

2 Introduction and Background

2.1 Product Information

Implanon is a progestin-only implant for subdermal use. It contains the progestin etonogestrel, a progestin also used in the U.S.-approved Nuvaring.

2.2 Currently Available Treatment for Indications

There are no subdermal implants for contraception currently marketed in the United States. U.S.-approved six-rod and two-rod implants, which contain the progestin levonorgestrel, are approved but not marketed in the United States. The U.S. market has numerous other hormonal contraceptive products, including birth control pills, a vaginal ring, a skin patch, long-acting injections, and an intrauterine device (IUD) containing progestin.

An effective implant can fill a need in the U.S. market for a highly effective contraceptive method that is simple to use and may be used by women who cannot use estrogen or intrauterine devices (IUDs).

2.3 Availability of Proposed Active Ingredient in the United States

The progestin etonogestrel is available in Nuvaring, an estrogen- and progestin-containing contraceptive ring for vaginal administration.

2.4 Important Issues with Pharmacologically Related Products

A major issue with one other approved implant has been difficulty with the insertion and removal. Norplant, a six-rod implant, has been the subject of litigation related to injuries caused by difficult removals. Norplant II, a two-rod implant, simplified insertion and removal but Norplant II has never been marketed in the United States. Implanon, a one-rod implant, should further simplify insertion and removal.

There are two categories of progestin-only contraceptive products: products that completely suppress ovarian production of estrogen (depot medroxyprogesterone acetate), and lower-dose products that do not completely suppress ovarian production of estrogen. Implanon appears to be in the latter category.

The risk profile of lower-dose progestin products includes but is not limited to

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

Unlike the high-dose progestin product, lower-dose progestin products have not been associated with loss of bone mineral density or with the amount of weight gain seen with depot medroxyprogesterone acetate.

Obese women may not experience the same effectiveness with hormonal contraceptives as women of normal weight because the serum concentration of hormone is inversely related to body weight. There is evidence in the medical literature that this is true for birth control pills and the levonorgestrel implant. Unfortunately, obese women are often excluded from clinical trials of contraceptive products, and so the opportunity to provide clear, data-driven guidance to obese women is lost.

Comment: To date, the uncertainty about contraceptive effectiveness in obese women has been handled by labeling. However, with obesity affecting almost 30% of U.S. women, sponsors should not exclude obese women from Phase 3 trials of contraceptive products.

Potent inducers of CYP enzymes can lower the serum concentrations of reproductive hormones and decrease effectiveness of hormonal contraceptive products. There is both PK evidence (decreased drug levels) and clinical evidence (pregnancies) of this problem. This problem is currently handled by labeling.

2.5 Presubmission Regulatory Activity

The following list summarizes regulatory activity for the NDA:

1. Approvable action on 29-Oct-2004 because of concerns about the quality of data from Study 34507 and because a sterilization facility was not ready for inspection. FDA asked the Applicant to address the following statement: "Irregularities in study conduct identified by European regulatory authorities' inspection of the clinical trial sites for Study 34507 (including its Canadian components) have raised concerns about the quality of the data from this study."
2. Second approvable action on 14-June-2005 because there were insufficient data of known and acceptable quality to provide the usual exposure that FDA expects for a new hormonal contraceptive. Data were insufficient because "Two of six studies (Indonesia) submitted in the original NDA submission had to be withdrawn from the NDA because of significant Good Clinical Practice violations that rose to the level of fraud." Also, there remained concerns about the conduct of Study 34507 because European authorities had concluded from their inspections that the reliability of data could not be assured. Without the Indonesian sites and the data from sites in Study 34507 that had not been inspected by the FDA, the remaining dataset "did not meet the FDA's customary 10,000 28-day cycle equivalents in the first year of use for a hormonal contraceptive application for a new molecular entity or a new delivery system." The Applicant was asked to submit new clinical trial data from a clinical trial (s) that has been conducted in accordance with Good Clinical Practices.

3. End-of-review meeting on 11-Aug-2005, during which the FDA agreed the Applicant could provide the requisite data from clinical pharmacology studies of appropriate duration, design, and quality. FDA also agreed that the outline that the Applicant provided of a post-marketing plan for monitoring insertion and removal events was “sufficient for a basis for a formal proposal.”
4. Submission of proposed training materials

The preceding activities were reviewed by a different primary clinical reviewer. On January 16, 2006, the Applicant submitted a “new” integrated summary of efficacy (ISE) and a “new” integrated summary of safety (ISS). About 31% of the clinical data in the “new” ISS and ISE had not been integrated into the old ISS and ISE; however, all “new” data, with the exception of some of the data from Study E-1729, previously had been submitted and reviewed in the first review cycle as clinical pharmacology data or as supportive efficacy and safety data.

2.6 Other Relevant Background Information

Implanon was first approved in Indonesia in 1997, is currently approved in 57 countries, and is marketed in 34 countries. Implanon has not been withdrawn from the market in any country due to safety or efficacy concerns.

3 Significant Findings from Other Review Disciplines

3.1 CMC (and Product Microbiology, if Applicable)

The chemistry review team did not identify any approvability issues.

3.2 Animal Pharmacology/Toxicology

The pharmacology/toxicology review team did not identify any approvability issues.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

The sources of clinical data include trials conducted by the Applicant, foreign postmarketing safety data, and literature.

4.2 Tables of Clinical Studies

For the integrated assessment of safety (ISS), the Applicant used the subjects in Table 3 plus three subjects who did not supply any postbaseline assessments, for a total of 942 subjects. Table 3 shows total exposure by year and study for all subjects who provided postbaseline data.

Shading shows studies that are newly integrated into the ISS for this submission. The integrated assessment of efficacy (ISE) included the same subjects and cycles except for the removal of 16 women who were breastfeeding.

Table 3. Database for the Integrated Safety Analysis

Study	Year 1		Year 2		Year 3		>3 years		Total of exposure	
	N	Cycles*	N	Cycles	N	Cycles	N	Cycles	Cycles	Woman-years
069001	327	3584.18	226	2522.25	136	79.79	0	0	6186.21	474.56
<i>US Total</i>	327	3584.18	226	2522.25	136	79.79	0	0	6186.21	474.56
34502	15	195.54	15	195.18	13	147.18	10	216.68	754.57	57.88
34505	100	1241.21	90	1117.57	77	825.93	57	677.82	3862.54	296.3
34507	267	3224.11	227	2729.18	178	1850.67	112	75.5	7879.52	604.44
34510	15	186.57	14	170.75	5	0.36	0	0	357.71	27.44
34511	40	514.89	39	489.23	35	24.14	0	0	1028.25	78.88
34512	20	224.29	14	150.36	9	1.39	0	0	376.04	28.85
34515	10	130.36	10	120.16	5	2.11	0	0	252.64	19.38
34522	46	561.79	39	477.55	34	15	0	0	1054.29	80.88
34525	30	363.14	24	23.16	0	0	0	0	386.32	29.64
E1729	69	839.71	60	773.18	56	705.64	52	222.86	2541.39	194.96
<i>Non-US Total</i>	612	7481.61	532	6246.25	412	3572.36	231	1192.86	18493.07	1418.65
Total	939	11065.79	758	8768.5	548	3652.14	231	1192.86	24679.29	1893.21

- *Cycles are 28-day intervals.
- Light shading marks "new" studies. These studies were previously submitted as pharmacology studies or other supportive studies that were not included in previous integrated summaries. Dark shading shows a study included in previous integrated summaries with data from three sites that were found acceptable on audit done for this submission.
- Three subjects (Study 069001) who had no post-baseline assessments were not included in the calculation of extent of exposure.
- Year 1: Day 1 - 365, Year 2: Day 366 - 730, Year 3: Day 731 - 1095, >3 years: Day > 1095

Source: ISS, Appendix F Table 1A

4.3 Review Strategy

The focus of my review of this resubmission was on the "new" ISS and ISE. Other areas were re-reviewed as needed to enhance my understanding of Implanon. However, I relied on the findings of the previous review team whenever possible for data submitted in the two previous review cycles.

4.4 Data Quality and Integrity

Both the FDA and the Applicant performed audits of the “new” data. The FDA team who reviewed Implanon during the previous two review cycles requested additional inspections by FDA’s Division of Scientific Investigations (DSI) of three clinical sites not previously inspected by the Agency. (See Table 4.) The sites were chosen based on the number of subjects enrolled by the site. This reviewer requested that FDA’s inspector

- Cross-check the diaries with the case report forms to ensure that there was assessment of pregnancy status following 45 days of amenorrhea, as required by protocol.
- Examine charts of all subjects who had pregnancies post-treatment with the estimated date of conception within two weeks of Implanon removal

Table 4. Sites Audited by FDA’s Division of Scientific Investigations (DSI)

Site # (Name, Address, Phone number)	Protocol #	Number of Subjects
Tambi, I (MY_002) Bangunan LPPKN 12 B Jalan Raja Laut Peti Surat 10416 50712 Kuala Lumpur Malaysia	E-1729	47
Dr. Orawan Kiriwat Siriraj Hospital Mahidol University Bangkok 10700, Thailand	34502 34505	115
Biswas, A. National University of Singapore National University Hospital Dept. of Obstetrics & Gynecology Lower Kent Ridge Road Singapore 051	34511 34515	40 10

Source: consult sent to DSI by previous review team

FDA’s inspections of the three clinical sites were satisfactory. The Clinical Inspection Summary from FDA’s Division of Scientific Investigations gave the three sites an “NAI” rating, which means “No deviation from regulations. Data acceptable.”

The Applicant conducted its own audit program and arranged for a third party audit conducted by . This Applicant’s audit program and the score of the review were presented to the FDA in August 2005 at the End-of-Review meeting.

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In summary, the Applicant identified 26 potential study sites from which additional first-year cycles might be obtained. 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 study sites were acceptable. reviewed the audit findings and concurred with inclusion of 13 of the 14 sites. However noted that one audit reviewed fewer subjects than pre-specified in the audit plan. The Applicant returned to the site to audit the

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records of two more study subjects, and then decided to exclude this study site because of discrepancies noted in adverse event reporting.

The submission includes the audit reports from all 25 sites and a summary from Group describing why sites were acceptable or unacceptable. All 13 sites that were acceptable to were added to the database that had been previously found to be acceptable by the FDA to produce a new ISS and ISE. **b(4)**

Comment: 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.

4.5 Compliance with Good Clinical Practices

The submission contains a full sub-study report for the site from Study E-1729 that provided data for the current submission's integrated summaries. Study E-1729 was a post-marketing study using Implanon in the approved population for the approved indication, and appeared to meet appropriate ethical standards. The study report contains an acceptable informed consent form and the name and address of the institutional review board. I reviewed the listing of protocol violations and found them unlikely to affect patient safety or to have a significant impact on the outcome of the trial.

In previous review cycles, the Applicant provided full study reports for all other studies included in the integrated summaries of the present submission.

Comment: The Study Report supports compliance with good clinical practices.

4.6 Financial Disclosures

The submission contains a signed Form 3454 certifying that Organon did not enter into any financial arrangement with clinical investigators whereby compensation could affect outcome (as defined in 21 CFR 54.2(a).) The form covers investigators and subinvestigators in Study E1729, the only study in the submission that had not been reviewed in previous review cycles. The previous clinical reviewer found the financial disclosures acceptable for the remaining studies.

5 Clinical Pharmacology

5.1 Pharmacokinetics

Mean peak serum concentrations in three studies ranged between 781 and 894 pg/mL, and declined over 3 years. By Year 3, mean serum concentrations of etonogestrel were 156 pg/mL in one study, and 177 pg/mL in another study. The following table from the biopharmaceutical review shows mean serum levels from three studies.

Table 5. Mean Serum Etonogestrel Concentrations in Implanon Users by Year and by Study

Study		n	Etonogestrel (ENG) concentration (pg/mL) Mean (SD)
34502	Year 1 (Week 48-53)	15	260.5 (94.3)
	Year 2 (Week 98-104)	15	190.6 (64)
	Year 3 (Week 150-155)	11	177.2 (68.8)
34508	Year 1 (Day 366)	10	196
	Year 2 (Day 731)	8	194
	Year 3 (Day 1096)	6	156
069001	Year 1	16	192.1 (47.2)
	Year 2 (23 month)	12	153.6 (32.3)

Source: Biopharmaceutical review

Nuvaring is the only U.S.-approved product that contains etonogestrel, and etonogestrel concentrations in women using Nuvaring are substantially greater than etonogestrel concentrations in women using Implanon. Etonogestrel concentrations in women using Nuvaring (in pg/mL) are 1,578 at one week, 1,476 at two weeks, and 1,374 at three weeks. (Nuvaring is removed in Week 4, and a new Nuvaring inserted the following week.)

Comment: Adverse events that are related to serum concentration of etonogestrel should be less frequent for women using Implanon compared with women using Nuvaring.

The mean half life of etonogestrel was 25 hours, and ENG concentrations fell below assay sensitivity by one week after removal of Implanon. In vitro data indicate that etonogestrel (ENG) is metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme.

Comment: There is potential for decreased effectiveness with concomitant and chronic use of drugs that induce CYP 3A4.

Serum concentrations of ENG are inversely related to body weight. Because the clinical trials excluded women who weighed more than 130% of their ideal body weight, and because there are few data to relate serum concentrations with risk of pregnancy, the contraceptive effectiveness of Implanon in obese women was not defined.

According to the biopharmaceutical review, during the first month after Implanon insertion in lactating women, about 100 ng of ENG may be ingested by the infant each day. "This corresponds to approximately 2.2% of the weight-adjusted maternal daily dose and to approximately 0.2% of the estimated absolute maternal daily dose."

Comment: Based on PK data, return to fertility may be rapid after removal of Implanon because etonogestrel clears rapidly.

The sponsor should do a study of Implanon in obese women to determine whether Implanon is reasonably effective in this group. According to the National Health and Nutrition Examination Survey, 28.4% of U.S. women between the ages of 20 and 39 years old are obese (defined as BMI ≥ 30 .⁵) Therefore the effectiveness of Implanon is uncertain for a large group of U.S. women.

