implanon™. Monitoring and inspection reports of the clinical trial sites that provide these data must not raise concerns about the reliability of the data.

In addition the Applicant needs to submit an acceptable program for post-marketing monitoring of Implanon™-related insertion and removal adverse events in U.S patients.

## 1.2 Basis for Recommendation Regarding Approvability

In our prior approvable letter dated October 29, 2004 we stated that irregularities in study conduct identified by European regulatory authorities' inspections of the clinical trial sites for Study 34507 (including its Canadian component) had raised concerns about the quality of the data from this study, concerns that were outlined in an October 11, 2004 letter from the Dutch Medicines Evaluation Board to European Union countries 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). The Applicant was given two options to address this issue. The first was to provide a detailed justification of why Study 34507 and Study 34507 Canada were in fact adequate and well-controlled trials that provide data sufficient to support a conclusion that Implanon is safe and effective for prevention of pregnancy and can support accurate product labeling. The second option was to conduct another clinical trial to provide safety and efficacy data to support product labeling.

The Applicant submitted a complete response on December 13, 2004, and pursued the first option offered in the approvable letter. They provided information they believed establishes that the data from Study 34507 and Study 34507 Canada are sufficient to support approval of Implanon. The materials submitted included an "independent audit" of the German study sites conducted by a contract research organization at the Applicant's request. The FDA review team evaluated the materials submitted in support of the original study data and did not find that they established that event reporting was complete and accurate at those sites. The inspection report issues have been thoroughly summarized in Dr. Monroe's Medical Team Leader review. In addition, the Applicant submitted post marketing spontaneous adverse event report summaries and a summary of Periodic Safety Update Reports of pregnancies for calculation of an approximate Pearl Index based on market use of Implanon™ and estimates of under-reporting. They believed these post-marketing assessments of safety and efficacy provided further support for approval of Implanon™ and for proposed labeling. We have concluded, however, that these types of post-marketing analyses cannot substitute for clinical trial data to establish the safety and efficacy of Implanon™, and that they are not sufficient to support product labeling.

The reviewers' conclusion that the data submitted are insufficient to determine whether the product is safe for use and to define its effectiveness and safety in labeling is based on the following issues:

1) Two of the six studies (Indonesia) submitted in the original NDA submission had to be withdrawn from the NDA because of significant Good Clinical Practice (GCP) violations that rose to the level of fraud.

2) Inspections by representatives of the Dutch Medicines Evaluation Board (DMEB) and regional inspectors, representing the European Regulatory Authorities, of clinical trial sites for two additional studies in the NDA submission, Study 34507 and Study 34507 Canada, resulted in revisions of the approved Implanon labeling in Europe, including removal of the specific number of treatment cycles, removal of the Pearl Index value, and modification of the safety data to suggest an increase in frequency of several adverse event categories. The DMEB concluded that the conduct of the inspected sites had not been consistent with GCP and that the reliability of the data from those sites could not be assured.

3) There are inconsistencies across studies in adverse event reporting, which contributes to a concern that collection and reporting of adverse events in the trials could be incomplete or inaccurate. For example, the proportion of patients that discontinued prematurely is different between the US Study 69001 (49%) compared to Study 34507 (33%) and Thailand Study 34505 (32%). The proportion of discontinuations for adverse events that included "bleeding complaints" also was higher in the US study (36%) compared to Study 34507 (28%) and the Thai study (12%).

4) With elimination of the Indonesian studies and the data from all sites in Study 34507 that have not been inspected by the FDA, the remaining dataset (consisting of data from the US Study 69001, the centers of Drs. Urbancsek and Croxatto in Study 34507, and Thai Study 34505 – a study that has not been inspected by the FDA) consists of 648 women treated for the equivalent of 7,520 28-day cycles in the first year. This total exposure is substantially less than the 10,000 28-day cycles equivalents in the first year of use that the Division customarily reviews in hormonal contraceptive applications for a new molecular entity or a new delivery system. Although there are 5,931 additional 28-day cycle equivalents available from the second year (505 women) and 2,737 28-day cycle equivalents from the third year (369 women), the minimum dataset considered adequate to establish safety and efficacy is 10,000 cycles in the first year. Ten thousand (10,000) 28-day cycles in the first year of treatment assures a minimum number of new exposures to the drug. Incorporating cycles beyond one year enriches the dataset with subjects who have demonstrated tolerance to therapy and diminishes the potential to identify the important adverse events of interest associated with hormonal contraceptive products, thrombotic and thromboembolic events. It has been our experience that these events are more likely to manifest in the earlier months of exposure to hormonal contraceptive products, and that women who tolerate the product in the first year are less likely to have thromboembolic events in cycles of exposure that occur in the years that follow. In addition, the available post-marketing data on pregnancies from Implanon product failures, suggest that these also tend to occur in the first year of use.

I agree with Dr. Wesley and Dr. Monroe that these issues render the data submitted in this NDA insufficient to support an adequate assessment of the safety of this product for a risk/benefit analysis and to support a product label that adequately describes the safety and effectiveness of Implanon™.

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Donna Griebel
6/14/05 05:41:48 PM
MEDICAL OFFICER

# DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
# CLINICAL TEAM LEADER MEMORANDUM

| | |
|---|---|
| **NDA** | NDA 21-529 |
| **Type of Application** | Complete Response to Approvable Action |
| **Applicant** | Organon USA, Inc.<br>West Orange, New Jersey |
| **Proprietary Drug Name** | Implanon™ |
| **Established Drug Name** | Etonogestrel implant |
| **Indication** | Prevention of pregnancy in women |
| **Route of administration** | Subdermal |
| **Dosage Form** | Subdermal implant (non-biodegradable) |
| **Dosage Strength** | 68 mg of etonogestrel per implant |
| **Dosing Regimen** | A single implant to be replaced or removed at or before 36 months after insertion |
| **CDER Receipt Date** | December 14, 2004 |
| **PDUFA Goal Date** | June 14, 2005 |
| **Date of Memorandum** | June 14, 2005 |
| **Reviewer** | Scott E. Monroe, MD<br>Clinical Team Leader, DRUDP |

## 1. RECOMMENDATIONS

### 1.1 Recommendation Regarding Approvability

This reviewer recommends an Approvable Action for Implanon™ (etonogestrel implant) for the prevention of pregnancy in women. Approval for marketing is contingent upon the following:

1. The Applicant's providing additional clinical trial data from adequate and well-controlled studies so that the safety profile of Implanon can be assessed from clinical trial data equivalent to that of at least 10,000 28-day treatment cycles during the first year of use. The acceptability of the clinical data must be supported by monitoring and inspection reports of the clinical trial sites that do not raise concerns about the reliability of the data.
2. Development of an acceptable post approval program for monitoring Implanon-related insertion and removal adverse events in U.S. patients.
3. Agreement on final product labeling.

### 1.2 Basis for Recommendation Regarding Approvability

This recommendation is a result of the Applicant's failure to provide sufficient reliable data from adequate and well controlled clinical trials to allow the Division "to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed label" as required by the Code of Federal Regulations in § 314.125 (b) (4).

To assess the safety and effectiveness of hormonal contraceptive drug products, the Division has required data from adequate and well controlled clinical trials that have included the equivalent of at least 10,000 28-day cycles of treatment. For all hormonal contraceptive drug products involving a new molecular entity or a new route of administration that have been approved since 2000, as well as for Norplant and Jadelle subdermal implants approved prior to 2000, the safety of the drug product has been supported by data from at least 10,000 28-day treatment cycles obtained during Year 1 of treatment. Although the Applicant's original NDA submission of September 2003 and the revised original NDA submission of May 2004 appeared to provide adequate exposure data to Implanon, questions regarding the reliability of the data rose during the original review cycle. Inspections by the Applicant and/or European regulators identified serious violations of Good Clinical Practice (GCP) at several sites in Study 34507. Because of these violations, the reliability of much of the data from Study 34507 submitted in support of the safety and effectiveness of Implanon cannot be assured. Consequently, approval of Implanon for marketing cannot be recommended until the Applicant provides additional safety data obtained in accordance with the guidelines for GCP.

### 1.3 Recommendation on Risk Management Steps and/or post Approval Studies

#### 1.3.1 Risk Management Steps

Since the insertion and/or removal of Implanon has continued to be problematic in markets where the product is presently approved, an effective training program for healthcare providers is important to maximize the safe use of the drug product. The Applicant has proposed a training program for healthcare providers that, for the most part, is acceptable. The program will include training on implant insertion/removal technique using model arms, information on implant localization techniques, and patient counseling. Only those clinicians who complete the training program will be able to order Implanon. The training proposal, however, lacks a process by which to assess the effectiveness of the program.

#### 1.3.2 Post Approval Studies

The Applicant should implement a post approval monitoring program for Implanon-related insertion/removal adverse events to ensure that the training program is meeting its objectives and to identify areas associated with insertion/removal of the implant that remain problematic.

## 2. INTRODUCTION AND BACKGROUND

### 2.1 Description of Drug Product

Implanon (etonogestrel implant) is a progestin-only contraceptive subdermal implant. The non-biodegradable implant is a co-axial rod with a length of 4 cm and a diameter of 2 mm. The core contains 68 mg of etonogestrel (ENG) dispersed in a polymeric matrix of ethylene vinyl acetate copolymer that is surrounded by a 60 µm skin of ethylene vinyl acetate copolymer. Etonogestrel,

structurally derived from 19-nortestosterone, is the biologically active metabolite of desogestrel, the progestin component of several combination oral contraceptives (COCs) approved for marketing in the U.S. Implanon is supplied in a ready-for-use disposable applicator and is inserted subdermally in the inner side of the upper arm. After insertion, etonogestrel is released through the rate-controlling skin for up to 3 years.