5.2 Pharmacodynamics

Implanon appears to belong among the progestin-only contraceptives that do not uniformly prevent follicular development and ovulation. Inhibition of ovulation is sufficient but not necessary for a progestin-only contraceptive. The IUD (Mirena), the implants (Jadelle and Norplant), and the progestin-only “minipills” do not uniformly inhibit ovulation. Despite some ovulatory cycles, these contraceptive methods are effective, perhaps as a result of changes in cervical mucus that decrease sperm transport into the uterus. The production of estrogen that accompanies the process of follicular development may explain why these products are not associated with bone loss. However, they are associated with ovarian cysts that are thought to be the result of follicular development.

In contrast, the higher-dose progestin-only contraceptive, depot medroxyprogesterone, prevents follicular development and ovulation. Suppression of follicular development and ovulation causes estrogen production to decrease, which in turn is associated with bone loss.

The following paragraphs summarize selected studies that evaluated pharmacodynamic effects of Implanon.

Study 34502 evaluated ovulation inhibition in Implanon users. In this study, 15 subjects were followed after Implanon insertion for up to five years. The study explored the relationships between serum progesterone, estradiol and etonogestrel concentrations. Return of ovulation, judged by return to ovulatory progesterone levels, occurred in 14 of 15 women within three months after implant removal.

One subject dropped out in the third year to become pregnant. A second subject, Subject 211, was discontinued when she was found to be taking excluded medications. She used isoniazid and rifampicin for tuberculosis starting on day 1505 and she was discontinued from the study on day 1587 as a protocol violator, *and her data were excluded from analysis during the time that she used rifampicin.* However, her mean etonogestrel levels fell from 150.5 pg/ml one to two months before treatment for tuberculosis to a mean of 44.6 pg/ml after taking rifampin for one to two months.

Comment: Subject 211 showed the potential for agents that induce liver enzymes to lower exposure to etonogestrel, and increase the risk for pregnancy. A high rate of pregnancy has

⁵ Flegal KM, Carroll MD, Ogde CL, Johnson CL. Prevalence and trends in obesity among US adults. JAMA. 288(14):1723-1727, 2002

been detected in women who use the implant Norplant and take anticonvulsants that are strong CYP 3A4 inducers (two of nine such women became pregnant). Implanon, like Norplant, provides a relatively low concentration of exogenous progestin, and may therefore be more vulnerable to decrease in efficacy when the serum concentration of etonogestrel is lowered by inducers of liver enzymes.

At screening, subjects had a mean age of 26 years, and mean BMI of 22.3 kg/m², and regular menses. Table 6 shows that progesterone (P) levels were generally suppressed through five years. A single subject had a maximum P concentration >30 nmol/l during weeks 24 to 29 that was possibly spurious, based on a value of 0.7 nmol/l three days earlier, and a value of 0.9 nmol/l four days later.

Table 6. Serum Progesterone Concentrations over Time

Assessment	N	Number of subjects with concentrations			No. of subjects with concentrations
		<10 nmol/l	10-<30 nmol/l	≥30 nmol/l	≥16 nmol/l
Screening	15		5	10	15
Week 1-6	15	15			0
Week 24-29	15	14		1	1
Week 45-53	15	15			0
Week 72-77	15	15			0
Week 98-104	15	15			0
Week 124-129	11	11			0
Week 150-155	11	10	1		0
Week 167-170	9	9			0
Week 180-183	9	9			0
Week 193-198	9	9			0
Week 206-209	9	9			0
Week 219-222	7	7			0
Week 232-235	7	7			0
Week 245-248	7	6	1		0
Week 258-261	7	7			0

To convert nmol/l to ng/ml, divide by 3.18.

Source: Study report for Study 34502, p.53

Estradiol levels were most suppressed in the first six months following insertion. After one year, mean estradiol levels approached those seen at baseline. Table 7 shows estradiol levels.

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Table 7. Estradiol concentrations over time

Assessment	n	Mean 17β-estradiol (pmol/l)		
		Mean	SD	Median
Screening	15	366.1	126.1	383
Week 1-6	15	79.4	73.4	75
Week 24-29	15	154.2	187.2	112
Week 48-53	15	290.7	373.9	135
Week 72-77	15	299.6	323.9	126
Week 98-104	15	368.9	303.8	283
Week 124-129	11	492.2	399.6	443
Week 150 - 155	11	418.9	315.5	264
Week 167-170	9	323.5	235.1	235
Week 180-183	9	362.8	319.9	316
Week 193-196	9	417.7	303.9	266
Week 206-209	9	378.7	314.0	211
Week 219-222	7	418.8	241.1	341
Week 232-235	7	505.3	390.0	313
Week 245-248	7	450.1	308.7	381
Week 258-261	7	405.5	326.0	251
Post-removal	0			

Divide by 3.671 to convert units from pmol/l to pg/ml.
 Source: Study report for Study 34502, p.55

Based on a previous study of prototypes of Implanon, 90 pg/ml was considered the threshold concentration of etonogestrel above which ovulation was rarely observed. None of the 15 subjects in the study had a mean etonogestrel <90 pg/m. on treatment except for the subject taking rifampin and isoniazid (this subject's data were censored from the study due to protocol violation). However, the proportion of subjects in the 90 to 120 pg/ml range increased as the study progressed.

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Table 8. Frequency table of mean etonogestrel per assessment

Assessment	N	Number of subjects with concentrations		
		≤90 pg/ml	90-≤120 pg/ml	>120 pg/ml
Screening	15	15		
Week 1-6	15			15
Week 24-29	15		1	14
Week 48-53	15			15
Week 72-77	15			15
Week 98-104	15		2	13
Week 124-129	11			11
Week 150-155	11		3	8
Week 167-170	9		3	6
Week 180-183	9		1	8
Week 193-196	9		3	6
Week 206-209	9		3	6
Week 219-222	7		1	6
Week 232-235	7		3	4
Week 245-248	7		2	5
Week 258-261	7		4	3

Source: Study report for Study 34502, p. 59

Another study, Study 34508, compared Norplant to Implanon with respect to hormonal changes in 20 Finnish women. The first clear ovulation in Norplant users occurred at 18 months; in women using Implanon at 30 months. Norplant is approved for up to five years of use.

Because another progestin contraceptive, depot medroxyprogesterone acetate, causes a decrease in bone mineral density, the sponsor studied bone loss in Study 34522. The study was reviewed by FDA reviewer Dr. Barbara Wesley during the first review cycle, and she concluded that the study “showed no signs of a negative effect of Implanon use on BMD.”

Comment: Based on my reading of the protocol, Study 34522 was not adequate to support claims about BMD because the study was a small, exploratory, two-year, non-randomized safety and efficacy study in women using Implanon (N=46) or a non-hormone IUD (N=30).

5.3 Exposure-Response Relationships

In an early dose-finding study⁶ (N=20) of Implanon prototypes, three pregnancies⁷ occurred among 21 women in three lowest-dose groups. The estimated *mean* in vitro release rate of etonogestrel at the time pregnancies occurred was between 10 µg/day and 16 µg/day. There were no pregnancies among 29 women who used implants had an estimated mean release rate of etonogestrel greater than 21 µg/day.

In a second dose-finding study,⁸ ten women received an implant with a mean initial in vitro release rate of 30.6 µg/day etonogestrel, and 13 women received an implant with a mean initial in vitro release rate of 16.4 µg/day etonogestrel. Pregnancy was diagnosed at 21 months in two of 13 women who were using the lower release implant, and there were no pregnancies detected in the higher release group. At 21 months, the mean in vitro release rate of etonogestrel for the lower release implant was 9.8 µg/day, and mean serum levels of etonogestrel were about 25 pg/ml, compared with a mean serum level of 101 pg/ml in the higher release group.

Based on these findings, the Applicant decided to pursue development of an implant that would have a release rate of 30 µg/day after 3 years.

At three years of use, both the in vitro release rate and the mean serum concentration of etonogestrel produced by the final formulation of Implanon are greater than the in vitro release rates and mean serum concentrations at which pregnancies occurred in the two dose-finding studies. The mean in vitro release rate of Implanon is about 25 to 30 µg/day at the end of the third year. The mean serum concentration of etonogestrel in Implanon users at three years was 177.2 pg/ml (N=11) in one study, and 156 pg/ml (N=6) in a second study.

Comment: Data from the early dose-finding studies supports the choice of dose and suggests that Implanon should be effective through three years.

6 Integrated Review of Efficacy

6.1 Indication

The proposed indication is “for women for the prevention of pregnancy for up to 3 years.”

⁶ See Diaz S, et al. Clinical trial with 3-keto-desogestrel subdermal implants. 1981 Contraception 44:393, and discussion starting on page 45 of ISE from original submission

⁷ One of the 3 pregnancies was ectopic. Although the numbers were small, this is consistent with previous findings of an enhanced risk of ectopic pregnancy when pregnancy occurs in the presence of low levels of exogenous progestin.

⁸ Study report found in the initial NDA submission, labeled “SDG Release Report No.2904”

6.1.1 Methods

Section 4.2 Tables of Clinical Studies, provides a complete listing of the studies used to support efficacy.

6.1.2 General Discussion of Endpoints

The endpoint for the analysis of efficacy was pregnancy. Pregnancy was assessed in each trial when pregnancy was suspected. Subjects visited the study sites at least every three months. At each three-month visit, any subject who had no bleeding recorded over the preceding 45 days was to have her pregnancy status assessed. The U.S. study was the only one in which the protocol included confirmation of pregnancy with a serum pregnancy test. In the non-U.S. studies, the method used for pregnancy assessment and confirmation was left to the discretion of the investigators.

Comment: This method of assessing pregnancy could miss women who did not record diary data or pregnant women who had bleeding or spotting during a pregnancy. However, over the course of three years any pregnancies that went beyond the first trimester should have been readily detected by other signs and symptoms.

The FDA has accepted historical controls for highly effective contraceptive methods because the effect size is large. In numerous published studies, the expected pregnancy rate for women who are sexually active, of reproductive age, and trying to conceive is at least 85% in the first year. In contrast, the expected pregnancy rate for women in clinical studies of hormonal contraceptives is less than 3% in the first year.

6.1.3 Study Design

Overall, the studies included subjects who were generally healthy women

- between 18 and 40 years old
- sexually active
- of childbearing potential
- had normal cycles
- were not pregnant or lactating
- had not used an injectable hormonal contraceptive for at least six months
- had not used any other hormonal contraceptive for at least two months
- had not had an abortion or delivery in the preceding two months

Use of antiepileptics, rifampicin, rifabutin, troglitazone, griseofulvin, and sex steroids was not permitted during the trial.

Comment: Drugs known to be strong CYP 3A4 inducers were excluded from study.

There were exceptions to the above criteria. Study 34502 (N=15 subjects) did not require sexual activity. Breastfeeding women were allowed to participate in Studies 34525 and E-1729, but were excluded from the efficacy calculations.

Comment: Even though Study 34502 did not require sexual activity, it seems likely that women between 18 and 40 years old who were willing to have an implant needed contraception. In fact, three of fifteen subjects became pregnant within the post-treatment follow-up period.

Subjects had pregnancy testing before implant insertion. Eligible subjects had Implanon inserted on or between Days 1 through 5 of the next menstrual period. Subjects were seen at three-month intervals. Vaginal bleeding was recorded on diary cards. The implant site was inspected at each visit. A post-treatment contact by telephone, letter, or visit occurred about three months after study termination. The subject was asked about menses, use of contraceptive methods, and adverse events.

Table 9 shows details of assessments by study.

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Table 9. Schedule of Study Assessments by Study

	First year					Second year					Third year					Fourth year			
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48		
Time in months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48		
Assessment no.	2 ^a	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18 ^c		
Study 069001																			
Status at implantation site	X	X	X	X	X	X	X	X	X										
Pregnancy status	X	X	X	X	X	X	X	X	X										
Blood pressure, body weight			X		X				X										
Pelvic and breast examination					X				X										
Physical examination					X				X										
Pap smear					X				X										
Study 34502^b																			
Status at implantation site	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Condom use	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood pressure, body weight			X		X				X				X				X		
Pelvic examination									X				X				X		
Physical examination			X		X				X				X				X		
Pap smear									X				X				X		
Hemoglobin			X		X				X				X				X		
ENG concentration ^c	X		X		X				X				X				X		

Source: Assessment schedules/Flow Charts as provided in Sections 4.4.1 of the individual study reports.

^aScreening (Assessment 1) not included in this overview; implant was inserted at Assessment 2.

^bStudy of 5-year duration; assessments Year 5 similar to those of Year 4, with visits at 51, 54, 57 and 60 months.

^cENG measured twice per week for consecutive 6-week periods; for Year 4 and 5 ENG measure twice per week for consecutive 4-week periods

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Clinical Review
 Lesley-Anne Furlong
 NDA 21529, 000 AZ
 Implanon (etonogestrel implant)

	First year					Second year					Third year					Fourth year				
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	18 ^d		
Time in months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48			
Assessment no.	2 ^a	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18 ^d			
Study 34505																				
Status at implantation site	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood pressure, body weight																				
Pelvic examination																				
Physical examination			X		X				X				X		X			X		
Pap smear ^b																		X		
Hemoglobin		X	X		X		X						X					X		
ENG concentration																		X		
Study 34507																				
Status at implantation site		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood pressure, body weight																				
Pelvic examination																		X ^c		
Physical examination					X				X									X ^c		
Pap smear ^b																		X ^c		
ENG concentration									X									X ^c		

Source: Assessment schedules/Flow Charts as provided in Sections 4.4.1 of the individual study reports.

^aScreening (Assessment 1) not included in this overview; implant was inserted at Assessment 2.

^bPAP smear at the end of the trial (completion or premature discontinuation)

^cFor women who continued into the third year, these investigations were optional

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Clinical Review
 Lesley-Anne Furlong
 NDA 21529, 000 AZ
 Implanon (etonogestrel implant)

	First year						Second year						
	0	3	6	9	12	15	18	21	24				
Time in months													
Assessment no.	2 ^a	3	4	5	6	7	8	9	10				
Study 34510													
Status at implantation site		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy status	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure, body weight		X	X		X		X		X		X		X
Pelvic examination													X
Physical examination					X								X
Pap smear ^b													X
ENG concentration													X
Study 34511													
Status at implantation site		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy status	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure, body weight		X	X		X		X		X		X		X
Pelvic examination													X
Physical examination					X								X
Pap smear ^b													X
ENG concentration													X

Source: Assessment schedules/Flow Charts as provided in Sections 4.4.1 of the individual study reports.

^aScreening (Assessment 1) not included in this overview; implant was inserted at Assessment 2.

^bPAP smear at the end of the trial (completion or premature discontinuation)

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Clinical Review
 Lesley-Anne Furlong
 NDA 21529, 000, AZ
 Implanon (etonogestrel implant)

	First year					Second year					Third year					Fourth year			
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48		
Time in months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48		
Assessment no.	2 ^a	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Study 34512																			
Status at implantation site		X	X	X	X	X	X	X	X										
Pregnancy status	X	X	X	X	X	X	X	X	X										
Blood pressure, body weight		X	X		X														
Pelvic examination									X										
Physical examination																			
Pap smear ^b																			
ENG concentration																			
Study 34515																			
Status at implantation site		X	X	X	X	X	X	X	X										
Pregnancy status	X	X	X	X	X	X	X	X	X										
Blood pressure, body weight		X	X		X														
Pelvic examination																			
Physical examination					X														
Pap smear ^b																			
ENG concentration		X	X	X	X	X	X	X	X										

Source: Assessment schedules/Flow Charts as provided in Sections 4.4.1 of the individual study reports.

^aScreening (Assessment 1) not included in this overview; implant was inserted at Assessment 2.

^bPAP smear at the end of the trial (completion or premature discontinuation)

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Clinical Review
 Lesley-Anne Furlong
 NDA 21529, 000 AZ
 Implanon (etonogestrel implant)

	First year			Second year			Third year			Fourth year							
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Time in months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Assessment no.	2 ^a	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Study 34522																	
Status at implantation site		X	X	X	X	X	X	X	X	X							
Pregnancy status	X	X	X	X	X	X	X	X	X								
Blood pressure, body weight		X	X	X	X	X	X	X	X								
Pelvic examination					X				X								
Physical examination					X				X								
Pap smear ^b									X								
ENG concentration					X				X								
Study 34525^c																	
Status at implantation site		X	X	X	X	X											
Pregnancy status	X	X	X	X	X	X											
Breastfeeding status	X	X	X	X	X	X											
Blood pressure, body weight		X	X	X	X	X											
Pelvic examination					X				X								
Physical examination					X				X								
Pap smear ^b					X				X								
ENG concentration					X				X								

Source: Assessment schedules/Flow Charts as provided in Sections 4.4.1 of the individual study reports.

^aScreening (Assessment 1) not included in this overview; implant was inserted at Assessment 2.

^bPAP smear at the end of the trial (completion or premature discontinuation)

^cProtocol-defined study period 1 year. Subjects were allowed to continue for another 2 years, visiting the clinic every 6 months for monitoring continued efficacy and safety.

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Clinical Review
 Lesley-Anne Furlong
 NDA 21529, 000 AZ
 Implanon (etonogestrel implant)

	First year						Second year						Third year						Fourth year					
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48							
Time in months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48							
Assessment no.	2 ^a	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18							
Study E-1729																								
Status at implantation site		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Pregnancy status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Breastfeeding status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Blood pressure, body weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Pelvic examination																								
Physical examination									X															
Pap smear ^b																								

Source: Assessment schedules/Flow Charts as provided in Sections 4.4.1 of the individual study reports.

^aScreening (Assessment 1) not included in this overview; implant was inserted at Assessment 2.

^bPAP smear at the end of the trial (completion or premature discontinuation)

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6.1.4 Efficacy Findings

Disposition:

Table 10 shows the disposition of subjects by foreign and domestic sites and by year.

Table 10. Disposition of Subjects in the ISE Database

Number of Subjects	U.S.	Foreign	Total
Treated	330	596	926*
Completed two years	169 (51%)	459 (77%)	628 (68%)
Entered 3 rd year	0	275	275
Completed 3 years	0	251	251
Entered 4 th year	0	67	67
Completed 4 years	0	63	63

Source: Modified from Applicant's Integrated Summary of Efficacy, Table 3, p.31

*Three subjects had no postbaseline assessments and were not included in calculations of extent of exposure

Twenty-one subjects (2%) were lost to follow-up. Eleven subjects were lost to follow-up in the U.S. study and ten subjects were lost to follow-up in the non-U.S. studies.

Comment: Loss-to-follow-up contributes uncertainty to pregnancy rates, but, overall, the number of subjects who were lost to follow-up is low and provides support for quality of the studies.

Demographics:

The Applicant presented demographic characteristics for each study. A summary table appears below. For non-U.S. subjects, a range of means is presented.

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Table 11. Selected Demographic Characteristics of Subjects in U.S. Study and Non-U.S. Studies (All Subjects Treated Group)

	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

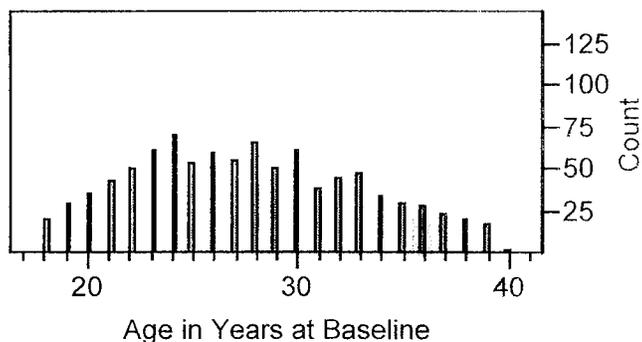
Source: ISE, Tables 5, 6, and 8.

Only 23 subjects had a BMI greater than 30 (2% of subjects). As noted earlier in the review, 28.4% of U.S. women between the ages of 20 and 39 years old have a BMI \geq 30.

Comment: Obese women were under-represented in the trials because of weight exclusions. Since the concentration of etonogestrel varies inversely with weight, it is possible that obese women may not experience the same effectiveness as lean women.

Figure 1 shows the distribution of subjects by age at baseline, for all 946 subjects in the ISS database.

Figure 1. Distribution of Ages at Baseline



Source: Created by reviewer from DEMOG dataset provided in ISS

Pregnancies:

Subjects were seen at least every three months. Pregnancy was to be assessed in all subjects who had no bleeding for at least 45 days. The method of assessment was left to the discretion of the investigator.

Comment: Although routine pregnancy testing would have been ideal, it would be difficult to miss a full-term pregnancy with a clinical assessment, and the studies were longer in duration than several full-term pregnancies. The lack of routine pregnancy testing introduces some uncertainty into pregnancy assessments at the end of each study since early pregnancies might be difficult to detect. However, the 63 women who completed four years of Implanon use without detectable pregnancies provide support for the continued effectiveness of Implanon through three years. Additionally, subjects either came to the study site or were contacted by phone three months after removal of Implanon to assess menses, pregnancy status, and use of contraceptives.

Condoms were permitted as protection against sexually transmitted disease, but the use of condoms was not assessed except in Study 34502. In Study 34502 (N=15), no one reported use of condoms.

Comment: Use of condoms may have impacted efficacy. Since the studies did not collect data about condom use, the number of cycles affected is unknown.

However, in a recent approval of a new formulation of depot medroxyprogesterone acetate, only 3% of cycles were removed from efficacy dataset because subjects used barrier methods. Based on my experience reviewing contraceptive trials and informal discussions with other reviewers in the Division, it seems unlikely that the use of condoms would have had a substantial impact on efficacy.

Use of other hormonal contraceptives was prohibited by protocol. Nonetheless, queries about concomitant medication revealed 35 subjects and 37 occasions of use of sex steroids. Of these

- six were confirmed concomitant use (ranging from one day to 41 days of hormonal therapy)
- 23 used hormones only pre-insertion or post-removal of Implanon
- four started hormonal contraception on the Implanon removal date
- four had incompletely recorded dates and therefore overlap with Implanon could not be refuted or confirmed

Comment: The small number of women who used other sex steroids while using Implanon and the generally short duration of use make it unlikely that use of concomitant sex steroids materially affected pregnancy rates. The short duration of hormone use suggests that therapy may have been used to treat bleeding problems.

Table 12 shows the total exposure by year in 28-day cycles for all women and for women who were 35 years old or younger at the start of the study.

Comment: Fertility declines with age, and therefore younger women provide the toughest test of contraceptive efficacy. Ninety percent of subjects were younger than 36 years old at the start of the study. Although ideally 100% of subjects would be in the younger group to assess efficacy, the older subjects provide important information about safety. Since this type of product is likely to appeal to older women of reproductive age who may have completed childbearing, it is important to have data from older subjects.

No one was older than 43 years old at the end of three years, and therefore it is likely that few women were menopausal at study termination.

Table 12. Total Exposure in Efficacy Database

	Year 1		Year 2		Year 3		Greater than 3	
	N	Cycles	N	Cycles	N	Cycles	N	Cycles
All Women	923	10,867	743	8,595	535	3,492	219	1,146
Women ≤ 35 years old at the start of study	833	9,817	671	7,780	484	3,115	195	1,066

Source: Modified by reviewer from ISE, Tables 12 and 14

According to the Applicant, the studies detected no on-treatment or pre-treatment pregnancies. Fifty post-treatment pregnancies were detected following removal of the implant. The estimated date of conception was within two weeks of removal of the implant for six subjects. Among those six subjects

- Four subjects discontinued the study because they were planning pregnancy
- One of the six discontinued the study because she had completed the study
- One subject discontinued treatment because she developed severe moodiness on treatment

Four of the six pregnancies come from studies that were included in the new ISE and therefore I examined the case report forms individually to assess adequacy of dating of pregnancies.

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Table 13. Subjects Who Conceived within Two Weeks of Implanon Removal

Study	Subject	Time on Implanon (Days)	Baseline Weight	Reason for Discontinuation	EDC in days after Implant removal	Reviewer's Notes on Reliability of Estimate of EDC
E-1729	0327	1082	43 kg	End of study	13	<i>Pregnancy dating was based only on last menstrual period (LMP))</i>
E-1729	0336	1077	59 kg	End of study, planning pregnancy	9	<i>Pregnancy dating was based only on LMP</i>
E-1729	0345	447	64 kg	Planning pregnancy	8	Documentation of pregnancy based on delivery of term infant
34522	0024	634	56 kg	Planning pregnancy	3	Based on LMP and delivery of term infant
069001	05014	172	69.5 kg	Severe moodiness	7	First trimester ultrasound
069001	10017	100	58.1 kg	Planning pregnancy	12	Ultrasound at 19 weeks and delivery at 40 weeks

Source: Modified from ISE, Table 13, page 51

Comment: Two of the six pregnancies had mediocre dating (LMP only), and could reasonably be questioned as on-treatment pregnancies. However, it is worth noting that one of the two questionable pregnancies occurred in a woman who was attempting to become pregnant. Dating for the remaining four pregnancies was reasonable, and consistent with post-treatment conception.

It is also worth noting that the pregnancies were not clustered in the final year of use as might be expected if they were related to waning levels of etonogestrel, but instead were evenly distributed such that two pregnancies occurred in each of the three years of use.

The Applicant's contention that these were post-treatment pregnancies is reasonable. Vagaries in dating pregnancies should misclassify on-treatment and post-treatment pregnancies with

equal likelihood on either side of study termination. The case report forms did not contain any evidence that the Applicant selected only dating parameters that would classify the pregnancies as post-treatment pregnancies.

Even if these pregnancies occurred during treatment, it does not affect the conclusion that Implanon is an effective birth control method. Based on historical data, the expected number of women to become pregnant in Year 1 if all 923 women were actively trying to conceive is 785. By Year 3 that number should be greater. Whether one assumes that zero or six pregnancies occurred, either number is considerably less than 785, and both numbers produce pregnancy rates that are better than or comparable to the rates seen with approved hormonal contraceptives.

Based on the rapid decline in etonogestrel levels when Implanon is removed and follicular development during Implanon use, pregnancies detected shortly after removal of Implanon support rapid return to fertility rather than method failure.

Table 14 shows annual Pearl indices with 95% confidence intervals for women who were 35 years old or younger at baseline, as calculated by the Applicant and confirmed by the FDA statistical reviewer. The confidence interval broadens each year. However, by the third year, the annual Pearl Index for Implanon still compares favorably to historical data from oral contraceptives.

Table 14. 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 (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)

Source: Table 3.1 of statistical review.

Not excluding cycles where any use of other birth control method (BCM) was reported

The Applicant also provided annual Pearl indices assuming all six pregnancies in the two week post-treatment period actually occurred on treatment. Table 15 shows this conservative analysis.

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Table 15. Pearl Indices if Six Pregnancies Occurring Within 14 Days of Implant Removal were On-Treatment: 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	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)

Source: Table 3.2 of statistical review.
 Not excluding cycles where any use of other birth control method (BCM) was reported

Comment: Pearl rates calculated by including all six pregnancies that occurred within 14 days of Implanon removal also compare favorably to historical data from oral contraceptives.

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.

Based on limited data from early dose-finding studies, pregnancies were detected with prototype implants that had a mean in vitro release rate of etonogestrel that was less than 16 µg/day. At three years, Implanon has a mean in vitro release rate of etonogestrel that is between 25 and 30 µg/day.

Limited data with Implanon prototypes suggest that pregnancies can occur at mean serum levels of etonogestrel that are less than or equal to 25 pg/ml. However, mean serum levels of etonogestrel are greater than 150 pg/ml at three years of use.

Comment: Limited PK data suggest that Implanon remains effective through three years.