### 2.2 Regulatory History and Approvability Issues

The original NDA submission of September 2003 included 6 studies classified by the Applicant as "adequate and well controlled." Following audits by the Applicant of several clinical trials sites prior to inspections by the FDA, the Applicant withdrew from the NDA all data from 2 of these 6 clinical trials (both trials had been conducted in Indonesia and enrolled a total of 649 subjects) because of significant Good Clinical Practice violations that rose to the level of fraud. The revised NDA (hereafter referred to as the "revised original submission") provided data from approximately 1,117 subjects in the 4 remaining studies classified as "adequate and well controlled" by the Applicant. Overall, the revised original submission included data from approximately 1,800 subjects obtained in 19 completed Phase II and III studies. These subjects were treated with Implanon™ for up to 2-5 years in 16 different countries located in Southeast Asia, Europe, North America, or South America.

The remaining 4 "adequate and well controlled clinical trials" consisted of Study 069001 (U.S.), Study 34505 (Thailand), Study 34507 (Europe and Chile), and Study 34507-CDN (Canada). These clinical trials were considered to be the principal studies supporting the safety and efficacy of Implanon for prevention of pregnancy by both the Applicant and the FDA medical reviewers. All 4 of the trials were non-comparative, open-label, historical controlled studies. A brief overview of the studies is provided in Table 1.

**Table 1 Principal Safety and Efficacy Studies in Revised Original Submission**

| Study Number | Region | Description of Study |
|---|---|---|
| 069001 | United States | 330 women, age 18-40, treated for up to 2 years |
| 34505 | Thailand | 100 women, age 18-39, treated for up to 2 to 4 years |
| 34507 | Europe & Chile | 635 women, age 18-40, treated for up to 2 to 3 years |
| 34507-CDN | Canada | 52 women, age 18-40, treated for up to 2 years |

Source: Original NDA submission, 30 September 2003.

Late in the original review cycle, the Division learned that the European Regulatory Authorities, represented by the Dutch Medicines Evaluation Board (DMEB) had decided to conduct their own inspections of several clinical trial sites that had participated in Study 34507 or Study 34507-CDN. (Study 34507 had provided much of the data that had supported the safety and efficacy of Implanon that resulted in the approval of the drug product for marketing in Europe). Based on the findings from these inspections, the DMEB concluded that (1) many aspects of clinical trial study procedures at the inspected sites had not been conducted in a manner consistent with GCP and (2) the reliability of the data from these sites could not be assured. Because of the violations of GCP and concerns about the completeness and integrity of the data from Studies 34507 and 34507-CDN, the DMEB recommended that Organon make several changes to the approved Implanon label. These changes included (1) eliminating a specific value for the Pearl Index and replacing it with a general statement about effectiveness, (2) deleting the actual number of cycles upon which the safety and effectiveness of the drug

product was based, and (3) increasing the reported frequency for several common adverse events in users of Implanon. The DMEB, however, concluded that there were "no reasons to doubt the efficacy and safety of the product provided it is inserted in the appropriate manner." This conclusion was "partly based on the large postmarketing experience and extensive monitoring and reporting" with the product.

Because of the concerns raised by the DMEB inspections regarding the quality and reliability of the data from Studies 34507 and 34507-CDN, Implanon received an Approvable Action by the Division during the original review cycle. The Applicant was given 2 options to address this review issue. The first option was to provide a detailed justification of why Study 34507 and Study 34507-CDN were adequate and well-controlled trials that provided data sufficient to support (a) a conclusion that Implanon is safe and effective for prevention of pregnancy and (b) accurate product labeling. The alternative option was that the Applicant could conduct another clinical trial to provide safety and efficacy data to support product labeling. The Applicant chose to follow the first option in their Complete Response (the present submission). Based on the information provided in the Complete Response, it cannot be concluded that (a) Studies 34507 and 34507-CDN were conducted in accordance with the standards of GCP and (b) that the data from these studies are reliable (with one exception). The exception is the data from the sites of Drs. Urbancsek [Budapest] and Croxatto [Santiago]). Both of these sites were inspected by the FDA, and the FDA inspectors assessed the data acceptable.

### 2.2.1 Basis for Conclusion that Data from Studies 34507 and 34507-CDN are not Reliable

The primary medical reviewer has provided the most important findings from the integrated inspection report of the Inspectorate of Health Care (IGZ) in the Netherlands (Integrated Inspection Report IGZ 2004-015) in her review (see Section 4.5 [Compliance with Good Clinical Practices] of her review). She states in her review that "Insufficient justification has been provided by Organon to allow this reviewer to discount the findings of the IGZ inspectors and to conclude that the data obtained at the sites that were not inspected are reliable."

The following are statements taken from the Summary and Conclusions section of the Integrated Inspection Report (IGZ 2004-015).

- "The issues surrounding ethical approval, regulatory approval and the informed process, which relate to patient protection and legal requirements, do not necessarily have an immediate effect on the quality of data. However, the many observations with respect study conduct, collection of adverse events, drug accountability and monitoring do have implications for the integrity and quality of the trial data and their representation in the final study report."
- "For most of the sites the observations were made that study visits were outside the windows set by the protocol, missed and/or conducted by telephone. The same was observed for the follow-up visits 3 months after removal of the implant as foreseen by the protocol. Accurate and complete capture of (S)AE for long periods in the trial is therefore questionable."
- "The lack of available source data and documents for many aspects, including the bleeding records kept by the subjects makes full data verification difficult if not impossible for many subjects."
- "In conclusion, the many systematic failures observed in the organisation, conduct, monitoring, management and reporting of the clinical trials that form the basis of the application dossier for Implanon demonstrate that Organon did not have control of the conduct of the trials at the various

sites. The majority of sites show serious deviations from GCP. The GCP claim for the clinical trials has to be withdrawn."

- "With respect to the reliability of data at the 4 sites that have been inspected, the respective inspection teams have doubts as to the integrity of the reported data. This is especially the case with respect to the safety reporting, available source data and the use of additional contraceptive methods."

**Medical Officer's Comment**

- *In their Complete Response, the Applicant provided information that they believed established that Study 34507 and Study 34507 CDN provided data of sufficient reliability to support approval of Implanon. This reviewer, however, does not believe that the submitted materials, including an "independent audit" of the German study sites conducted at the Applicant's request by a contract research organization, established that (1) event reporting was complete and accurate at most sites that participated in Study 34507 and 34507-CDN and (2) the overall data from these studies are sufficiently reliable to support the safety and effectiveness of Implanon for marketing approval.*
- *Although the Applicant formally disagreed with many of the most serious deficiencies identified in the report of the IGZ in the Netherlands (Integrated Inspection Report IGZ 2004-015), the DMEB never acknowledged that the inspection reports were in error or were unduly critical.*

### 2.3 Extent of Subject Exposure to Implanon

An overview of the clinical data submitted by the Applicant that was considered by the Applicant or the FDA medical reviewers during various stages of the review process as likely to have been obtained from "adequate and well controlled" clinical trials is presented in Table 2.

In the original submission, the Applicant considered 6 clinical trials, which enrolled more than 1,700 subjects and included the equivalent of approximately 21,000 28-day treatment cycles in Year 1, as "adequate and well controlled." These were Studies 069001 (U.S.), 34505 (Thailand), 34506 (Indonesia), 34507 (Europe/Chile), 34507-CDN (Canada), and 34520 (Indonesia). Following an internal audit of the 2 Indonesian sites, the Applicant withdrew from the NDA all data from Studies 34506 and 34520 because of evidence of significant violations of GCP and data falsification. The resulting database was therefore reduced by about 35% and included 1,114 subjects who provided data from the equivalent of 12,887 28-day treatment cycles in Year 1.

Following the issuance of the report of the Inspectorate of Health Care in the Netherlands (Integrated Inspection Report IGZ 2004-015), the FDA reviewers concluded that the data from Studies 34507 and 34507-CDN (with the exception of that obtained from the sites of Drs. Urbancsek and Croxatto) could not be considered as sufficiently reliable to be used in support of the safety and effectiveness of Implanon. The resulting database (considered likely to be reliable by the FDA reviewers) was therefore reduced to less than 50% of the Applicant's original submission. It included 648 subjects who provided data from the equivalent of 7,520 28-day treatment cycles in Year 1.

**Table 2 Numbers of Subjects and 28-day Cycle Equivalents by Study Year in Clinical Trials considered to "Adequate and Well Controlled" by Applicant or FDA Clinical Reviewers**

| "Adequate and Well Controlled" Trials | Year 1 | | Year 2 | | Year 3 | |
|---|---|---|---|---|---|---|
| | No. Pts | No. Cycles [E] | No. Pts | No. Cycles | No. Pts | No. Cycles |
| Original Submission [A] (Data from 6 principal studies) | 1,763 | 21,281 | 1,495 | 18,114 | 1,094 | 9,619 |
| Revised Original Submission [B] (Data from 4 of 6 original principal studies) | 1,114 | 12,887 | 862 | 10,158 | 597 | 2,989 |
| Data Assessed as likely to be reliable [C] (Data from 2 principal studies plus 2 additional sites from another study) | 648 | 7,520 | 505 | 5,931 | 369 | 2,737 |
| Data from FDA Inspected Studies or Sites [D] (Data from one principal study plus 2 additional sites from another study) | 548 | 6,279 | 415 | 4,813 | 292 | 1,911 |

Source: Prepared by primary medical reviewer from various sources.

A: Studies 069001 (U.S.), 34505 (Thailand), 34506 (Indonesia), 34507 (Europe/Chile), 34507-CDN (Canada), and 34520 (Indonesia).

B: Studies 069001 (U.S.), 34505 (Thailand), 34507 (Europe/Chile), and 34507-CDN (Canada).

C: Studies 069001 (U.S.), 34505 (Thailand), and 34507 (only sites of Drs. Urbancsek [Budapest] and Croxatto [Santiago]).

D: Studies 069001 (U.S.) and 34507 (only sites of Drs. Urbancsek and Croxatto).

E. Values are approximate and based on the equivalent of a 28-day treatment cycle.

## 3. EFFICACY OF IMPLANON

### 3.1 Organon's Assessment of Efficacy (Treatment Years 1 and 2)

The annual Pearl Index values and the annual exposure to Implanon (based on 28-day cycle equivalents) for subjects < 36 years of age in the 4 clinical trials considered to be "adequate and well controlled) by the Applicant are listed in Table 3. Based on the Applicant's interpretation of the clinical trial data, there were no on-treatment pregnancies, resulting in a Pearl Index value of 0 for each of Years 1 and 2.

**Table 3 Annual Pearl Index Values for Subjects < 36 Years of Age (Studies 069001, 34505, 34507, and 34507-CDN)**

| Parameter | Year 1 | Year 2 |
|---|---|---|
| No. Pregnancies | 0 | 0 |
| Pearl Index | 0.00 | 0.00 |
| 95% Confidence Interval (CI) | (0, 0.42) | (0, 0.53) |
| 28-day Cycle Equivalents | 11,552 | 9,011 |

Source: Applicant's submission of 12 October 2004, Table 13b

Excluding all data from Trial 34507 (other than that for the sites of Drs. Urbancsek [Budapest] and Croxatto [Santiago], had no impact on the point estimate of the Pearl Index (i.e., 0 for both

Years 1 and 2) but increased slightly the upper bound of the 95% confidence interval (CI) as shown in Table 4.

**Table 4 Annual Pearl Index Values for Subjects < 36 Years of Age (Studies 069001, 34505, and 34507 [only sites of Drs. Urbancsek and Croxatto])**

| Parameter | Year 1 | Year 2 |
|---|---|---|
| No. Pregnancies | 0 | 0 |
| Pearl Index | 0.00 | 0.00 |
| 95% CI | (0, 0.69) | (0, 0.88) |
| 28-day Cycle Equivalents | 6,988 | 5,489 |

Source: Applicant's e-mail submission of 7 June 2005, Table A-2.

**Medical Officer's Comment**

- *The Applicant did not collect information on the use of back up contraception, particularly condoms. Had this information been collected, cycles in which backup contraception was used would have been excluded from consideration and would have resulted in a small increase in the upper bound of the 95% CI.*

### 3.2 Primary Medical Reviewer's Assessment of Effectiveness

Among the studies/study sites from which reliable data was likely obtained, the primary medical reviewer (Dr. Wesley) identified 2 pregnancies (both in Study 069001) for which she estimated conception to have occurred within 7-10 days of removal of Implanon and a single pregnancy that may have occurred within 2 weeks of implant removal at the site of Dr. Urbancsek in Study 34507. These pregnancies were classified by the primary medical reviewer as on-treatment pregnancies (i.e., a method failure). All 3 of these pregnancies also occurred within 365 days of implant insertion (i.e., during Treatment Year 1). If these pregnancies are considered to be "method failures," the point estimate for the Pearl Index for Year 1 would be 0.56 (95% CI: 0.12, 1.64) as shown in Table 5.

**Table 5 Annual Pearl Index Values for Subjects < 36 Years of Age (Studies 069001, 34505, and 34507 [only sites of Drs. Urbancsek and Croxatto])**

| Parameter | Year 1 | Year 2 |
|---|---|---|
| No. Pregnancies | 3 | 0 |
| Pearl Index | 0.56 | 0 |
| 95% CI | (0.12, 1.64) | (0, 0.88) |
| 28-day Cycle Equivalents | 6,988 | 5,489 |

Source: Applicant's e-mail submission of 7 June 2005, Table A-6.

If data from Study 34505 (conducted at a single site in Thailand) also are disqualified (since the site has not been inspected by the FDA), the Pearl Index for Year 1 (based only on data from Study 069001 and the sites of Drs. Urbancsek and Croxatto from Study 34507) is 0.67 (95% CI: 0.14, 1.97) as shown in Table 6.

**Table 6 Annual Pearl Index Values for Subjects < 36 Years of Age (Studies 069001 and 34507 [only sites of Drs. Urbancsek and Croxatto])**

| Parameter | Year 1 | Year 2 |
|---|---|---|
| No. Pregnancies | 3 | 0 |
| Pearl Index | 0.67 | 0 |
| 95% CI | (0.14, 1.97) | (0, 1.08) |
| 28-day Cycle Equivalents | 5,812 | 4,437 |

Source: Applicant's e-mail submission of 7 June 2005, Table A-8.

**Medical Officer's Comments**

- *As a general policy, the Division requires that 200 women use a new contraceptive drug product for at least one year and that the drug product be investigated in the equivalent of at least 10,000 28-day treatment cycles during study Year 1. Based on clinical data considered to be reliable by FDA medical reviewers, the Applicant has provided data from 200 subjects who have used the drug product for at least one year, but has not provided data from at least 10,000 28-day treatment cycles during study Year 1.*
- *This reviewer believes that the effectiveness of a hormonal contraceptive product can be demonstrated based on the equivalent of fewer than 10,000 28-day treatment cycles if (1) the data are highly reliable and (2) both the point estimate for the Pearl Index and the upper bound of a 2-sided 95% CI are comparable or better than those associated with presently approved hormonal contraceptive products. The analysis represented in Table 6 is based on conservative criteria (i.e., (1) only data from Study 069001 and from the study sites of Drs. Urbancsek and Croxatto from Study 34507 have been used in defining the "at risk population" and (2) the 3 pregnancies that likely occurred following removal of the implant have been classified as "method failures"). In this conservative analysis, both the point estimate of the Pearl Index (0.67 pregnancies per 100 women years of use) and the upper bound of the 95% CI (1.97) for the first year of use are acceptable for a hormonal contraceptive product. The point estimate of the Pearl Index and the upper bound of the 95% CI for the second year of use also are acceptable.*
- *The Applicant should collect information about the effectiveness of Implanon in the subjects who will be studied to obtain additional safety data to support approval of the drug product for marketing. These additional efficacy data will allow for improved product labeling and will permit a more precise estimate of the true Pearl Index.*

### 3.3 Effectiveness of Implanon during Year 3 of Use

Data supporting the effectiveness of Implanon during Year 3 of use were obtained from the sites of Drs. Urbancsek and Croxatto (Study 34507) and Study 34505. Two hundred and fifteen (215) subjects formally entered into Year 3 of treatment, and according to the FDA statistician, 195 subjects completed 3 years of use. There were no reported pregnancies in these 195 subjects or in those subjects who did not complete Year 3 (Table 7). Overall, in the subjects who completed 3 years of use with Implanon, there were 2,535 cycles of exposure of which 2,132 were in women < 36 years of age. The Pearl Index for all completers during Year 3

was 0 (95% CI: 0, 1.87). The Pearl Index for subjects < 36 years of age at entry who completed Year 3 was 0 (95% CI: 0, 2.23).

**Table 7 Exposure and Pearl Index Values Based on Treatment Year 3 (Study Days 731-1095) (only Subjects Who Completed Year 3)**

| Age Group | # of women | Total cycle of exposures | # of Pregnancies | Pearl index | Upper bound of the 95% CI * |
|---|---|---|---|---|---|
| All subjects | 195 | 2,535 | 0 | 0 | 1.87 |
| < 36 year old | 164 | 2,132 | 0 | 0 | 2.23 |

From Non-US Studies 34505 and 34507 combined
* Confidence intervals are 2-sided
Source: FDA Statistical Report, addendum to statistical review.

**Medical Officer's Comments**

- *The number of subjects/cycles (195/2535) studied in Treatment Year 3 was less than that submitted to support 3 years of effectiveness for previously approved implantable contraceptive products (e.g., Norplant and Jadelle). However, when the < 36 year old group (the most fertile group) was analyzed considering only women who completed Year 3 of use with Implanon, the Pearl Index was calculated to be 0 with an upper limit for the 95% CI of 2.23. Based on the upper bound, this analysis could be sufficient to support approval for a third year of use for a single Implanon implant, assuming that the data were highly reliable.*
- *If the data from Study 34505(Thailand) can not be fully validated, the number of 28-day treatment cycles Year 3 for subjects< 36 years of age at entry would be 1,670. Based on no reported pregnancies, the Pearl index and 95% CI would be 0 (0, 2.88).*
- *Even if the data represented in Table 7 are assessed as being highly reliable following inspection of the single clinical trial site in Study 34505 (Thailand), it is still recommended that the Applicant conduct an additional clinical trial, or supply confirmatory clinical data obtained in accordance with GCP, as a Phase IV commitment, to provide additional support for the effectiveness of the 3-year treatment regimen. This recommendation is made because 2 or 3 pregnancies, if not detected or not reported, in an at risk population consisting of only 2,132 28-day treatment cycles, would have a significant impact on the Pearl index. In addition, such information about the effectiveness of Implanon in Year 3 is particularly important for obese women since PK data indicated that plasma levels of etonogestrel are lower in women with higher body mass index (BMI) values.*

## 3.4 Postmarketing Reports of Pregnancy

### 3.4.1 Overall Number of Reported Pregnancies

Spontaneous reports describing the occurrence of 836 medically confirmed pregnancies in women using Implanon have been reported to Organon during the period from market introduction of the implant in August 1998 up to September 2004. An additional 50 medically unconfirmed reports of pregnancies (e.g., pregnancies reported by consumers or others) have been received by Organon. Using the number of 886 total pregnancies, the Applicant calculated an overall pearl index of 0.02725 (95% CI: 0.0255, 0.0291) based on sales of implants and an estimate of 3,259,896 woman-years of exposure (see Table 8). b(4)

**Table 8 Pearl Index for Implanon Based on Reported Postmarketing Pregnancies**

| Parameter | September 1998 to September 2004 |
|---|---|
| Total Pregnancies | 886 |
| Pearl Index | 0.02725 |
| 95% CI | (0.0255, 0.0291) |
| Woman Years of Use | 3,259,896 |

Source: Submission of December 13, 2004 (Vol. 1, pg 30, Table 1).