Postmarketing 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, _____ implants have been sold. Pregnancy rate per 100 sold implants is less than or equal to 0.05. (This number includes all pregnancies, both confirmed and unconfirmed.)

b(4)

Comment: A high Pearl Index would be worrisome, but a low Pearl Index has little utility because the extent of under-reporting is not known.

Postmarketing, the single most frequent reason that has been identified as a cause of pregnancy in the post-marketing arena is “missing implant” (N=).

Comment: Pregnancy caused by “missing implant” is largely avoidable by the simple expedient of confirming the presence of Implanon by palpation. The importance of checking that Implanon is in place should be emphasized during training. A placement check should be done by both healthcare provider and subject.

Postmarketing reports have not suggested a substantial increase in failure rates by duration of use. Using literature-based estimates of yearly rates of continuation of Implanon, and using data on whether a woman conceived in the first, second, or third year of use, Organon has calculated that there may be a slightly higher risk of failure with consecutive years. (The relative risk of failure in 1st, 2nd, and 3rd years are 1, 1.25, and 1.27, respectively, based on 70, 78, and 74 pregnancies reported in 1st, 2nd, and 3rd years, respectively.)

Similarly, postmarketing reports have not suggested a substantial increase in failure rates with increasing weight. By comparing the weights of women who have confirmed contraceptive failures with the weights of all women in the postmarketing database for Implanon, Organon detected a tendency for a slight increased risk of failure with increasing weight. However, a majority of heavy women with contraceptive failures in the database also took interacting drugs, making it difficult to draw any conclusions about the effect of weight alone. Furthermore, Organon’s analysis of the percentage of pregnancies by weight and duration of use did not reveal a pattern of increasing pregnancies with increasing weight and duration of use.

Postmarketing, among 61 of pregnancies that Organon has been able to classify as contraceptive method failures, subjects concomitantly used a hepatic enzyme-inducing drug (usually an anticonvulsant).

Comment: It is important but not surprising that 57 of pregnancies classified as contraceptive failures have occurred in subjects using drugs that induce hepatic enzymes. The ability of CYP inducers to dramatically affect serum levels of etonogestrel was shown by Subject 211 in Study 34502, as summarized in Section 5.2. Like Norplant, and unlike oral contraceptives, Implanon produces serum levels of progestin that are not an order of magnitude or more above the threshold of ovulation suppression. Therefore a drug that causes a several-fold decrease in concentration of progestin may make Implanon less effective. This has been clearly shown for the related implant, Norplant.

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).

Comment: An increased proportion of ectopic pregnancies to total pregnancies is seen when other progestin-only methods of contraception fail. Postmarketing reports suggest that Implanon is not an exception.

6.1.6 Efficacy Conclusions

The studies support the effectiveness of Implanon for prevention of pregnancy for up to three years of continuous use. For three years, the Pearl rates for pregnancy were less than or equal to the Pearl rates usually seen in trials of oral contraceptives. The population studied included generally healthy women who were not obese.

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.

However, it would be useful to have data regarding the effectiveness of Implanon in obese women so that the labeling can provide 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.

The effectiveness of Implanon is more likely than the effectiveness of oral contraceptives to decline in the presence of drugs that induce liver enzymes. Like the levonorgestrel implant, and unlike oral contraceptives, Implanon produces serum levels of progestin that are less than an order of magnitude above the threshold of ovulation suppression. Therefore a drug that induces liver enzymes and causes a several-fold decrease in concentration of Implanon's progestin may make Implanon less effective. This has been clearly shown for the levonorgestrel implant, and is supported by postmarketing data for Implanon. In addition, a single patient who inadvertently violated protocol and took rifampin while using Implanon had a 3.4-fold decline in her serum etonogestrel levels.

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

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

Loss to follow-up is a problem for most clinical trials, and the loss to follow-up in the Implanon studies is not remarkable. Ideally the use of other contraceptives should be recorded and the cycles during which other contraceptives were used should be removed from calculation of pregnancy rates. However, based on our experience with other contraceptive 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 encompasses enough time to allow for ready diagnosis of pregnancy on clinical grounds.

7 Integrated Review of Safety

7.1 Methods and Findings

For all studies except Study 34502, adverse events (AEs) were collected by general questioning. In Study 34502, AEs were collected from a follow-up form asking if there had been any complaint or hospital admission since the last assessment. AEs were also detected by evaluating concomitant medication forms. The WHO dictionary for adverse events was the coding dictionary.

The entire data set for the ISS included 942 women, 24,679 cycles, and 1,892 women-years of exposure.

The Applicant excluded bleeding events from the analysis of AEs, and analyzed bleeding events separately in the Integrated Summary of Efficacy. The rationale for this approach was not provided. The review will evaluate bleeding problems as part of the safety section.

7.1.1 Deaths

No deaths were detected.

7.1.2 Other Serious Adverse Events

Fifty-six of 942 subjects had a total of 77 serious adverse events (SAEs). Narrative summaries for all SAEs were provided in the original NDA which was reviewed by a different primary reviewer. Table 16 presents each SAE using mainly investigator terms.

Table 16. Serious Adverse Events Detected in All Studies

Study	Subject	Event
069001	01014	Congenital heart disease
	01022	Ruptured ovarian cyst, appendectomy
	02004	R breast malignancy
	02010	Gallbladder surgery
	06019	Cholelithiasis
	07014	Fractured right ankle
	09003	Bronchospastic disorder
	11003	Cholelithiasis diagnosed
	12002	Asthma attack
	15002	Acute exacerbation of depression
34502	0211	Tuberculosis
	0217	Ovarian cyst
34503	0212	Acute hemorrhagic fever
34507	00089	Appendicitis
	00124	Appendicitis
	00130	Basalioma in the face

Study	Subject	Event
	00131	Gall surgery (sic)
	00114	Sternal fracture, slipped on ice
	00116	Fibroadenoma of breast
	00449	Tonsillitis
	00508	Glomerulonephritis suspicion
	00519	Cholelithiasis
	0524	Appendicitis
	0533	Headache
	0538	Suicide attempt
	00544	Stomach ache
	00549	Condyloma vulva
	00555	Plastica portio uterine
	00558	Phlebectomia (surgery) for varicose veins
	00568	Subileus
	00682	Transient ischemic attack
	00696	Cervical smear result III, Bartholin's abscess
	00705	Discopathia lumbalis
	00522	Surgery nasal septum
	00596	Hyperthyroidism
	00610	Cholelithiasis
	00643	Obstruction of esophagus
	00648	Cerebral hemorrhage, confusion, severe headache, vomiting
	00652	Cholecystitis
	00660	Cholecystectomy
	00679	Acute gastritis
	00683	Arthroscopy for meniscus
34511	00035	Severe headaches, fever
	00044	Dermoid cyst
	00067	Asthma
34522	00018	Vaginal hysterectomy (prolapse)
	00046	Dermoid tumor left ovary
	00049	Pelvic pain, vomiting, fever, appendectomy
1729	00338	Backache due to an operation done in the past, slipped disc
	00315	Ductal carcinoma right breast
	00354	Allergic rash
	00356	Malignancy of breast

Source: ISS, modified by reviewer from information in Tables 10, 11, and 12

Most SAEs seem unlikely to be related to Implanon. Those that may have some relationship to 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

It is difficult to interpret these numbers in the absence of concomitant controls. To get an idea about the expected number of gall bladder problems in this age group, I checked the 2003 data from the U.S. National Hospital Discharge Summary (NHDS). The rates of cholecystectomy in

users of Implanon are similar to the rate of cholecystectomy in the NHDS. The rate of cholecystectomy in American men and women aged 15 to 44, as calculated by this survey, was 10.8 per 10,000 people in one year. The rate is likely higher for women alone as gallbladder disease affects four women to every one man. The rate in the Implanon ISS was 3 in 1,892 women-years, or 15 per 10,000 women-years.

Comment: Although the use of historical controls is scientifically shaky, in the absence of in-study controls, it is one way to try to put the incidence of certain SAEs in perspective.

Implanon may be similar to Norplant in causing a small increase in the risk of gallbladder disease. The relative risk of gallbladder disease in women using Norplant⁹ implants is reported to be 1.5, which is consistent with the findings for Implanon in the ISS. Pregnancy is also a risk factor for gallbladder disease.

Whether diagnosis of three cases of breast cancer is expected in this population is unclear. Regular medical care in a study may enhance detection. According to the National Cancer Institute, one out of 229 women aged 30 to 39 will develop breast cancer,¹⁰ which is an incidence of 1 in 2,290 women-years over ten years. While it is reassuring that there is not an order of magnitude difference in breast cancer rates in Implanon treated subjects, smaller increases cannot be ruled out.

Although I was unable to find data about the incidence of ovarian cysts or depression for women in the age range of women using Implanon, four women with ovarian cysts and two women with depression among 942 women does not seem excessive based on my clinical experience.

Of note, the data presented in the ISS contained no venous thromboembolic events, a risk 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.

Comment: It is difficult to interpret a single DVT. Current medical opinion recognizes estrogen as a thrombogenic hormone, but opinion remains divided about the role of progestins in thrombotic events. Nonetheless, the timing of the DVT is consistent with what is seen with combination oral contraceptives, and a gross estimate of the rate of DVT per 10,000 women-years is also consistent with what is seen with combination oral contraceptives. (This is one deep vein thrombosis [DVT] during 2,253 women-years of Implanon therapy because the safety update added 361 women-years of data from clinical studies to the 1,892 women years from the ISS. One per 2,253 women-years is roughly 4.3 per 10,000 women-years, which is not distinguishable from the incidence of DVTs seen in FDA-reviewed clinical trials of combination oral contraceptives [5.2 per 10,000 women-years]).

⁹ Sivin I. Risks and Benefits, Advantages and disadvantages of levonorgestrel-releasing contraceptive implants. Drug Safety 2003;26:303-335

¹⁰ National Cancer Institute. <http://www.cancer.gov/cancertopics/factsheet/Detection/probability-breast-cancer>

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Thirty-five percent of subjects discontinued before completing studies. The Applicant did not fully integrate the reasons for dropping out because pre-defined reasons for discontinuation on case report forms in the U.S. study were different from pre-defined reasons for discontinuation in non-U.S. studies.

Table 17 shows the profile of dropouts from U.S. Study 069001

Table 17. Subjects Who Discontinued by Reason (U.S. Study 069001)

Primary reason for discontinuation	U.S. Study 069001 Implanon™ (N=330)	
		(%)
Protocol violation	4	(1.2)
Adverse experience	119	(36.1)
• Bleeding irregularity as primary reason	43	(13.0)
• Other adverse experience as primary reason	76	(23.0)
Intercurrent illness	1	(0.3)
Unwillingness to continue	8	(2.4)
Other reasons(including lost to follow-up)	29	(8.8)
Total	161	(48.8)

Source: ISS, p.33

Table 18 shows reasons for discontinuation in non-U.S. studies.

Table 18. Subjects Who Discontinued by Reason in non-U.S. Studies

Primary reason for discontinuation	Non-U.S. Studies (N=612)	
	n	(%)
Amenorrhea	3	(0.5)
Bleeding irregularities	59	(9.6)
Adverse experience	52	(8.5)
Other reasons	45	(7.4)
Lost to follow-up	10	(1.6)
Total	169	(27.6)

Source: ISS, p. 34

Overall, the discontinuation rate was less in non-U.S. studies compared with the U.S. study (27.6% versus 48.8%), although the discontinuation rates for bleeding irregularities (including

amenorrhea) was similar (10.1% versus 13%). The main difference is in discontinuation rates for “other adverse events” (8.5% versus 23.3%). Among the other adverse events, the biggest difference in discontinuations between U.S. and non-U.S. subjects fell into the system-organ class “psychiatric disorders.” A total of 9.4% of U.S. women discontinued for psychiatric reasons such as emotional lability or depression, whereas only 0.8% of non-U.S. subjects discontinued for psychiatric conditions.

Comment: It is not apparent why U.S. women were more likely to drop out (primarily for psychiatric reasons) than non-U.S. women. The differences may be cultural.

When various bleeding abnormalities are combined, dropouts for vaginal bleeding abnormalities become the most common reason for discontinuation. Although the dropout pattern suggests that irregular bleeding was a major nuisance for many women, investigators detected no hospitalizations or surgery related to bleeding.

To explore what happened to bleeding over time, the Applicant analyzed the bleeding data by 90-day reference periods. The data were further subgrouped into women who completed two years of therapy and women who discontinued due to bleeding irregularities other than amenorrhea. As expected, women who discontinued therapy due to bleeding irregularities had a greater number of bleeding/spotting days. After the first reference period, no time trends were identified. The first reference period had the greatest number of days of bleeding/spotting. This was expected because Implanon was placed during a menstrual period. See Section 7.1.7.5.2 for further discussion of bleeding data.

7.1.3.2 Adverse events associated with dropouts

Table 19 provides a simple summary of the main adverse events responsible for study termination. It shows adverse events leading to study termination detected in more than one percent of subjects.

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On Original

Table 19. Adverse Events Leading to Study Termination in 1% or More of Subjects by Preferred Term (All-Subjects-Treated Group)

Preferred term	U.S. N=330 %	Non-U.S. N=612 %	All Studies N=942 %
Bleeding irregularities*	13	10.1	11
Emotional Lability	6.1	0.3	2.3
Weight Increase	3.3	1.8	2.3
Headache	1.2	1.8	1.6
Acne	1.5	1.1	1.3
Depression	2.4	0.2	1.0

Source: Created by reviewer from Tables 5, 6 and 13, ISS.

*Separately coded into protocol-defined categories including “frequent”, “heavy”, “prolonged”, “spotting”, “amenorrhea”, and “other”.

Comment: Overall, the profile of dropouts is similar to what is expected for a progestin-only contraceptive. For example, 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. In an FDA review of a levonorgestrel two-rod implant, the most common medical reasons for termination over five years were headache (4.2%), weight increase (3.4%), acne (1.0%) and depression (1.0%).

Table 20 shows in more detail the adverse events causing dropouts. The Applicant states that “The most common system-organ class for which adverse experiences resulting discontinuation were reported was Psychiatric Disorders.” However, the Applicant analyzed bleeding irregularities separately. If the 102 subjects (10.8%) who dropped out for bleeding irregularities were added to Table 20, Reproductive Disorders would be the most common system-organ class for discontinuations.