### Medical Officer's Comment

- *There is likely to be significant underreporting of unplanned postmarketing pregnancies. However, even if the true number of unplanned pregnancies were 50-fold greater (i.e., 44,300) the Pearl Index based on this number of reported pregnancies and estimated exposure data would be acceptable for a hormonal contraceptive product.*

### 3.4.2 Pregnancies Based on Time of Conception post Insertion of Implanon

During the original review of NDA 21-529, the Applicant was asked to submit a summary of reported postmarketing pregnancies based on the estimated dates of conception relative to months after insertion of the implant. Information on 486 medically confirmed pregnancies was provided (see Table 9).

**Table 9 Number of Reported Postmarketing Pregnancies Based on Interval from Insertion of Implanon to Conception**

| Time of Conception (Months post Implanon Insertion) | Number (%) of Reported Pregnancies N=485 | |
|---|---|---|
| 0-12 | 121 | 25% |
| 12-24 | 50 | 10% |
| 24-36 | 19 | 4% |
| >36 | 0 | 0% |
| Unable to determine | 295 | 61% |

Source: Response to Information Request, submission of 30 June 2004.

### Medical Officer's Comment

- *The Applicant was unable to provide information about the time of conception for 60% of the reported pregnancies. However, for those pregnancies for which data were available, the greatest number occurred in the first year of use, which may be related to problems that occurred with insertion. There was no observed increase in the rate of pregnancies in Years 2 or 3. These data support the limited clinical trial data indicating that Implanon continues to be effective throughout a third year of use.*

### 3.5 Overall Conclusion Regarding the Efficacy of Implanon

**Medical Officer's Comments**

- *A single Implanon implant appears to be effective for prevention of pregnancy for up to 2 years, assuming that it is implanted properly. This conclusion is based on a conservative analysis of the data submitted in NDA 21-529 that (1) utilized only clinical trial data from U.S. study 69001 (of which 3 sites were inspected by the FDA) and the clinical sites of Drs. Urbancsek and Croxatto (both inspected by the FDA) and (2) considered the 3 pregnancies that likely occurred 7-10 days after removal of the implant as method failures. Although this conservative analysis included the equivalent of only 5,812 and 4,437 28-day treatment cycles in Years 1 and 2, respectively, the point estimates of the Pearl Index and the upper bound values for the 95% CI for the Index were acceptable for a hormonal contraceptive product. These values were 0.67 (95% CI: 0.14, 1.97) and 0 (95% CI: 0, 1.08) for Treatment Years 1 and 2, respectively.*
- *Although the data presented in the NDA also support the effectiveness of a single Implanon implant through 3 years of use, approval for Year 3 is not recommended at this time because of the limited number of subjects for whom reliable data are available (i.e., sites inspected by the FDA).*

## 4. SAFETY PROFILE OF IMPLANON

The safety profile of Implanon, based on clinical trial and postmarketing safety data provided by the Applicant in the revised original NDA submission, was thoroughly reviewed and discussed in the Primary Medical Review of Dr. Wesley (dated October 28, 2004) and discussed in the Clinical Team Leader Memorandum of Dr. Monroe (dated October 29, 2004). Both of these earlier reviews were based on the assumption that the data provided in the Applicant's revised original submission were reliable. The Applicant, however, has not been able to provide in the Complete Response convincing data (as requested in the Division's Approvable Letter of October 29, 2004) that the data obtained in Trial 34507 (with the exception of that obtained at 2 sites) and Trial 34507-CDN are reliable. Consequently, this reviewer cannot conclude that there is sufficient information about Implanon in NDA 21-529 "to determine whether the product is safe for use under the conditions prescribed, recommended for use, or suggested in its proposed labeling" as required by §314.125 (b) (4) of the Code of Federal Regulations. The basis for this reviewer's opinion regarding the reliability of the clinical trial data has been provided earlier (see Section 2.2.1) and is discussed further in Section 4.1.

In the present submission (Complete Response), the Applicant also has provided (1) limited new safety data from one completed clinical trial (identified by the Applicant as not having been conducted in accordance with GCP) and two ongoing clinical trials and (2) updated postmarketing safety data. These data are briefly reviewed in Section 4.2 of this Memorandum.

### 4.1 Safety Data from "Adequate and Well Controlled" Clinical Trials

#### 4.1.1 Applicant's Assessment of Reliable Safety Data (Extent of Subject Exposure)

In the revised original submission of NDA 21-529 (submitted on May 3, 2004 and the Complete Response (present submission), the Applicant identified 4 studies that were considered to be "adequate and well controlled" and to have been conducted in accordance with GCP (Table 10).

These studies provided clinical trial data from 1,114 Implanon-treated subjects, resulting in safety data from 12,887 28-day cycle equivalents and 10,158 28-day cycle equivalents in Treatment Year 1 and Year 2, respectively.

**Table 10 Numbers of Subjects and 28-day Cycle Equivalents per Year from "Adequate and Well Controlled" Clinical Trials as Assessed by Applicant or FDA**

| | Year 1 | | Year 2 | | Year 3 | |
|---|---|---|---|---|---|---|
| **Trials/Sites Providing Reliable Safety Data** | **No. Pts** | **No. Cycles** | **No. Pts** | **No. Cycles** | **No. Pts** | **No. Cycles** |
| *Applicant's assessment of trials that were "adequate and well controlled" (i.e., provided reliable data)* | | | | | | |
| Revised Original Submission (See "A" below) | 1,114 | 12,887 | 862 | 10,158 | 597 | 2,989 |
| *FDA's assessment of data likely to be reliable* | | | | | | |
| See "B" below for studies/sites | 648 | 7,520 | 505 | 5,931 | 369 | 2,737 |
| *FDA's assessment of data likely to be reliable based on FDA site inspections* | | | | | | |
| See "C" below for studies/sites | 548 | 6,279 | 415 | 4,813 | 292 | 1,911 |

Adapted from table prepared by primary medical reviewer.

A: Studies 069001 (U.S.), 34505 (Thailand), 34507 (Europe/Chile), and 34507CDN (Canada).

B: Studies 069001 (U.S.), 34505 (Thailand), and 34507 (only sites of Drs. Urbancsek [Budapest] and Croxatto [Santiago]).

C: Studies 069001 (U.S.) and 34507 (only sites of Drs. Urbancsek and Croxatto).

D. Values are based on the equivalent of a 28-day treatment cycle.

### 4.1.2 FDA's Assessment of Reliable Safety Data (Extent of Subject Exposure)

#### 4.1.2.1 Basis for Assessment

**Medical Officer's Comments**

- *Because of the concerns raised by the reports of the Dutch and local regulatory inspectors based on their inspection of several study sites for Trial 34507 and the single site for Trial 34507-CDN, this reviewer does not consider the data obtained from these trials (with one exception) as sufficiently reliable to be used in assessing the overall safety profile of Implanon. The exception is the data from the clinical sites of Drs. Urbancsek (Budapest) and Croxatto (Santiago) because both sites were found to have provided acceptable clinical data by FDA inspectors. Data from the single site for Trial 34505 (Thailand) may be acceptable (subject to an FDA inspection and/or FDA review of Organon's audit of the site). Additional information concerning the specific deficiencies identified by the Dutch and local regulatory inspectors is presented in Section 2.2.1 of this Memorandum.*

This reviewer's concern as to the overall reliability of the safety data from Studies 34507 and 34507-CDN is further supported by the findings represented in Table 11. The percentage of subjects discontinuing prematurely was higher in Study 069001 (49%, conducted in the U.S.) than in any of the other 3 trials (32% to 37%). The differences were even greater when the reason for discontinuation was listed as an adverse event other than a bleeding complaint

(23% of subjects discontinuing for a non-bleeding adverse event in Study 069001 compared to 5%, 9.3%, and 9.6% discontinuing in Studies 34505, 34507 and 34507-CDN, respectively).

**Table 11 Primary Reasons for Subject Discontinuation in Principal Safety Studies**

| Study | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | **069001 (United States)** | **34505 (Thailand)** | **34507 (Europe/Chile)** | **34507 CDN (Canada)** |
| Number subjects randomized | 330 | 100 | 636 | 52 |
| Completed Study | 169 (51%) | 68 (78%) | 427 (67%) | 33 (63%) |
| **Discontinued Prematurely** | **161 (49%)** | **32 (32%)** | **209 (33%)** | **19 (37%)** |
| Adverse Event | 119 (36.1%) | 12 (12%) | 180 (28.3%) | 12 (23.1%) |
| Amenorrhea | -* | 1 (1%) | 11 (1.7%) | - |
| Bleeding complaints | 43 (13%) | 6 (6%) | 110 (17.3%) | 7 (13.5%) |
| **Other adverse events** | **76 (23%)** | **5 (5%)** | **59 (9.3%)** | **5 (9.6%)** |
| Lost to follow-up | - | 8 ( 8%) | 4 ( 0.6%) | 1 (1.9%) |
| Protocol violation | 4 (1.2%) | - | - | - |
| Unwilling to continue | 8 (2.4%) | - | - | - |
| Intercurrent illness | 1 (0.3%) | - | - | - |
| Other reasons | 29 ( 9%) | 12 (12%) | 25 (3.9%) | 6 (11.5%) |

*: No data available
Source: Protocol 069001 (Table 4), Protocol 34505 Table 5), Protocol 34507 (Table 6), & Protocol 34507 CDN (Table 6).

Further information about the specific adverse events that were associated with premature terminations is provided in Table 12. The greatest disparity was observed in the category of "psychiatric disorders" for which 9.4% of subjects in Study 069001 discontinued prematurely compared to 1.4% in Studies 34505 and 34507 combined. Although the magnitude of the differences were each small, the percentages for premature discontinuations in Study 069001 were numerically higher for all "system organ classes" other than "reproductive disorders."

**Table 12 Number (%) of Subjects who Discontinued due to an Adverse Event (Study 069001 [U.S.] and Studies 34505 [Thailand] and 34507 [Europe/Chile] Combined; System Organ Classes with ≥ 2 Events)**

| WHO system-organ class | Preferred term | U.S. (N=330) | | Europe/ Thailand (N=787) | |
|---|---|---|---|---|---|
| | | n | (%) | n | (%) |
| Reproductive disorders, | | >43 | >13 | >123 | >15.6 |
| | Bleeding complaints | 43 | 13 | 123 | 15.6 |
| | Amenorrhea | 0 | | 12 | 1.5 |
| | Sexual function abnl. | 4 | 1.2 | 0 | |
| | Dysmenorrhea | 2 | 0.6 | 0 | |
| | Premenstrual tension | 2 | 0.6 | 0 | |
| | Breast pain female | 0 | | 3 | 0.4 |
| Psychiatric disorders | | 31 | 9.4 | 11 | 1.4 |
| | Emotional lability | 20 | 6.1 | 3 | 0.4 |
| | Depression | 8 | 2.4 | 2 | 0.3 |
| | Nervousness | 3 | 0.9 | 2 | 0.3 |
| | Anxiety | 2 | 0.6 | 1 | 0.1 |
| | Libido decreased | 0 | | 4 | 0.5 |
| Metabolic disorders | | 11 | 3.3 | 22 | 2.8 |
| | Weight increase | 11 | 3.3 | 18 | 2.3 |
| | Weight decrease | 0 | | 3 | 0.4 |
| Skin disorders | | 7 | 2.1 | 14 | 1.8 |
| | Acne | 5 | 1.5 | 8 | 1.0 |
| | Alopecia | 2 | 0.6 | 4 | 0.5 |
| Nervous system disorders | | 6 | 1.8 | 11 | 1.4 |
| | Headache | 4 | 1.2 | 8 | 1.0 |
| | Paraesthesia | 1 | 0.3 | 1 | 0.1 |
| | Dizziness | 0 | | 2 | 0.3 |
| Body as a whole disorders | | 5 | 1.5 | 2 | 0.3 |
| | Fatigue | 2 | 0.6 | 0 | |
| Application site disorders | | 3 | 0.9 | 1 | 0.1 |
| | Injection site pain | 3 | 0.9 | 1 | 0.1 |
| Neoplasms | | 2 | 0.6 | 1 | 0.1 |
| | Breast neoplasm (malig.) | 1 | 0.3 | 0 | |
| Gastrointestinal disorders | | 1 | 0.3 | 1 | 0.1 |
| Vascular disorders | | 0 | | 2 | 0.3 |
| | Cerebral hemorrhage | 0 | | 1 | 0.1 |
| | Cerebrovas. disorder | 0 | | 1 | 0.1 |

Source: Table 32 from revised ISS submitted on 4 May 2004.

## Medical Officer's Comment

- *Although the differences in percentages of subjects discontinuing prematurely across studies may accurately reflect the findings from these studies, the European and local inspectors noted in their reports that there appeared to be a lack of documentation and possibly an underreporting of adverse events at the inspected sites. This could be an alternative explanation for these differences.*

- *Adverse events, in general, also were reported for a greater number of subjects in Study 069001 (282 of 330 subjects [86%]) compared to that for the non-U.S. studies (569 of 787 subjects [72%]).*
- *In view of (1) these differences between the U.S. and non-U.S. studies, (2) the concerns raised by the Dutch and local regulatory inspectors, and (3) the labeling changes requested by the DMEB, only the data from Study 069001, the study sites of Drs. Urbancsek and Croxatto in Study 34507, and possibly the data from Study 34505 can be considered to be sufficiently reliable "to determine whether the product is safe for use under the conditions prescribed, recommended for use, or suggested in its proposed labeling" in accordance with §314.125 (b) (4) of the Code of Federal Regulations.*

#### 4.1.2.2 Adequacy of Clinical Trial Safety Database

Based on the data obtained from Study 069001 (U.S.), Study 34505 (assuming that these data can be determined to be reliable), and Study 34507 (only study sites of Drs. Urbancsek and Croxatto), the primary clinical trial safety database consists of 648 subjects treated with Implanon for up to 3 years. Based on data from these subjects, there are 7,520 and 5,931 28-day cycle equivalents of exposure in Year 1 and Year 2, respectively (see Table 10). If the data from Study 34505 are not considered to be reliable and therefore eliminated from the safety database, the number of Implanon treated subjects is reduced to 548 with 6,279 and 4,813 28-day cycle equivalents of exposure in Year 1 and Year 2, respectively.

#### Medical Officer's Comment

- *The Division presently requires that NDAs for hormonal contraceptive products involving a new molecular entity, a significant change in dosage, or a change in route of administration (e.g., oral tablet versus subcutaneous implant) include safety and efficacy data from the equivalent of at least 10,000 28-day treatment cycles, including data from 200 women who complete one year of treatment. In most instances, Applicants for such drug products have provided safety and efficacy data from "adequate and well controlled" trials consisting of considerably more than 10,000 28-day equivalent treatment cycles. In all instances, NDAs for contraceptive hormonal products approved by the Division since 2000, as well as the NDAs for Norplant and Jadelle (both products are subcutaneous implants approved for marketing in the U.S. in the 1990s), that have involved a new molecular entity or a significant change in dosage have provided at least 10,000 28-day equivalent treatment cycles during Year 1 of treatment.*
- *In the present NDA for Implanon, the Applicant has provided safety data assessed to be reliable by FDA reviewers from more than 200 women treated for at least one year and data representing an overall exposure of more than 10,000 28-day treatment cycles over 2 years. Total exposure in Year 1, however, was at most 7,520 cycles and perhaps only 6,279 (if data from Study 34505 are excluded). Although not explicitly stated by the Division in its pre-NDA communications with the Applicant or in its 1987 Guidance, it was, and continues to be, the Division's intent that exposure for new hormonal contraceptive products include the equivalent of at least 10,000 treatment cycles during Treatment Year 1. The rationale for this expectation is based on the Division's observation that those adverse events of most concern (serious thrombotic and thromboembolic events, including stroke) in users of hormonal contraceptive products are most likely to occur within the first year of use. Thus,*

*the likelihood of identifying such events would be greater in a safety database consisting of 10,000 28-day treatment cycles based on data from a greater number of subjects treated for one year than on a lesser number of subjects treated on average for 2 years.*

- *The Applicant stated in their communication of May 25, 2005 that this requirement of 10,000 28-day treatment cycles in Year 1 had not previously been communicated to them in regard to the Implanon NDA. Although this statement by the Applicant is likely to be correct, the Applicant's clinical development program as originally presented to the Division would have provided more than 20,000 28-day treatment cycles in Year 1(if no trials had been disqualified) and 12,887 28-day treatment cycles in Year 1 after disqualification of the 2 Indonesian sites if most of the data from Study 34507(Europe) could have been assessed as being reliable. In the Approvable Letter of October 29, 2004, the Division provided the Applicant with 2 options by which the Division's concern about the adequacy of reliable clinical trial data could be resolved. The first option was "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." The second option was "Alternatively, you can conduct another clinical trial" in accordance with the GCP guidelines "to provide safety and efficacy data to support product labeling."*
- *In this Complete Response, the Applicant did not provide convincing information that "Study 34507 (including its Canadian component) are adequate and well-controlled trials" and did not "conduct another clinical trial to provide safety and efficacy data to support product labeling." Consequently, the safety database submitted in support of this NDA is not considered to be adequate. There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling in accordance with §314.125 (b) (4) of the Code of Federal Regulations.*

## 4.2 Safety Update

### 4.2.1 Clinical Trial Data

The present submission contained new safety data from one completed non-U.S. clinical trial (Study 34525 [completed in October 2003 that enrolled 60 subjects]) and 2 ongoing non-U.S. trials (Studies E-1729 and L-1784).

**Medical Officer's Comment**

- *No safety findings of concern were reported.*
- *The Applicant stated that Study 34525 was not conducted in accordance with GCP.*

### 4.2.2 Post Marketing Safety Data Reports

#### 4.2.2.1 Reports of Deaths and Other Serious Adverse Events

According to the Applicant, since the approval of Implanon for marketing in 1998, total worldwide sales up to March 1, 2005 are estimated at implants. Based on the assumption that all units sold have been implanted and an estimate of the average time that an

b(4)

implant remains in place before removal, the Applicant has estimated total exposure in terms of woman-years of use to be 3,832,824 and 2,031,754 worldwide and in Europe, respectively, as of March 1, 2005.

The number and estimated rates (number of events per 100,000 woman-years of use) for deaths and serious thrombotic and thromboembolic adverse events in users of Implanon, based on postmarketing safety reports received by the Applicant through March 1, 2005, are listed in Table 13. Data are presented both in terms of worldwide reports and reports for Europe only. Of the 5 reported deaths, 3 were secondary to a pulmonary embolus, one was secondary to sepsis, and one occurred in a neonate.