Table 20. Number (%) of Subjects Who Discontinued due to Adverse Experiences by WHO System-organ Class and Preferred Term (All-Subjects-Treated Group) (Excludes AEs related to vaginal bleeding irregularities)

WHO system-organ class	WHO preferred term	Implanon					
		U.S. (n=330)		Non-U.S. (n=612)		All studies (n=942)	
		N	(%)	N	(%)	N	(%)
Psychiatric disorders	Body system total	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
	Anorexia	0	0	1	0.2	1	0.1
	Appetite increased	0	0	1	0.2	1	0.1
	Somnolence	0	0	1	0.2	1	0.1

WHO system-organ class	WHO preferred term	Implanon					
		U.S. (n=330)		Non-U.S. (n=612)		All studies (n=942)	
		N	(%)	N	(%)	N	(%)
Metabolic and nutritional disorders	Body system total	11	3.3	14	2.3	25	2.7
	Weight increase	11	3.3	11	1.8	22	2.3
	Weight decrease	0	0	3	0.5	3	0.3
Skin and appendages disorders	Body system total	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
	Hypertrichosis	0	0	1	0.2	1	0.1
	Urticaria	0	0	1	0.2	1	0.1
Central and peripheral nervous system disorders	Body system total	6	1.8	14	2.3	20	2.1
	Headache	4	1.2	11	1.8	15	1.6
	Hypoesthesia	1	0.3	0	0	1	0.1
	Migraine	1	0.3	0	0	1	0.1
	Paraesthesia	1	0.3	0	0	1	0.1
	Dizziness	0	0	3	0.5	3	0.3
Reproductive disorders, female	Body system total	10	3.0	4	0.7	14	1.5
	Sexual function abnormal, female	4	1.2	0	0	4	0.4
	Dysmenorrhoea	2	0.6	0	0	2	0.2
	Premenstrual tension	2	0.6	0	0	2	0.2
	Cervical dysplasia	1	0.3	0	0	1	0.1
	Dyspareunia	1	0.3	0	0	1	0.1
	Breast pain female	0	0	3	0.5	3	0.3
	Uterovaginal prolapse	0	0	1	0.2	1	0.1
Body as a whole - general disorders	Body system total	5	1.5	3	0.5	8	0.8
	Fatigue	2	0.6	1	0.2	3	0.3
	Hot flushes	1	0.3	0	0	1	0.1
	Malaise	1	0.3	0	0	1	0.1
	Pain	1	0.3	0	0	1	0.1
	Infection tbc	0	0	1	0.2	1	0.1
	Oedema	0	0	1	0.2	1	0.1
Application site disorders	Body system total	3	0.9	1	0.2	4	0.4
	Injection site pain	3	0.9	0	0	3	0.3
	Injection site reaction	0	0	1	0.2	1	0.1
Neoplasms	Body system total	2	0.6	1	0.2	3	0.3
	Breast neoplasm malignant female	1	0.3	1*	0.2	2*	0.2
	Ovarian cyst	1	0.3	0	0	1	0.1
Gastro-intestinal system disorders	Body system total	1	0.3	0	0	1	0.1
	Gastroesophageal reflux	1	0.3	0	0	1	0.1
Vision disorders	Body system total	1	0.3	0	0	1	0.1
	Vision abnormal	1	0.3	0	0	1	0.1
Secondary terms	Body system total	1	0.3	0	0	1	0.1
	Cervical smear test pap ii	1	0.3	0	0	1	0.1
Musculo-skeletal system disorders	Body system total	0	0	1	0.2	1	0.1
	Arthritis	0	0	1	0.2	1	0.1
Respiratory system disorders	Body system total	0	0	1	0.2	1	0.1
	Pleural effusion	0	0	1	0.2	1	0.1
	Pleurisy	0	0	1	0.2	1	0.1
Vascular (extracardiac) disorders	Body system total	0	0	2	0.3	2	0.2
	Cerebral haemorrhage	0	0	1	0.2	1	0.1
	Cerebrovascular disorder	0	0	1	0.2	1	0.1

WHO system-organ class	WHO preferred term	Implanon					
		U.S. (n=330)		Non-U.S. (n=612)		All studies (n=942)	
		N	(%)	N	(%)	N	(%)
Cardiovascular disorders, general	Body system total	0	0	1	0.2	1	0.1
	Hypertension **	0	0	1	0.2	1	0.1
Cardiovascular disorders, general	Body system total	0	0	2	0.3	2	0.2
	Hypertension	0	0	2	0.3	2	0.2
Resistance mechanism disorders	Body system total	0	0	1	0.2	1	0.1
	Herpes simplex	0	0	1	0.2	1	0.1

Source: Table 13, ISS, p. 60

*As noted in the text, there were three breast malignancies, not two (one in a U.S. site and two in a non-U.S. site). The number in this table is incorrect. In the AE dataset, one of the breast cancer cases did not have a WHO coding and only appeared under investigator terms. A search of the dataset for similar miscoded events did not reveal any further clinically significant errors.

**Hypertension appears twice on this table without explanation. It appears to be an error in combining data from different sources. Based on the AE dataset, the correct number of withdrawals due to hypertension is three (all from non-U.S. sites).

7.1.3.3 Other significant adverse events

None detected.

7.1.4 Other Search Strategies

No special algorithms were constructed to look for particular toxicities as none were expected.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Subjects recorded vaginal bleeding events on daily diary cards. At clinic visits every three months, subjects were questioned about the use of concomitant medications and occurrence of adverse events from the time of the last visit. Also, the implant site was inspected every three months.

About three months after discontinuation or completion of a study, subjects had a post-treatment evaluation either as a visit or a telephone contact. The contact included queries about menses, use of contraceptive methods and the occurrence of adverse events.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

AEs were coded as dictionary terms using the World Health Organization (WHO) adverse reactions dictionary, one of several standard dictionaries. Investigator terms were provided in the case report tabulations (CRTs). To create incidence tables, subjects were counted only once for a given preferred term even if the subject reported the same AE more than once.

7.1.5.3 Incidence of common adverse events

Adverse events that were detected in more than 5% of subjects appear in Table 21.

Table 21. Adverse Events that Occurred in More than 5% of Subjects

WHO Preferred Term	n	%
Headache	235	24.9
Vaginitis	137	14.5
Weight increase	129	13.7
Acne	127	13.5
Breast pain female	121	12.8
Upper Respiratory Tract Infection	119	12.6
Abdominal pain	103	10.9
Pharyngitis	99	10.5
Leukorrhoea	90	9.6
Influenza-like symptoms	72	7.6
Dizziness	68	7.2
Dysmenorrhoea	68	7.2
Back pain	64	6.8
Emotional lability	61	6.5
Nausea	60	6.4
Pain	53	5.6
Nervousness	53	5.6
Sinusitis	53	5.6
Depression	52	5.5
Injection site pain	49	5.2

Source: Modified by reviewer from Table A.1.a, response to FDA information request. Submitted by Applicant on 6Apr2006.

Comment: It is difficult to estimate the impact of etonogestrel on the incidence of AEs because all events except injection site pain are expected in this population regardless of exposure to Implanon. Events that have been associated with progestin in other studies include headache, weight increase, acne, breast pain, breast cancer, emotional lability, and abdominal pain. Some of the abdominal pain may be related to the formation of enlarged or persistent ovarian follicles, an event that has been described for other low-dose progestin products.

7.1.5.4 Common adverse event tables

Please see previous section.

7.1.5.5 Identifying common and drug-related adverse events

Although the numbers are small, the open-label comparative study with a nonhormonal medicated IUD suggests which AEs may be etonogestrel-related.

Table 22. Adverse Events Occurring in >5% of Subjects Using Implanon (All Subjects Treated Group) in (Study 34522)

WHO Preferred Term	Implanon N=46 %	IUD* N=30 %
Headache	41	30
Upper respiratory infection	22	7
Leucorrhoea	20	20
Abdominal pain	17	20
Vaginitis	13	13
Sinusitis	13	13
Breast pain female	13	10
Acne	11	0
Pharyngitis	9	10
Back pain	9	7
Emotional lability	9	0
Tooth ache	9	0
Influenza-like symptoms	7	10
Fatigue	7	0
Weight increase	7	0
Vaginal discomfort	7	0
Bronchitis	7	0
Cervical smear test Pap II	7	0
Depression	7	0
Nervousness	0	10
Tooth disorder	0	7
Ovarian cyst	0	2
Inflicted injury	0	7
Dysuria	0	7

*Investigator's choice of a nonhormonal medicated IUD

Source: Simplified by reviewer from Table A.3.a, response to FDA information request, submitted by Applicant on 6 Apr 2006.

Comment: The numbers are small and therefore limit any conclusions. Also, the study was open-labeled and the difference in incidence of AEs may reflect the expectations of the subjects and the investigators. However, as expected based on other progestin products, emotional complaints, headaches, weight increase, and acne appear in a higher percentage of subjects using Implanon.

7.1.5.6 Additional analyses and explorations

The Applicant provided exploratory subgroup analyses for age and weight. The incidence of most common AEs did not appear to change with age. The incidence of acne tended to decrease with age.

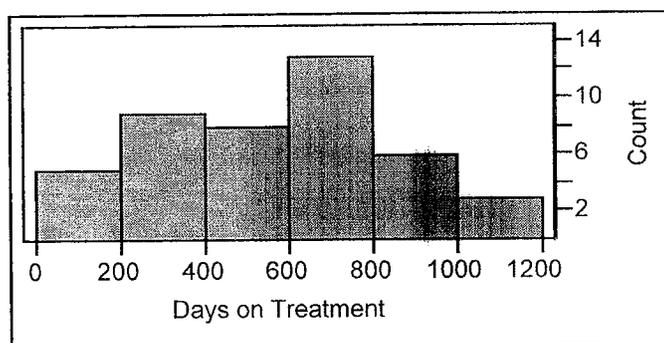
The incidence of the most common AEs did not appear to change with weight except for complaints of weight gain. The studies detected a higher incidence of reports of "weight increase" among women who were heavier at baseline.

The Applicant did not provide an analysis based on racial subgroups because only one study collected demographic data.

Comment: I would not expect any important findings from a racial subgroup analysis of AEs for a progestin product. As noted elsewhere in the review, the difference in frequency of reporting of AEs seems more likely related to cultural issues or perhaps differences in study design.

Because follicular cysts of the ovary have been linked to some progestin-only contraceptives, I explored the Applicant's AE dataset for ovarian cysts by preferred term. Thirty-four (3.6%) subjects had ovarian cysts detected as an adverse event. The number of ovarian cysts seems to increase with time on treatment in the first two to three years (Figure 2), perhaps reflecting increased follicular activity as etonogestrel levels waned. The decline after three years likely reflects the large drop in numbers of subjects who used Implanon beyond three years.

Figure 2. Estimated Start Date of Ovarian Cysts



Source: Created by reviewer from Applicant's AE dataset

Because insertion site AEs appeared under several preferred terms (Table 21 and Table 23), I explored the AE dataset in the Applicant's ISS for the investigator term "injection site". A total of 92 subjects with insertion site complaints were detected in this manner. A scan of investigator terms suggested that most complaints were minor. However, eight subjects had insertion site problems listed as a reason for terminating the study. Among these eight subjects, complaints included pain, burning, itching, sensation of loss of strength in arm, and one abscess/inflammation.

Comment: Insertion site complaints were common, but few were serious enough to result in study termination.

7.1.6 Less Common Adverse Events

Adverse events reported by $\geq 1\%$ and $< 5\%$ of subjects are shown in Table 23.

Comment: The granularity of the coding dictionary leads to related events having different preferred terms and therefore appearing to occur less frequently than they actually do. For example, "urinary tract infection" (4.5%) and cystitis (1.3%) could reasonably be combined.

Table 23. Adverse Events Detected in $\geq 1\%$ * of Subjects and $< 5\%$ * of Subjects (All-Subjects-Treated Group)

WHO Preferred term	US study[a] (N = 330)		Non-US studies[b] (N = 612)		All studies (N = 942)	
	n	%	n	%	n	%
INJECTION SITE REACTION	10	3.0	36	5.9	46	4.9
FLATULENCE	17	5.2	27	4.4	44	4.7
FATIGUE	26	7.9	16	2.6	42	4.5
URINARY TRACT INFECTION	33	10.0	9	1.5	42	4.5
ALLERGY	20	6.1	20	3.3	40	4.2
WEIGHT DECREASE	2	0.6	29	4.7	31	3.3
BRONCHITIS	10	3.0	21	3.4	31	3.3
FEVER	9	2.7	21	3.4	30	3.2
ALOPECIA	10	3.0	20	3.3	30	3.2
DYSURIA	4	1.2	26	4.2	30	3.2
PRURITUS GENITAL	5	1.5	23	3.8	28	3.0
OVARIAN CYST	5	1.5	22	3.6	27	2.9
CERVICITIS	2	0.6	25	4.1	27	2.9
DIARRHOEA	8	2.4	17	2.8	25	2.7
LIBIDO DECREASED			25	4.1	25	2.7
RHINITIS	10	3.0	15	2.5	25	2.7
CERVICAL SMEAR TEST PAP II	22	6.7	3	0.5	25	2.7
BREAST FIBROADENOSIS	12	3.6	10	1.6	22	2.3
ACCIDENTAL INJURY	21	6.4	0	0	21	2.2
RASH	12	3.6	9	1.5	21	2.2
HOT FLUSHES	4	1.2	15	2.5	19	2.0
ANXIETY	8	2.4	10	1.6	18	1.9
VOMITING	3	0.9	14	2.3	17	1.8
APPETITE INCREASED	8	2.4	9	1.5	17	1.8
SEXUAL FUNCTION ABNORMAL, FEMALE	17	5.2	0	0	17	1.8
OEDEMA	3	0.9	13	2.1	16	1.7
TOOTH ACHE	2	0.6	14	2.3	16	1.7
ARTHRALGIA	16	4.8	0	0	16	1.7
PELVIC CRAMPING	16	4.8	0	0	16	1.7
CONSTIPATION	2	0.6	13	2.1	15	1.6
VAGINAL DISCOMFORT	6	1.8	9	1.5	15	1.6
OTITIS MEDIA	12	3.6	3	0.5	15	1.6
MIGRAINE	7	2.1	7	1.1	14	1.5
GASTROENTERITIS	6	1.8	8	1.3	14	1.5
MYALGIA	6	1.8	8	1.3	14	1.5
INSOMNIA	5	1.5	9	1.5	14	1.5
SKIN DISORDER	6	1.8	8	1.3	14	1.5