**Table 13 Postmarketing Reports of Deaths and Serious Thrombotic and Thromboembolic Adverse Events (Number and Rate of Events)**

| | Number of events worldwide | Number of events Europe[a] only | Worldwide rates (events per 100,000 woman-years of use)[b] | Europe[a] only rates (events per 100,000 woman-years of use)[b] |
|---|---|---|---|---|
| Death | 5 | 3 | 0.13 | 0.15 |
| Pulmonary embolus | 13 | 7 | 0.34 | 0.34 |
| Deep vein thrombosis[c] | 18 | 13 | 0.47 | 0.64 |
| (Venous thromboembolic events (VTE))[d] | (31) | (20) | (0.81) | (0.98) |
| Cerebrovascular accident (CVA) | 18 | 14 | 0.47 | 0.69 |
| Myocardial infarction | 2 | 2 | 0.05 | 0.10 |

[a]The following countries were included for Europe: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Portugal, Sweden, United Kingdom, Czech Republic, Finland, Malta, Norway, Slovak Republic, Spain, Switzerland, Norway, and Iceland.
[b] Both medically confirmed and medically unconfirmed reports are included.
[c] Superficial venous thrombosis are excluded from this analysis. Cases in which it is unclear whether it involves a deep or superficial thrombosis (e.g. only "thrombosis" was reported) are included.
[d]Venous thromboembolic events is the total rate of pulmonary embolus and deep vein thrombosis.

Source: Applicant's submission of 18 May 2005.

### Medical Officer's Comments

- *There have not been any significant changes in these rates since the Applicant's last submission during the original review cycle.*
- *The rates per 100,000 women-years of use for death and serious thrombotic and thromboembolic adverse events in users of Implanon do not appear to be excessive. However, it is difficult to assess the true significance of the calculated rates because of uncertainty as to the percentages of events that have been reported to the Applicant.*

### 4.2.2.2 Insertion and Removal Related Adverse Events and Pregnancies

An update on postmarketing reports for "Insertion and Removal Related Events (IRREs) and Pregnancies submitted to the Applicant is provided in the review done by the primary medical reviewer (Dr. Wesley).

### Medical Officer's Comment

- *Based on the information provided in the primary medical reviewer's report, there have been no significant changes in the overall rate for these events, based on estimated insertions and removals, during the most recent reporting period. Reports of incorrect or difficult insertions continue to be submitted to the Applicant, supporting the need for an effective training program for U.S. healthcare providers.*

- *The proposal outlined by the Applicant for healthcare provider training is, for the most part, adequate and acceptable. The major deficiencies of the proposed training program are the absence of adequate mechanisms (1) to assess the effectiveness of the training program and (2) to obtain an accurate assessment of the incidence of IRREs in the U.S. in the post marketing setting.*

### 4.3 Overall Conclusions Regarding the Safety of Implanon

**Medical Officer's Comment**

- *If the safety data from the clinical trials designated by the applicant as "adequate and well controlled (i.e., Studies 069001, 34505, 34507, and 34507-CDN) accurately reflects the true safety profile of Implanon, this reviewer finds the profile to be acceptable for a highly effective hormonal contraceptive as stated in the Team Leader Memorandum for NDA 21-529, dated October 29, 2004. The additional limited safety data provided in this Complete Response do not raise any new safety concerns.*

The 4 trials designated by the applicant as "adequate and well controlled" enrolled 1,114 women and provided safety data from approximately 12,887 and 10,158 28-day cycle equivalents in Treatment Year 1 and Treatment Year 2, respectively. A clinical trial safety database of this size has been considered by the Division to be acceptable to assess the safety profile of a new contraceptive product. Because of instances of (1) falsification of data in Studies 34506 and 34520 and (2) violations of GCP at several (possibly most) sites in Study 34507 and the single site for Study 34507-CDN, the size of the clinical trial database that can be used to support the safety of Implanon has been significantly reduced (see Table 10).

**Medical Officer's Comment**

- *This reviewer believes that at the present time, only the data from Clinical Trial 069001 conducted in the U.S. (and inspected by the FDA's Division of Scientific Investigation) and the 2 sites in Clinical Trial 34507 inspected by the FDA (i.e., the sites of Drs. Urbancsek and Croxatto can be considered to be sufficiently reliable to (1) assess the safety profile of Implanon and (2) use for product labeling. This reliable database includes only 548 subjects treated with Implanon who provided a total of 6,279 and 4,813 28-day cycle equivalents in Treatment Year 1 and Treatment Year 2, respectively.*
- *A clinical trial safety database of this size has not previously been considered by the Division to be adequate to support the safety of a contraceptive product that involves a new route of administration (i.e., subdermal implant). Inclusion of safety data from the single site in Study 34505 (conducted in Thailand and inspected by the Applicant but not the FDA) would increase the safety database by 100 subjects and approximately 1,200 28-day cycle equivalents in Treatment Year 1.*

The Applicant argues that because of the large postmarketing safety database that does not raise concerns about the safety of Implanon (assuming that Implanon is inserted and removed correctly), a limited clinical trial database (based only on data from Clinical Trials 069001 and 34505 and the 2 sites in Clinical Trial 34507 inspected by the FDA) would be sufficient to support approval of Implanon for marketing in the U.S.

**Medical Officer's Comment**

- *This reviewer does not concur with the Applicant regarding this issue. Although postmarketing safety data (based on spontaneous voluntary reports) need to be considered in assessing the safety profile of a new drug product, such data are generally most useful when they identify a safety concern. Postmarketing spontaneously reported safety data cannot be the basis for product approval in the absence of sufficient safety data obtained from adequate and well controlled clinical trials.*

## 5. RECOMMENDATIONS OF OTHER DISCIPLINES AND CONSULTATIONS

Information in this section is limited to those disciplines and consultations for which new information, not provided in the original submission, was provided in the Complete Response.

### 5.1 Chemistry

The primary Chemistry Reviewer (Amit Mitra, Ph.D.) made the following recommendation regarding NDA 21-529:

> "From Chemistry, Manufacturing and Controls point of view, NDA 21-529 may be approved pending resolution of minor labeling issues... "

The CMC deficiency noted in the Approvable Letter of October 29, 2004 has been resolved in that the sterilization facility has been inspected and the Office of Compliance has given it an overall "Acceptable" recommendation. b(4)

### 5.2 Biopharmaceutics

The primary Clinical Pharmacology and Biopharmaceutics (Myong-Jin Kim, Pharm.D) stated the following in her review:

> "The overall Human Pharmacokinetic Section of NDA 21-529 is acceptable to the OCPB/DPE-II. Labeling comments outlined in this addendum to Clinical Pharmacology and Biopharmaceutics Review should be conveyed to the sponsor as appropriate."

### 5.3 Division of Drug Marketing, Advertising, and Communications (DDMAC)

DDMAC made many suggestions regarding the Applicant's proposed Package (Physician) Label. All suggestions will be considered by the Division's in the development of final product labeling.

### 5.4 Office of Drug Safety

#### 5.4.1 Division of Drug Risk Evaluation (DDRE)

DDRE was consulted regarding the following 2 issues:

- Does DDRE have any suggestions/recommendations regarding the proposed training program and method by which the Applicant proposes to distribute the product?
- The Division seeks suggestions from DDRE as to mechanisms by which the Applicant could collect data on insertion/removal adverse events beyond that which would be submitted to the FDA's Adverse Event Reporting System (AERS).

DDRE provided several recommendations regarding both of the questions listed above. These recommendations will be incorporated into the Division's guidance to the Applicant regarding

(1) healthcare provider training, (2) assessing the effectiveness of the healthcare provider training program, and (3) a post approval monitoring program for Implanon-related insertion/removal adverse events.

### 5.4.2 Division of Surveillance, Research, and Communication Support (DSRCS)

DSRCS made recommendations regarding the format and simplification of language for the Patient Package Insert and Patient Consent Form. All recommendations will be considered in the Division's revision of the Patient Package Insert and Patient Consent Form in the development of final product labeling.

### 5.4.3 Division of Medication Errors and Technical Support (DMETS)

DMETS did not have any objection to the use of the proprietary name "Implanon." DMETS made several recommendations regarding carton labeling that were accepted by the Applicant. DMETS recommended that the implants to be used for training not contain active drug. The Division does not agree with this recommendation since (1) use of a training implant containing active drug does not pose a safety concern and (2) a training implant that does not contain active drug may not have the same physical characteristics as the to-be-marketed implant and thus would be a less effective training tool.

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/s/
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Scott Monroe
6/14/05 05:28:09 PM
MEDICAL OFFICER

Donna Griebel
6/14/05 05:34:47 PM
MEDICAL OFFICER
I have read Dr. Monroe's review. I concur with his recommendation for an Approvable Action and concur with the review issues he has cited to support his recommendation.

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | 21529 |
| Submission Number | 000 |
| Submission Code | AZ |
| Letter Date | 16-Jan-2006 |
| Stamp Date | 17-Jan-2006 |
| PDUFA Goal Date | 17-Jul-2006 |
| Reviewer Name | Lesley-Anne Furlong |
| Review Completion Date | 13-Jul-2006 |
| Established Name | Etonogestrel Implant |
| (Proposed) Trade Name | Implanon |
| Therapeutic Class | Contraceptives/Not Oral |
| Applicant | Organon USA Inc |
| Priority Designation | S |
| Formulation | Implant |
| Dosing Regimen | One implant every three years |
| Indication | Prevention of pregnancy |
| Intended Population | Women who need contraception |

## Table of Contents

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On Original

# 1 Executive Summary

## 1.1 Recommendation on Regulatory Action

From a clinical perspective, I recommend approval of the subdermal implant, Implanon, for the indication prevention of pregnancy. A single Implanon implant may be used continuously for up to three years.

Studies showed efficacy by detecting no pregnancies among 923 women, 219 of whom were followed for over three years.

The safety profile of Implanon is similar to that of non-implantable progestin contraceptives except for events related to insertion and removal of the implant. However, ease of use and high efficacy are benefits of the implant. The Applicant plans a training program and a postmarketing surveillance study to decrease problems related to insertion and removal. In addition, I recommend a boxed warning in labeling to highlight the importance of subdermal placement of Implanon, and the importance of checking for a palpable implant following insertion.