WHO Preferred term	US study[a] (N = 330)		Non-US studies[b] (N = 612)		All studies (N = 942)	
	n	%	n	%	n	%
HYPERTENSION	1	0.3	12	2.0	13	1.4
SKELETAL PAIN	1	0.3	12	2.0	13	1.4
HYPOAESTHESIA	5	1.5	7	1.1	12	1.3
TOOTH DISORDER	3	0.9	9	1.5	12	1.3
SOMNOLENCE	7	2.1	5	0.8	12	1.3
CYSTITIS	2	0.6	10	1.6	12	1.3
ALLERGIC REACTION	4	1.2	7	1.1	11	1.2
DYSPEPSIA	7	2.1	4	0.7	11	1.2
BONE DISORDER	0	0	11	1.8	11	1.2
LACTATION NONPUERPERAL	0	0	11	1.8	11	1.2
INFECTION VIRAL	9	2.7	2	0.3	11	1.2
PRURITUS	2	0.6	9	1.5	11	1.2
ASTHENIA	0	0	10	1.6	10	1.1
DENTAL PROCEDURE NOS	10	3.0	0	0	10	1.1
CERVICAL SMEAR TEST POSITIVE	9	2.7	1	0.2	10	1.1
BREAST ENLARGEMENT	3	0.9	7	1.1	10	1.1
ASTHMA	7	2.1	3	0.5	10	1.1
DERMATITIS	3	0.9	7	1.1	10	1.1

* $\geq 1\%$ and $< 5\%$ were applied to the "All Studies" column

Source: Simplified by reviewer from Table B.1.a, response to FDA information request, submitted by Applicant on 6Apr2006.

Comment: I explored the preferred term "Bone Disorder" in the AE dataset provided by the Applicant because bone density is an issue with another progestin-only product. The investigator terms for the AEs listed as "bone disorder" included eight fractures, a slipped disc, a lesion of meniscus, and three twisted joints. There were no listings reporting bone density issues.

7.1.7 Laboratory Findings

The Applicant did not provide any new analyses of laboratory data in this resubmission, stating that all laboratory data were presented and analyzed in the previous two submissions. The studies were reviewed by the clinical reviewer and the biopharmaceutical reviewer in the first and second review cycles, and will not be re-reviewed here. The previous clinical reviewer concluded that laboratory results, including results related to hematology, chemistry, liver function, hemostasis, and lipid metabolism, raised no safety concerns.

7.1.7.1 Overview of laboratory testing in the development program

Laboratory data were reviewed in previous review cycles. The Applicant did not provide any new data for review.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Reviewed in previous review cycles.

7.1.7.3 Standard analyses and explorations of laboratory data

Reviewed in previous review cycles.

7.1.7.4 Additional analyses and explorations

Reviewed in previous review cycles.

7.1.7.5 Special assessments

7.1.7.5.1 Insertion and removal

Investigators recorded insertion and removal times as shown in Table 24. (The case report form asked for the time (in minutes) required for insertion or removal, without specifying upper or lower limits, and without specifying whether to include time spent setting up or anesthetizing the skin.)

Table 24. Summary Statistics for Implanon Insertion and Removal Times (All-Subjects-Treated Group)

Parameter	Time in minutes
Insertion (n=927)	
Mean+SD	1.3+1.9
Median	0.5
Max	5
Removal (n=875)	
Mean+SD	3.8+4.9
Median	2
Max	60

Source: Modified by reviewer from ISS, Table 30, p. 95

Comment: As expected from experience with other implants, removal takes longer than insertion and the maximum (60-minute) removal time indicates that removal may be difficult.

Complications were reported by investigators with 1% of implant insertions, and were

- Implant stayed in needle
- Slight bleeding and compression
- Hematoma
- Difficult insertion

Complications were reported by investigators with 1.7% of removals and included

- Broken implant
- Difficulty finding the implant
- Adherent implants

Postmarketing, there have been reports of implants that have not been retrievable because the implants were non-palpable and could not be localized with MRI or ultrasound. The submission contains a report on postmarketing insertion/removal problems covering the period 28-Aug-1998 to 1-Mar-2006. The report was prepared at the request of the Dutch Medicine Evaluation Board, the responsible authority for all European Member States concerning Implanon. During the time period, Organon sold Implanon implants. There were reports of events related to insertion or removal (IRRE), for an incidence of 58 IRRE reports per 10,000 implants sold.

b(4)

There have been reports of events where Implanon was present based on etonogestrel levels, but could not be localized. At the time of the report, postmarketing reports had identified subjects who had a non-retrievable implant, which is one irretrievable implant per 10,000 implants sold. The extent of under-reporting is unknown.

Comment: Implanon as currently formulated is not radio-opaque, and this is a design flaw. It may be difficult to locate a non-palpable implant, and an implant that cannot be removed is a serious problem for the affected woman. Every other contraceptive implant (IUD and subdermal implant) currently approved in the United States contains barium sulfate to make it radio-opaque. Ultrasound or MRI may fail to locate an Implanon that has migrated to a distant site. For example, an intravascular insertion into a large vein could lead to an Implanon in the pulmonary vascular tree. This might be quite difficult to find or remove without X-ray guidance.

A lost implant may result in infertility or continued adverse events if etonogestrel levels remain elevated. If etonogestrel levels wane, a lost implant may result in ectopic pregnancy. Although some of these problems would not qualify for the regulatory definition of serious, these are serious concerns to the affected woman.

The Applicant has an ongoing bioavailability study comparing a new, radio-opaque version of Implanon to the current formulation. If bioequivalence is demonstrated, this product should be used instead of the current formulation.

7.1.7.5.2 Bleeding patterns

As bleeding problems were the most common reason for women dropping out of studies early, it is clear that many women viewed bleeding problems as significant.

The submission contains bleeding data from 926 subjects. Data were recorded on daily diary cards. Regular menses with a mean length of 24 to 35 days was an inclusion criterion. Bleeding was analyzed in 90-day reference periods. A "bleeding day" was a day when a woman had

vaginal bleeding and required more than one sanitary product, and a “spotting day” was a day when a woman had vaginal bleeding and required one or no sanitary products.

The Applicant defined bleeding patterns as follows

- Amenorrhea was no bleeding or spotting for an entire 90-day reference period
- Prolonged bleeding was any bleeding-spotting episode lasting more than 14 days
- Frequent bleeding was more than five bleeding-spotting episodes in a 90-day reference period
- Infrequent bleeding was less than three bleeding-spotting episodes in a 90-day reference period
- Excessive bleeding was frequent or prolonged bleeding

The Applicant provided analyses for three groups

- Women who completed the studies
- Women who discontinued the studies for bleeding problems
- All subjects who provided data.

Overall, numbers of bleeding and spotting days showed little change after the first reference period for any of the three groups. As shown in Table 25, the most common pattern for completers was amenorrhea (22.2%) while the most common pattern for discontinuers was prolonged bleeding (61.3%).

Table 25. Bleeding Pattern Indices for Subjects Who Completed 2 Years, Discontinued Due to Bleeding Irregularities Other than Amenorrhea, and Total Group

Bleeding pattern indices	Implanon™					
	Completers		Discontinuers due to bleeding irregularities		Total (Completers + Discontinuers for any cause)	
	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

*RP denotes a 90-day reference period.

Source: ISE, Table 21, page 65

After the first reference period, the mean number of bleeding-spotting days for the entire group ranged from 17 to 20 days in a 90-day reference period. The first reference period had more

bleeding-spotting days, possibly because the implant was generally inserted during a menstrual flow. Otherwise, there were no apparent trends over time. Table 26 shows these data.

Table 26. Bleeding Parameters for Subjects Who Completed 2 Years, Discontinued Due to Bleeding Irregularities Other than Amenorrhea, and Total Group

Parameters	RP*	Implanon™											
		Completers				Discontinuers due to bleeding irregularities				Total (Completers + Discontinuers for any cause)			
		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	22.85	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
Number of bleeding-days	1	555	7.64	10.00	4.00	78	16.85	13.79	12.00	802	8.44	10.36	5.00
	2	566	6.14	9.17	2.00	50	17.54	15.23	16.00	745	6.72	9.86	3.00
	3	559	6.18	9.01	3.00	37	18.30	15.81	15.0	690	6.98	9.90	3.00
	4	554	6.86	9.04	4.00	27	21.26	19.07	16.00	657	7.45	10.03	4.00
	5	547	6.94	8.40	4.00	16	22.88	17.11	20.50	620	7.40	9.09	5.00
	6	548	7.36	8.75	5.00	12	23.17	14.48	20.50	603	7.83	9.23	5.00
	7	547	7.65	9.54	5.00	4	21.75	19.87	18.00	569	7.73	9.68	5.00
	8	547	8.58	8.94	7.00	0	0	0	0	547	8.58	8.94	7.00
Number of bleeding-spotting episodes**	1	555	2.81	2.09	2.00	78	3.28	1.99	3.00	802	2.84	2.08	2.50
	2	566	2.46	2.13	2.00	50	3.44	2.29	3.00	745	2.48	2.11	2.00
	3	559	2.16	1.99	2.00	37	3.32	1.75	3.00	690	2.20	1.99	2.00
	4	554	2.27	1.91	2.00	27	3.41	1.67	3.00	657	2.31	1.93	2.00
	5	547	2.36	1.94	2.00	16	3.81	2.23	3.50	620	2.39	1.95	2.00
	6	548	2.32	1.87	2.00	12	4.08	1.31	4.00	603	2.38	1.87	2.00
	7	547	2.34	1.82	2.00	4	6.75	3.10	6.00	569	2.34	1.86	2.00
	8	547	2.47	1.65	3.00	0	0	0	0	547	2.47	1.65	3.00

*RP denotes a 90-day reference period.

**An bleeding or spotting episode was one or more consecutive days during which bleeding or spotting, respectively, was entered on the diary card, bounded by bleeding-free days.

Source: ISE, Table 22, page 66.

Hemoglobin parameters were reviewed in the previous two review cycles by a different reviewer. Overall, there was no significant mean change in hemoglobin from baseline to last measurement.

However, to see if there was any evidence of bleeding to the point of severe anemia, I explored the datasets for subjects with low hemoglobin values on treatment, and then looked at their bleeding patterns. Subject 00004, Study Protocol 34511, developed severe anemia with hemoglobin on Day 737 of treatment equal to 5.9 G/dL. In her reference periods 6, 7, and 8 of treatment, she had 49, 35, and 50 days of bleeding or spotting (mostly bleeding). Her complaints included dizziness, headaches, and a fainting spell. She had no gynecologic complaints at screening. It seems likely that her vaginal bleeding contributed to her severe anemia. I did not find any other subject with hemoglobin less than 7 G/dL on therapy.

Comment: Irregular bleeding appears to be a nuisance for many women. However, one subject had severe and symptomatic anemia, possibly as a result of irregular bleeding. It is standard of care to evaluate a woman who complains of prolonged, symptomatic, bleeding, and a woman using Implanon should be no exception to the standard of care.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Blood pressure and weight were checked at screening, at three months, at six months, and every six months thereafter for most studies. Heart rate was measured at baseline and at three to six month intervals for Study 069001. For all other studies, heart rate was measured at baseline only.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Analysis of blood pressure changes used all data available in the ISS.

7.1.8.3 Standard analyses and explorations of vital signs data

Studies detected no significant mean changes in blood pressure or heart rate. Table 27 shows changes in blood pressure from baseline to the last assessment.

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Table 27. Mean Change in Blood Pressure and Heart Rate from Baseline to Last Assessment (All-Subjects-Treated Group)

Assessment	Implanon		
	U.S. (N=330)	Non-U.S. (N=612)	All Studies (N=942)
Heart Rate			
(N) Mean Change ± SD	(322) -0.6 ± 9.8	Not done	(322) -0.6 ± 9.8
Systolic Blood Pressure			
(N) Mean Change ± SD	(323) -0.2 ± 10.2	(608) 1.1 ± 13	(931) 0.7 ± 12.2
Diastolic Blood Pressure			
(N) Mean Change ± SD	(323) -0.4 ± 8.9	(608) 0.2 ± 9.8	(931) 0 ± 9.5

Source: ISS, Table 20, p. 79

In the only study with nonhormonal control group (Study 34522), no significant blood pressure differences were noted over two years between women using Implanon and women using a medicated, nonhormonal IUD.

Table 28 shows weight gain by year in all subjects using Implanon, and Table 29 shows weight gain by year in U.S. subjects using Implanon. The weight gain appears similar between the U.S.-group and the all-subjects groups.

Comment: Like other hormonal contraceptives, Implanon use is associated with a mean weight gain, although the weight gain is less than the weight gain seen with depot medroxyprogesterone acetate (DMPA). For Implanon, the overall mean weight gain at 1 year was 2.6 pounds, and 2.3% of subjects reported weight gain as a reason for discontinuing Implanon. For comparison, DMPA (subcutaneous) users gained on average 5.7 pounds at 1 year, and 14% of subjects reported weight gain as a reason for discontinuing DMPA. In the United States, average aging-related weight gain for young women over 10 years is about 1.2 pounds per year for Caucasian women and 2.1 pounds per year for African-American women.¹¹

In the U.S. study of Implanon, 12% of subjects were African American and 71% of subjects were Caucasian. The age-related weight changes in the U.S. study of Implanon should therefore be closer to what is expected for Caucasian women than what is expected for African-American women (1.2 pounds per year compared with 2.1 pounds per year.) Table 29 shows that weight gain in the U.S. study was somewhat more than expected for age-related weight gain alone.