## 1.2 Recommendation on Postmarketing Actions

### 1.2.1 Risk Management Activity

The Applicant plans a training program for healthcare providers, and a monitoring program for adverse events related to insertion and removal of Implanon in U.S. patients. To order Implanon, healthcare providers must participate in the training program.

### 1.2.2 Required Phase 4 Commitments

I do not recommend any required Phase 4 Commitments.

### 1.2.3 Other Phase 4 Requests

The Applicant should replace the current Implanon with a radio-opaque version as soon as feasible. A radio-opaque version of Implanon is desirable in unusual cases where Implanon cannot be otherwise located. The radio-translucency of the current Implanon is a design flaw. Risks of being unable to locate and remove Implanon include

- iatrogenic infertility
- ectopic pregnancy
- continued drug-related adverse events in women having adverse events

These risks are serious to the individual user.

The Applicant has an ongoing bioavailability study (Study 34528) comparing a radio-opaque version of Implanon to the current product. If bioavailability is shown, the radio-opaque version should replace the marketed product.

The Applicant should do a study of effectiveness of Implanon in obese women so that the labeling can provide more useful information for a group that represents almost 30% of U.S. women of reproductive age. The study design would not have to be a large clinical trial: a case-control or surveillance design would be reasonable.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

The submission is the second complete response to an approvable action. FDA took a second approvable action because of concerns about the accuracy and completeness of data obtained at certain clinical sites. The data remaining from acceptable sites were insufficient to show safety and efficacy of Implanon by the usual standards of the Division. The second action letter requested:

- Enough new clinical trial data to provide at least 10,000 28-day cycles of exposure in the first year of treatment[1]
- A plan for postmarketing monitoring for insertion and removal problems in U.S. patients
- Labeling
- A safety update

To provide the 10,000 cycles, the Applicant added 3,346 cycles to the 7,520 cycles that were acceptable to the FDA during the previous two review cycles. The "new" cycles came from clinical pharmacology studies and from additional sites from Study 34507, Study 34525, and the Malaysian site of Study E-1729. Study E-1729 was ongoing at the time of the original NDA submission and only a synopsis was presented in the original NDA submission.

FDA agreed with the plan to use these "new" cycles at an End-of-Review Meeting in August 2005, if Organon could conclude through its audit program that the data were reliable. Included in the present submission is a summary of the Applicant's audit program and results of the audits. In total, 25 audits were conducted resulting in acceptance of data from 13 clinical sites.

The present submission provides a new analysis of efficacy and a new analysis of safety, integrating the data from the "new" cycles and the previously reviewed cycles. In addition, the Applicant has provided audit reports for every "new" clinical site.

A different primary clinical reviewer wrote the two previous reviews[2]. The focus of the present review is on the integrated summaries of efficacy and safety that use data from the sites whose

[1] Twenty-eight day cycles or months are often used to describe exposure in clinical trials of contraceptive products because the time interval corresponds to the length of a menstrual cycle.

data were acceptable based on audits conducted either by the Applicant or the FDA following the second approvable action. Table 1 shows that 31% of the exposure in the integrated summaries in the current submission is from newly integrated data.

**Table 1. Data Used to Create ISS***

**IMPLANON™ Clinical Dataset cited in June 14, 2005 Approvable Letter**

| Trial No. | Investigator | Site No. | Country | Year 1 | Year 2 | Year 3 | > 3 Years | TOTAL |
|---|---|---|---|---|---|---|---|---|
| 069001 | All Sites | | US | 3584.18 | 2522.25 | 79.79 | - | 6186.21 |
| 34505 | Koetsawang | T-001 | Thailand | 1241.21 | 1117.57 | 825.93 | 677.82 | 3862.54 |
| 34507 | Urbancsek | H-003 | Hungary | 1378.32 | 1112.93 | 863.11 | 51.46 | 3405.82 |
| 34507 | Croxatto | RCH-001 | Chile | 1316.5 | 1177.89 | 968.07 | 24.04 | 3486.5 |
| Sub-Totals | | | | 7520.21 | 5930.64 | 2736.9 | 753.32 | 16,941.07 |

**Cycles added to Clinical Dataset**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 34502 | Koetsawang | T-001 | Thailand | 195.54 | 195.18 | 147.18 | 216.68 | 754.57 |
| 34507 | Stietzel | D-019 | Germany | 213.36 | 174.5 | 7.5 | - | 395.36 |
| | Hoffman | D-021 | Germany | 221.43 | 183 | 9.96 | - | 414.39 |
| | Huber | A-004 | Austria | 94.5 | 80.79 | 1.96 | - | 177.25 |
| 34510 | Dusitsin | T-002 | Thailand | 186.57 | 170.79 | 0.36 | - | 357.71 |
| 34511 | Viegas | SGP-001 | Singapore | 514.89 | 489.21 | 24.14 | - | 1028.25 |
| 34512 | Simpanen | SF-019 | Finland | 224.29 | 150.36 | 1.39 | - | 376.04 |
| 34515 | Viegas | SGP-001 | Singapore | 130.36 | 120.18 | 2.11 | - | 252.64 |
| 34522 | Croxatto | RCH-001 | Chile | 195.39 | 175.96 | 6.96 | - | 378.32 |
| | Makarainen | SF-020 | Finland | 170.75 | 156.39 | 5.29 | - | 332.43 |
| | Beerthuizen | NL-027 | Netherlands | 195.64 | 145.14 | 2.75 | - | 343.54 |
| 34525 | Aylamaziam | RU-003 | Russia | 337.07 | 19.11 | - | - | 356.18 |
| E-1729 | Tambi | MY-002 | Malaysia | 666.54 | 603.71 | 545.25 | 176.25 | 1991.75 |
| Sub-Totals | | | | 3346.32 | 2664.32 | 754.86 | 392.93 | 7158.43 |
| Totals (Dataset for primary efficacy analysis in ISE, excludes breastfeeding subjects) | | | | 10,867 | 8595 | 3492 | 1146 | **24,100** |
| Totals (dataset for primary safety analysis in ISS, includes data from breastfeeding subjects in studies 34525 and E-1729) | | | | 11,066 | 8768 | 3652 | 1193 | **24,679** |

Source: Applicant's cover letter 16-Jan-2006
*ISE used the same data as ISS except for cycles in which women were breastfeeding. By convention, cycles are 28-day intervals.

## 1.3.2 Efficacy

Overall the efficacy dataset provides data from 923 women from 11 studies. Subjects used Implanon for up to five years in 11 different countries. The studies provided 24,100 28-day-cycles of exposure, including 10,867 cycles in Year 1. The primary endpoint was pregnancy rate. Subjects were assessed every three months. The studies were open-label and used historical or active controls. No on-treatment pregnancies were detected.

[2] Earlier primary clinical reviews are dated 9-Jun-2005 and 28-Oct-2004.

Table 2 shows annual Pearl Indices with 95% confidence intervals for those subjects who were younger than 36 years old at baseline. For each of three years, the Pearl rates for pregnancy were less than the Pearl rates usually seen in FDA-reviewed trials of approved oral contraceptives.

**Table 2. Pearl Indices for All Cycles – All Treated Subjects 18-35 Years of Age at Baseline**

| Treatment Period | N | Number of On-Treatment Pregnancies | Number of Cycles | Pearl Index | 95% Confidence Interval* |
|---|---|---|---|---|---|
| Year 1 (Day 1 – 365) | 833 | 0 | 9816 | 0 | (0, 0.49) |
| Year 2 (Day 366 – 750) | 671 | 0 | 7766 | 0 | (0, 0.62) |
| Year 3 (Day 731 – 1095) | 482 | 0 | 3066 | 0 | (0, 1.57) |
| Cumulative 3 Year (Day 1 – 1095) | 833 | 0 | 20648 | 0 | (0, 0.23) |

Source: Table 3.1 of statistical review.

Investigators detected six pregnancies with an estimated date of conception within two weeks after removal of Implanon. If all six pregnancies actually occurred during Implanon use, the annual Pearl rate remains less than or equal to what is typically seen in trials of approved oral contraceptives. Because two pregnancies occurred in each of Years 1, 2, and 3, the six pregnancies did not suggest declining efficacy in the final year of Implanon use.

The population studied included generally healthy women who were not obese and not taking concomitant medications that induce liver microsomes. There remains uncertainty regarding the effectiveness of Implanon in obese women and women using medications that induce liver microsomes. There is similar uncertainty for other hormonal contraceptive products, and to date this uncertainty has been handled by labeling.

The following deficiencies in the studies create additional uncertainty regarding precise Pearl rates

- Loss to follow-up
- Unknown number of women using other contraceptive methods
- Infrequent chemical pregnancy testing

Loss to follow-up is a problem for most clinical trials and, at two per cent of subjects, the loss to follow-up in the Implanon studies was not remarkable. Ideally, the use of other contraceptives should have been recorded and the cycles during which other contraceptives were used could be removed from calculation of pregnancy rates. However, based on our experience with other studies, this is likely to affect less than 5% of cycles. The lack of chemical pregnancy testing is not a large issue for two- and three-year studies because pregnancy assessments were done after 45 days of amenorrhea, and because the duration of the studies covers enough time to allow for diagnosis of pregnancy on clinical grounds.

Supportive information for efficacy comes from three sources:

1. Follow-on data in clinical trials

2. In vitro release rates of etonogestrel from Implanon after three years
3. Post-marketing reports

In clinical trials, 219 subjects provided 1,146 cycles of data beyond three years. Sixty-three women completed four years of use. No pregnancies were detected among these women.

Limited data from early dose-finding studies suggest that pregnancies can occur at mean serum levels of etonogestrel of 25 pg/ml. However, mean serum levels of etonogestrel are greater than 150 pg/ml at three years of use.