Although comparisons of different trials and use of historical controls can be precarious, the absence of concomitant controls in most of the Implanon studies makes it necessary. Implanon appears to be associated with less weight gain than DMPA, as expected based on its similarity to lower-dose progestin-only contraceptives. However, Implanon also seems to be associated with more than just age-related weight gain.

¹¹ Lewis C et al. Weight gain continues in the 1990s. 10-year trends in weight and overweight from the CARDIA study. Am J Epidemiol 2000;151:1172

Table 28. Weight Gain in Pounds by Year (All-Subjects-Treated Group)

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

Source: Table 3a, Applicant response (14 Mar 2006) to reviewer request. Weight changes were calculated as changes from the baseline weight.

Table 29. Weight Gain in Pounds by Year in US Study (All-Subjects-Treated Group)

Statistic	End of Year 1	End of Year 2
Number of Subjects [n]	217	164
Mean of weight change	2.8	3.7
Standard error of mean wt. change ^(b)	0.68	0.91
Minimum of weight change	-42.5	-38.5
Maximum of weight change	30	37.3

Source: Table 1a, Applicant response (14 Mar 2006) to reviewer request. Weight changes were calculated as changes from the baseline weight.

7.1.8.4 Additional analyses and explorations

No further analyses were done.

7.1.9 Electrocardiograms (ECGs)

There were no new ECG data in this resubmission.

7.1.10 Immunogenicity

There were no special studies to assess immunogenicity, nor were any requested. Allergic reactions are expected in some individuals who use any “non-self” product.

7.1.12 Special Safety Studies

Study 34522 assessed bone mineral density changes, and was reviewed in previous review cycles by a different reviewer who concluded that there was “no evidence of a decrease in BMD” in Implanon users.

Comment: The BMD study was small (N=46 Implanon users, N=30 IUD users) and exploratory, and therefore not adequate to support labeling claims. According to the protocol, Study 34522 was open-labeled and nonrandomized, and the statistical analysis was observational and exploratory.

7.1.14 Human Reproduction and Pregnancy Data

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.”

Exposure to etonogestrel during pregnancy has been reported for women using Nuvaring and women using Implanon, and no teratogenic effect has been identified. According to the current review in *Reprotox*, “progestin exposure during pregnancy has been associated in some studies with an increase risk of hypospadias in male offspring. There does not appear to be an increase in other congenital anomalies.” (last updated on 1-Oct-2005)

A search of FDA’s AERS DataMart on April 5, 2006 using the search terms “etonogestrel” and “congenital anomaly” revealed six reports. No pattern emerged. The reports included

1. Tetralogy of Fallot
2. Club foot
3. Caudal regression syndrome
4. Flat head and gastroesophageal reflux
5. Trisomy 18
6. Hypoplastic left heart and partial deletion and partial duplication of X chromosome

Ectopic pregnancy is a risk for low-dose progestin products *when they fail to prevent pregnancy*. The problem may be related to the decrease of Fallopian tube motility that is observed in the presence of progestin. The failure rate of Implanon should be so low that the risk of pregnancy, including ectopic pregnancy, is low. However, Implanon’s label should inform healthcare providers that they should be alert for ectopic pregnancy *when Implanon fails to prevent pregnancy*. This may be a particular problem when Implanon implants cannot be removed.

7.1.17 Postmarketing Experience

From 28-Aug-1998 through 1-Mar-2006, the Applicant received 11,306 spontaneous reports listing 17,677 spontaneous AEs. Most were expected based on the clinical studies. During the same time period, the Applicant estimated that the total exposure to Implanon was 5,017,580 woman-years. Events have generally occurred at a lower-than-expected incidence based on population incidences; however, the extent of under-reporting is unknown. For example, there have been 53 reports of venous thromboembolism (0.1 per 10,000 women-years) and 29 reports of breast cancer (0.06 per 10,000 women-years). Although the incidences of venous thromboembolism and breast cancer are lower than expected, the extent of under-reporting cannot be estimated.

Notable findings include five adult deaths and two fetal deaths:

- Tetanus infection in a woman who died three to four days after insertion
- Three pulmonary emboli
- Suicide two weeks after removal of Implanon
- Premature delivery and death at 27 weeks gestation, twin pregnancy, with the death of one twin in a pregnancy complicated by fetofetal transfusion syndrome and hydramnios. Implanon was removed at seven weeks gestation.
- Premature delivery and death at 21 weeks gestation. Implanon was removed at seven weeks gestation. The fetus had intrauterine growth restriction.

Comment: The first five deaths may have some association with Implanon, although all are also expected, though rare, events in young women. Tetanus may arise from wound infection, particularly in someone who has not had routine vaccinations, and particularly in "dirty" wounds. Standard aseptic technique and routine vaccination should make the risk of tetanus from Implanon insertion quite rare.

There remains some uncertainty about the association between progestins and thrombotic events. However, overall, studies suggest a small increase in the risk of thromboembolic events in women using progestins. Estrogens have been more clearly associated with increased risk of thromboembolic events. Suicide is a result of severe depression, and depression has also been associated with progestin exposure.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

See Section 4 Data Sources, Review Strategy, and Data Integrity.

7.2.1.1 Study type and design/patient enumeration

See Table 3 for patient enumeration.

Table 30 is a list of studies and a synopsis of study design for the entire development program for Implanon.

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Table 30. List of Studies for the Entire Development Program for Implanon

Study	Design	Duration
RM01	Open label, noncomparative, PK and PD	2 years, extended to 4.5 years
RM02	Open label, noncomparative, efficacy and safety	2 years, extended to 4 years
BKKBN	Open label, noncomparative, multicenter, postmarketing surveillance	3 years
L-1784	Double blind, multicenter safety study, to assess mefenamic acid for treatment of bleeding in users of Implanon. Blinding is to mefenamic acid assignment.	6 months (ongoing)
E-1729	Open label, noncomparative, multi-center efficacy and safety	3 years
34502	Open label, noncomparative, PK, PD	2 years, extended to 5 years
34503	Open label, noncomparative, PK, PD	2 years, extended to 5 years
34504	Open label, noncomparative, PK, PD, using leached implant (lower release rate)	1 year, extended to 4 years
34505	Open label, noncomparative, single-center safety and efficacy	2 years
34506	Open label, noncomparative, single-center, safety and efficacy	2 years, extended to 4 years
34507	Open label, noncomparative, multicenter safety, efficacy, subset for bioavailability	2 years, extended to 3 years in Hungary and Chile
34508	Open label, bicenter, randomized, comparative (vs. Norplant), PK and PK	2 years, extended to 3 years in Finland
34509	Open label, randomized, comparative (vs. Norplant) efficacy and safety (hemostasis and liver function)	2 years
34510	Open label, randomized, comparative (vs. Norplant) lipid	2 years
34511	Open label, randomized, comparative (vs. Norplant), CHO metabolism, thyroid and adrenal functions	2 years
34512	Open label, randomized, comparative (vs. Norplant) lipid	2 years
34513	Open label, randomized, comparative (vs. IUD), lactation	2 years
34514	Open label, randomized, comparative (vs. Norplant) endometrium	2 years extended to 3 years
34515	Open label, single center, absolute bioavailability	2 years
34520	Open label, comparative (vs. Norplant), multicenter, safety, efficacy, acceptability	2 years, extended to 3 years
34522	Open label, nonrandomized, comparative (vs. IUD) bone mineral density	2 years
34523	Open label, nonrandomized, comparative (vs. IUD) lactation	2.7 years
34524	Open label, noncomparative	2-3 years
34525	Open label, noncomparative	1-3 years
34528	Double-blind, parallel group, bioequivalence	3 years (ongoing)

Study	Design	Duration
	study (Implanon vs. Implanon with barium sulfate)	
069001	Open label, noncomparative, multicenter, safety and efficacy. Subsets for CHO, lipid, endometrium, PK, ophth., only US study	2 years

Source: Modified by reviewer from Applicant's "List of Studies", ISS, liststudies.pdf

7.2.1.2 Demographics

This section should include demographic information for Phase 1 and Phase 2-3 study pools separately. Since these studies were reviewed in the first review cycle, I did not re-review them here.

7.2.1.3 Extent of exposure (dose/duration)

For the ISS in this re-submission, 942 women provided 1,893 women-years of data. Table 3 provides a summary of year-by-year exposure.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The submission included interim synopses of three ongoing studies:

- Study 34528
- Study L-1784
- Study E-1729 *

(*As noted earlier in the review, a final sub-study report for Study E-1729 was provided for the site that provided data used in the integrated summaries of the current submission.)

Comment: The interim synopses raised no new safety or efficacy issues.

7.2.2.2 Postmarketing experience

See summary in Section 7.1.17 Postmarketing Experience.

7.2.2.3 Literature

The Applicant provided articles to support the resubmission. I searched PubMed on April 21, 2006, for "Implanon" using the limit "published in the last 2 years." Among 54 abstracts retrieved with this search, there were no unexpected findings. Two postmarketing studies (one from France and one from Australia) found that the most common reason for pregnancy among women who think they are using Implanon is failure of insertion. There were several titles

suggesting tips for difficult removals, one article about ectopic pregnancy in an Implanon user, and one article about pregnancy in an Implanon user who was taking carbamazepine, a CYP 3A4 inducer, for epilepsy.

7.2.3 Adequacy of Overall Clinical Experience

The Applicant met FDA recommendations for testing a new contraceptive method that is not expected to have unusual safety issues.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The Applicant submitted no new information about animal or in vitro testing in this resubmission.

7.2.5 Adequacy of Routine Clinical Testing

The protocol provided for routine clinical testing that met or exceeded routine clinical standards for testing healthy young women of reproductive age who seek contraceptive health services.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

There were no biopharmaceutical issues outstanding after the previous two review cycles.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

As noted elsewhere in the review, I recommend a postmarketing study of efficacy in obese women.

7.2.8 Assessment of Quality and Completeness of Data

Data quality has been an issue through two previous submissions. The Applicant's efforts to provide audited data appear adequate to me. FDA's Division of Scientific Investigations inspected three clinical sites during this review cycle and concluded for all three sites: "No deviation from regulations. Data acceptable."

7.2.9 Additional Submissions, Including Safety Update

The resubmission included a safety update incorporated into the integrated summary of safety.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Overall, AEs were similar to those seen with other progestin-only contraceptives except for events related to insertion and removal. The main limitation of the data is that few studies had non-progestin control groups.

The delivery system confers both benefit and risk. While ideal for ease of use, implants can be inserted incorrectly and can be difficult or even impossible to remove. There are postmarketing reports of women who, surprised by an unplanned pregnancy, discovered that they did not have an implant. 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. There have been rare postmarketing reports of implants that cannot be found by palpation, ultrasound, or MRI, but are nonetheless still present. Women with irretrievable implants may want to become pregnant and be unable to do so, or may wish to rid themselves of a troublesome side effect and be unable to do so. Although these problems may not achieve a regulatory definition of serious, they may be very serious to the affected young woman.

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 Norplant removals should provide extra incentive for the Applicant to train healthcare providers with care. In addition, the Applicant has an ongoing bioavailability study of an implant containing 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 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.

Other problems expected in women using progestin-only contraceptives include

- Functional ovarian cysts
- Ectopic pregnancies in the unlikely event of a pregnancy
- Cholecystitis

The incidence of serious but uncommon disorders such as breast cancer and thrombotic events cannot be defined from the clinical study database because these serious disorders are uncommon. Based on what is known about other progestins, there may be a small increased risk of both breast cancer and thrombotic events in women using progestin-containing contraceptives.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The most notable difference in adverse event rates when comparing the pooled vs. the individual study data was the greater discontinuation, largely related to psychiatric complaints, in U.S. sites compared with foreign sites. The differences may be cultural.

7.4.1.2 Combining data

Data were simply combined. No weighting was used.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The section was not applicable because Implanon has only one dosage strength.

7.4.2.2 Explorations for time dependency for adverse findings

The Applicant did not provide any explorations for time dependency. My own explorations for time dependency of common adverse events in the AE dataset in the Applicant's ISS did not reveal any notable findings.

7.4.2.3 Explorations for drug-demographic interactions

The Applicant analyzed the common AEs (occurring in >5%) of subject by age and weight. Since racial data were not collected except in the U.S. study, an analysis by race was not done. Exploratory analyses suggested that the incidence of acne and emotional lability may decrease as subject age increased; the incidence of weight gain appeared to increase as baseline body weight increased.

Comment: The importance, if any, of these exploratory analyses is unclear.

7.4.2.4 Explorations for drug-disease interactions

The section was not applicable because subjects were generally healthy, reproductive-aged women.

7.4.2.5 Explorations for drug-drug interactions

Since subjects using potent CYP 3A4 inducers were generally excluded from the studies, these explorations were not done. One subject inadvertently showed the effect of rifampicin on etonogestrel levels when she developed tuberculosis during a Phase 1 trial. (See Section 5.1.)

7.4.3 Causality Determination

Since the studies were mainly historically controlled, causality determination rests largely on what is already known about progestin products in general, and implants in particular.

8 Additional Clinical Issues

8.1 Dosing Regimen and Administration

Comment: Data from the early dose-finding studies supports the choice of dose and suggests that Implanon should be effective through three years.

8.2 Drug-Drug Interactions

According to the Applicant, etonogestrel is metabolized by CYP 3A4 enzymes. Although there were no formal clinical studies, a single subject in a Phase 1 PK study inadvertently provided data on the potential for chronic use of CYP 3A4 inducers to greatly reduce etonogestrel concentrations. This problem is shared with other progestins, most especially other implants, and is addressed in labeling.