Post-marketing reports support the efficacy of Implanon. A total of pregnancies have been reported, of which 247 have been confirmed as method failures. Since market introduction of Implanon in August 1998 up to 1-March-2006, Implanon implants have been sold. Pregnancy rate per 100 sold implants is $\leq 0.05$. (This number includes all pregnancies, both confirmed and unconfirmed.) However, a pregnancy rate based on spontaneous postmarketing reports is only relevant if it is unexpectedly high because the extent of under-reporting is unknown. b(4)

Postmarketing, the single most common reason that has been identified as a cause of pregnancy is "missing implant" , a problem that is largely avoidable by the simple expedient of palpating for the presence of the Implanon rod after insertion. Postmarketing reports have not suggested a substantial increase in failure rates by weight or by duration of use, or by weight and duration of use. b(4)

### 1.3.3 Safety

The "new" integrated summary of safety (ISS) contains data from 942 subjects and includes 24,679 x 28-day cycles of use (1,898 women-years). By year, exposure was:

- Year 1: 11,066 cycles, or 851 women-years
- Year 2: 8,768 cycles, or 674 women-years
- Year 3: 3,652 cycles, or 281 women-years
- More than 3 years: 1,193 cycles, or 92 women-years

There were no deaths. Fifty-six of 942 subjects had a total of 77 serious adverse events (SAEs). Most SAEs seem unlikely to be related to Implanon. Those that may have been exacerbated by hormone use based on past studies of progestins include:

- eight cases of gall bladder disease
- three cases of breast cancer
- two cases of ovarian cysts (excluding two dermoid cysts that are not functional in origin)
- one depression and one suicide attempt

Of note, the studies in the ISS detected no venous thromboembolic events, known risks of both pregnancy and hormonal contraceptives. However, in a safety update submitted during the review cycle, the Applicant reported a subject in Study 34528 who had a deep vein thrombosis after four months of therapy. It is difficult to interpret a single DVT. While medical experts recognize estrogen as a thrombogenic hormone, opinion is divided about the role of progestins in thrombotic events. Nonetheless, both the timing of the DVT in Study 34528 and the overall rate of DVT per 10,000 women-years is consistent with what is seen in clinical trials of oral contraceptives containing estrogen and progestin.

An increased proportion of ectopic pregnancies to total pregnancies is seen when other progestin-only methods of contraception fail.[3] Postmarketing reports suggest that Implanon is no exception. Postmarketing, among confirmed method failures, were ectopic pregnancies (for a 1:9 ratio of ectopic pregnancies to total pregnancies). In contrast, among "control" pregnancies caused by failure to insert Implanon, pregnancies were ectopic (for a 1:196 ratio of ectopic pregnancies to total pregnancies). b(4)

Implanon may be similar to the six-rod levonorgestrel-containing implant in causing a small increase in the risk of gallbladder disease. The relative risk of gallbladder disease in women using the six-rod implant is reported to be 1.5, which is consistent with the findings for Implanon.

A small increase in breast cancer related to Implanon cannot be ruled out from the clinical trial data. However, regular medical care in a study may enhance detection.

The reasons for study discontinuation provide a picture of the problems that were most troublesome to Implanon users. By far the most common reason reported for study discontinuation was bleeding irregularity (11%), followed by emotional lability (2.3%), weight increase (2.3%), headache (1.6%), acne (1.3%), and depression (1%). These problems are expected in women of reproductive age, and may be more frequent in women using progestins.

In general, common adverse events were those expected in the population studied. Since the studies did not contain placebo-controls, it is difficult to determine what role Implanon played in common adverse events. Based on a small open-labeled study with a non-hormonal intrauterine device as comparator, Implanon users may have an increased risk of emotional complaints, headaches, weight increase, and acne. These complaints have been described with other progestin-containing contraceptives. These complaints are also common in pregnancy, which also produces a long-term exposure to a progestin.

Postmarketing, the most notable adverse events have been problems with insertion or removal of Implanon. The implant delivery system confers both benefit and risk. While the implant is both

[3] Rough estimates derived from clinical trial data of the proportion of ectopic pregnancies to all pregnancies range from 1:2 for the levonorgestrel-IUD to 1:21 for progestin-only pills. See Furlong LA Ectopic pregnancy risk when contraception fails: a review. J Repro Med 2002; 47:881-885

highly effective and ideal for ease of use, it may be inserted incorrectly and may be difficult or even impossible to remove. There are postmarketing reports of women who, surprised by an unplanned pregnancies, discovered that they did not have an Implanon in place. The reports show that healthcare providers and Implanon users do not always properly check for the presence of Implanon after insertion.

Overly deep insertions or intravascular insertions can lead to difficult or impossible removals. Difficult removals may lead to scarring or damage to the arm. In theory, an intravascular insertion could lead to an Implanon lodged in the pulmonary vascular tree. There have been rare postmarketing reports of implants that cannot be found by palpation, ultrasound, or MRI, but are nonetheless present based on serum etonogestrel levels. (There have been 281 reports of irretrievable implants during seven years in which 2,532,300 Implanon rods were sold. This is one irretrievable implant per 10,000 sold implants, but the extent of under-reporting is unknown.) A woman with an irretrievable implant may

- Want to become pregnant and be unable to conceive. Although it does not meet the regulatory definition of a serious adverse event, iatrogenic infertility may be a very serious adverse event for the affected couple.
- Wish to rid herself of a troublesome side effect and be unable to do so.
- Conceive an ectopic pregnancy. Based on experience with other progestin-only contraceptives and postmarketing experience with Implanon, a pregnancy conceived in the presence of low concentrations of a progestin may be ectopic.

All of these problems are serious to the affected young woman.

Unlike other contraceptive implants, Implanon is not radio-opaque. It should be. Although usually detectable with ultrasound or magnetic resonance imaging, non-palpable Implanon rods have occasionally been impossible to find. The Applicant has an ongoing bioavailability study of a new formulation of Implanon that contains barium sulfate to make it radio-opaque. Radio-opacity should help with difficult retrievals. The new formulation should replace the current formulation if the two formulations are bioequivalent.

The Applicant hopes to minimize insertion and removal problems with a training program that the healthcare provider must complete before obtaining implants. The effectiveness of the training program will be monitored. The history of lawsuits related to removals of a six-rod implant should provide added incentive for the Applicant to carefully train healthcare providers.

Overall, the data indicate that Implanon has a safety profile similar to non-implantable progestin contraceptives. However, while providing excellent ease-of-use and excellent effectiveness, Implanon's dosage form confers the risk of problems related to insertion and removal. Insertion and removal problems are largely avoidable with careful placement of the implant. A boxed warning can highlight both the importance of subdermal placement and the importance of checking for a palpable implant following insertion.

I recommend a boxed warning because "There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug."[4] Some sequelae of insertion and removal problems include unplanned pregnancies, ectopic pregnancies, iatrogenic infertility, and inability to mitigate a drug-related adverse event. Patients are likely to view all of these events as serious. These events can be reduced in frequency by the simple expedient of ensuring that Implanon is properly inserted. Healthcare providers and patients should confirm correct placement by palpation after every insertion. For healthcare providers who insert Implanon incorrectly, the inconvenience of having to locate a nonpalpable implant will likely encourage improved technique with subsequent insertions.

### 1.3.4 Dosing Regimen and Administration

Implanon has a single dose and dosing regimen: one implant subcutaneously for three years. Each Implanon rod contains 68 mg of etonogestrel. The release rate of etonogestrel is 60-70 µg/day in week 5-6, and the release rate gradually declines to 25-30 µg/day at the end of the third year. The dose was appropriately chosen based on early dose-ranging studies and clinical studies for safety and efficacy support the dosing regimen.

### 1.3.5 Drug-Drug Interactions

Implanon is likely less effective in women who chronically use potent CYP 3A4 inducers. The clinical studies of Implanon provided little data about drug-drug interactions because the studies excluded women who used potent CYP 3A4 inducers. However, one subject demonstrated the profound effect of a CYP 3A4 inducer when she inadvertently violated a protocol by starting rifampicin for tuberculosis. She experienced a 70% decrease in her serum levels of etonogestrel after starting antitubercular drugs. (See Section 5.2.) Postmarketing reports further support a decrease in efficacy in women using hepatic-enzyme-inducing drugs. In postmarketing reports, among 61 of 247 pregnancies that occurred during use of Implanon, subjects concomitantly used a hepatic-enzyme-inducing drug (usually an anticonvulsant).

Potent inducers of CYP enzymes can lower the serum concentrations of reproductive hormones and decrease effectiveness of hormonal contraceptive products. There is both pharmacokinetic (PK) and clinical evidence of this phenomenon with other hormonal contraceptives. The problem may be particularly acute for implants because implants provide a low concentration of contraceptive steroid relative to other hormonal contraceptives. This problem is currently handled by labeling.

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4 From the section titled "When to Use a Boxed Warning" in FDA's *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format. http://www.fda.gov/cder/guidance/index.htm*

## 1.3.6 Special Populations

Overweight women may not experience the same effectiveness with Implanon as women of normal weight because the serum concentration of etonogestrel declines as body weight increases. The Applicant's studies excluded women who were more than 130% of their ideal body weight, and therefore did not provide clinical data addressing the effectiveness of Implanon in overweight women. The problem of decreased effectiveness in overweight women has been described for other hormonal contraceptives and is currently handled by labeling. However, it would be ideal to have premarketing data for overweight women, and developers of hormonal contraceptives should not exclude overweight women from their Phase 3 studies.

According to the first clinical review, Implanon has not been studied in women who have renal or hepatic impairment. Since etonogestrel is metabolized by the liver, the applicant proposed to make "active liver disease" a contraindication, as it is with other steroid contraceptives. Additionally, proposed labeling contains a section on renal insufficiency stating that no studies were done.

The primary medical reviewer for the first two review cycles reviewed the lactation data and concluded "It appears that in lactating women, Implanon is safe for the newborn and may be labeled as such."