Subjects used many concomitant medications during the studies, but the generally healthy nature of the population and the trial exclusions meant that most women who took concomitant medication were using medication for short-term, routine indications such as headaches and minor infections. For example, among 4,995 medications listed in the dataset containing concomitant medications, the following receive more than 100 mentions:

- Paracetamol (430)
- Ibuprofen (230)
- Metronidazole (209)
- Metamizole (132)
- Amoxicillin (110)
- Tinidazole (106)

I looked for three medications that have chronic indications and are known CYP 3A4 inducers, and found

- no subjects who used phenytoin
- 1 subject who used phenobarbital for 1 month

- no subjects who used rifampicin

Comment: Trial exclusion criteria ensured that the ISE database provided scant data about effectiveness of Implanon among women who use CYP 3A4 inducers for chronic indications.

Users of a similar implant, Norplant, experience decreased effectiveness and decreased serum levels of progestin when taking antiepileptic drugs that are potent CYP 3A4 inducers. In one study¹², two of nine epileptic women became pregnant while using Norplant and taking antiepileptic drugs. In the same study, mean plasma concentrations of levonorgestrel were about 100 pg/ml lower in six women who were taking phenytoin alone or in combination with other anticonvulsants than in a control group. (Expected mean concentrations of levonorgestrel in women using Norplant are between 200 and 300 pg/ml.)

8.3 Special Populations

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. Additionally, proposed labeling contains a section on renal insufficiency stating that no studies were done.

Implanon has not been studied in obese women. However, the FDA biopharmaceutical reviewers have concluded, based on pharmacokinetic data, that serum concentrations of etonogestrel are inversely related to body weight. Therefore, Implanon may not be as effective in obese women as it is in women who are not obese. There are published data suggesting that this problem affects other hormonal contraceptives. To date, the problem has been handled with labeling. See Section 9.3.3 Other Phase 4 Requests.

8.4 Pediatrics

Implanon is not indicated for pre-menarchal girls.

Comment: I recommend waiving the requirement for “data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations”¹³, as described in the Code of Federal Regulations. Based on over 40 years of experience with progestin-containing contraceptives, no special safety or efficacy issues are anticipated in post-menarchal adolescent girls who use Implanon.

8.5 Advisory Committee Meeting

There was no Advisory Committee meeting for Implanon.

¹² Haukkamaa M, “Contraception by Norplant subdermal capsules is not reliable in epileptic patients on anticonvulsant treatment”, *Contraception* 1986 Jun;33(6):559-65

¹³ 21CFR314.55 Pediatric use information and 21CFR314.55(c) Waivers.

8.6 Literature Review

Literature is referenced in appropriate sections of the review. My literature review is summarized in Section 7.2.2.3 Literature

8.7 Postmarketing Risk Management Plan

In the letter from FDA explaining the second approvable action, FDA stated that the Applicant “will also need to submit an acceptable plan for a post-marketing monitoring program for Implanon-related insertion and removal adverse events in U.S. patients.”

The Applicant presented the basic concept for the post-marketing program to the Division during the end-of-review meeting on August 11, 2005. The Division of Drug Risk Evaluation in the Office of Drug Safety provided the Division with comments before the meeting. Based on the discussions at the end-of-review meeting, Organon “formalized the proposal for post-marketing risk management”, and provided it in this submission.

Organon proposes two approaches:

- Spontaneous reporting (called the “Pharmacovigilance Plan”)
- Active monitoring (called the “Active Monitoring Plan”)

The “Pharmacovigilance Plan” is routine postmarketing surveillance AND a separate report for insertion/removal-related events (IRREs). AEs and SAEs will be coded in MedDRA as usual¹⁴, but Organon also has developed a series of IRRE codes to further classify events. For example, the IRRE code “ultrasound presence” will be used if ultrasound was attempted (whether successful or not). An IRRE report will be included in the routine safety reports, and Organon will present both U.S. and world-wide data in the routine safety reports. Organon is already preparing these reports at the request of European regulators, and provided the latest report as an Appendix to the ISS in this submission.

Comment: I reviewed the IRRE report submitted in the present submission, and it adequately presents insertion and removal events.

The “Active Monitoring Plan” will involve 20 to 40 U.S. centers and at least 10,000 insertions with a 3-year follow-up to capture data about insertions. The centers will be trained with the same program as the one rolled out to all clinicians, and will receive no special training. Data will be collected on a questionnaire. The Applicant included the questionnaire in the current submission. The training program has been previously evaluated by the Division, and the Applicant submitted an update during this review cycle. The Applicant has previously agreed that only healthcare providers who have completed the training program may order Implanon.

¹⁴ MedDRA has numerous terms to capture device-related problems, such as preferred terms: “device failure”, “device dislocation”, “extrusion of device”, etc. However, Organon’s additional terms provide further details about device-related problems.

Data collected will be monitored monthly with queries related to

- Incidence of IRREs
- Comparative IRREs (U.S., foreign, Pharmacovigilance Plan versus Active Monitoring Plan)
- IRRE incidence as a function of distribution to provider (incidence of IRREs per number of implants shipped to provider)
- IRRE incidence as a function of training program
- Frequency of specific information from insertion and removal evaluation form such as deviation from correct procedure

Internal employees and an external expert panel will analyze results and decide on need for change in the training program or instruction in the labeling text based on results. Reports from the Active Monitoring Plan will be sent to the FDA along with the routine Periodic Safety Reports (every 3 months for 3 years, then yearly thereafter).

Comments: The questionnaire appears to train as well collect AEs. Questions such as "Was the applicator held upright when the needle cap was removed right before insertion?", and "Did patient review and sign the consent form?" etc., appear designed to instruct. If so, the clinicians who participate in the program may not be representative of the broader group of clinicians who only undergo standard training. However, inclusion of this type of question was recommended by FDA previously to evaluate the effectiveness of the training program.

For many reasons, I think a more useful design would be a brief questionnaire filled out by Implanon users. However, FDA (the review Division and the Division of Surveillance, Research, and Communication Support [DCRCS]) has tacitly agreed with the approach of the provider-based questionnaire by not raising the issue at the end-of-review meeting.

The proposed approach is likely to provide some useful information about incidence of provider-perceived IRREs in a practice environment, as well as perhaps identifying areas where training or labeling could be improved.

I viewed the updated training materials and they appear adequate. In addition, they include a 1-800 number for problems, and instructions to provide a patient package insert to patients, as recommended by FDA's DSRCS.

8.8 Other Relevant Materials

I identified no other relevant materials.

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9 Overall Assessment

9.1 Conclusions

Implanon is effective for the proposed indication, prevention of pregnancy for up to three years. Except for events related to insertion and removal of the implant, Implanon's safety profile is similar to that of other progestin-only contraceptives. However, the implant provides excellent ease-of-use and, overall, the safety profile of Implanon is acceptable.

9.2 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.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The Applicant included FDA recommendations related to 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 will need to participate in the training program.

9.3.2 Required Phase 4 Commitments

The primary clinical reviewer does not recommend any Phase 4 commitments.

9.3.3 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

- 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.

9.4 Labeling Review

The proposed labeling is the Applicant's response to the FDA response to the labeling in the first submission. FDA sent comments to the Applicant's original proposed labeling in a FAX dated 21-Oct-2004.

My approach to labeling included

- Assessment of the data to support labeling
- Assessment of the Applicant's changes to the labeling in the first round of labeling negotiations (dated 21-Oct-2004)
- Evaluating internal consults (related to trade name, PPI, PI, cartons) and incorporating appropriate recommendations into labeling
- Comparing the labeling to the labeling of another progestin-only implant (Jadelle), the progestin-containing intrauterine device (Mirena), a recently approved oral contraceptive (YAZ), and the only other U.S.-approved product containing etonogestrel (Nuvaring)
- Comparing the labeling to the SPC labeling in Europe

Highlights of my recommended changes included

- Adding a boxed warning about subdermal placement and confirmation of placement by palpation
- Removing inadequately-supported and promotional labeling about bone mineral density
- Simplifying the language in the Patient Package Insert and Consent form from a 10-11th grade reading level to a 7-8th grade reading level, as recommended by FDA consultants, in order to make the information accessible to more patients
- Simplifying the presentation of comparative information about other contraceptive methods in the Patient Package Insert to make the information accessible to more patients
- Removing the Trussell table (a table containing comparative information about other contraceptives derived from varied sources) from the package insert because it does not contribute to "adequate directions for use" (as specified in the Code of Federal Regulations)

Comment: 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."¹⁵ The most serious sequelae of insertion and removal problems include unplanned pregnancies, ectopic

15 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>

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 ensuring that Implanon is inserted where it should be. Healthcare providers should confirm correct placement by simple palpation after every insertion.

My proposed changes are shown in Section 10.2, Line-by-Line Labeling Review.

9.5 Comments to Applicant

I recommend conveying to the Applicant the comments in Section 1.2.3. I have no additional comments to address to the Applicant beyond the interactions that occurred during the course of the review.

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10 Appendices

10.1 Review of Individual Study Reports

See Cycle 1 and Cycle 2 reviews.

10.2 Line-by-Line Labeling Review

Changes proposed by the clinical reviewer are marked in red. Two changes in the Description section, proposed by the chemistry reviewer, are also marked in red. Changes proposed by the biopharmaceutical reviewer are marked in green. A clean copy of the proposed label is in Section 10.2.2.

The following labeling represents my primary labeling review only. It is not final labeling for Implanon. Final labeling for Implanon represents the input of other reviewers, particularly the Acting Division Director of the Division of Reproductive Products and the Medical Team Leader for Implanon. The final labeling also reflects the result of negotiations with the Applicant.

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10.2.1 Marked Label

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68 Page(s) Withheld

 Trade Secret / Confidential

 x Draft Labeling

 Deliberative Process

10.2.2 Clean Label

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49 Page(s) Withheld

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 4 Draft Labeling

 Deliberative Process

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/s/

Lesley-Anne Furlong
7/14/2006 05:58:12 PM
MEDICAL OFFICER

Lisa Soule
7/14/2006 06:13:46 PM
MEDICAL OFFICER

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

CLINICAL REVIEW

Application Type NDA (Complete Response)
Submission Number 21-529
Submission Code BZ

Letter Date December 13, 2004
Stamp Date December 14, 2004
PDUFA Goal Date June 14, 2005

Reviewer Name Barbara Wesley M.D., M.P.H.
Review Completion Date June 9, 2005

Established Name Etonogestrel Implant
(Proposed) Trade Name Implanon
Therapeutic Class Progestin
Applicant Organon USA Inc.

Priority Designation S

Formulation Subcutaneous implant
Dosing Regimen 68 mg every 3 years
Indication Prevention of pregnancy in
women of childbearing potential
Intended Population Women of childbearing potential

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends an approvable action for Implanon (etonogestrel implant). This recommendation is a result of failure of the applicant to satisfy the requirements for regulation § 314.125 (b) (5) of the Code of Federal Regulations: “There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in § 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling”. Approval is contingent on the following:

- Provision of additional clinical trial data so that the efficacy and safety of Implanon will be supported by at least 10,000 28-day cycle equivalents during the first year of use that are from adequate and well-controlled studies. 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 and integrity of the data.
- Development of a Phase 4 program in the U.S. for monitoring insertion and removal related events that is acceptable to the FDA.
- Completion of a final product labeling.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Training of Health Care Providers. Organon will form a Steering Committee to develop a program to train Health Care Providers (HCP) on proper technique for inserting or removing Implanon. Each training session will include clinical information, insertion/removal/localization procedures, hands on training using model arms, and patient counseling. Only those clinicians who complete the program will be able to order and insert Implanon. Effectiveness of the training programs will be monitored in the following ways: (1) evaluation forms and surveys completed by HCPs, (2) Organon clinical Contact Specialist’s reviews of the skills of Health Care Providers (HCPs), and (3) an Organon sponsored Steering Committee review of the progress of the training programs, surveys and evaluations, and issues that have arisen.

1.2.2 Required Phase 4 Commitments

Organon should develop a Phase 4 program in the U.S. for monitoring insertion and removal related adverse events. This reviewer believes it is essential that the company obtains accurate information on these adverse events beyond that which will be identified through spontaneous adverse event reporting. A representative sample of the population using Implanon could be evaluated for obtaining this information.

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Description of Drug Product. Implanon (etonogestrel implant) is a progestin-only contraceptive subdermal implant. The 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. Using a ready-for-use disposable applicator, the non-biodegradable Implanon implant is inserted subdermally at the inner side of the upper arm. After insertion, ENG is slowly released through the rate-controlling skin.

Regulatory History and Issues. The original NDA submission of September 2003 included six studies classified by the Applicant as principal safety and efficacy studies. Following inspection by the Applicant of clinical trials sites prior to inspection by the FDA, the Applicant withdrew data from two of the six clinical trials (both trials had been conducted in Indonesia and enrolled 649 subjects) because of significant Good Clinical Practice violations that rose to the level of fraud. The modified original submission (hereafter referred to as the “original submission” for NDA 21-529, following removal of the data from the 649 Indonesian subjects) provided data from approximately 1803 subjects in 19 completed Phase II and III studies. These subjects were treated with Implanon™ for up to 2-5 years in 16 different countries (including studies in Southeast Asia, Europe, North America and South America).

After removal of the two studies conducted in Indonesia, 4 of the remaining clinical trials (Studies 069001 [U.S.], 34505 [Thailand], 34507 [Europe and Chile], and 34507-CDN [Canada]) were considered to be the principal efficacy and safety studies by both this reviewer and the Applicant. All were non-comparative, open-label, historical controlled studies. In addition to efficacy and safety, these 4 studies also provided limited data on clinical pharmacology, including drug levels (subsets of Studies 069001 and 34507), lipid metabolism, carbohydrate metabolism, ophthalmological parameters, and endometrial histology (subsets of Study 069001). An overview of the number of subjects enrolled in each of the principal safety and efficacy studies is provided in Table A.

Table A. Principal Safety and Efficacy Studies

069001 (U.S.)	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 Sep 2003

Late in the original review cycle, the Division learned that the European Regulatory Authorities via the Dutch Medicines Evaluation Board (DMEB) had decided to conduct their own inspection of several sites that had participated in Study 34507 and the single site in Study 34507-CDN (studies that had supported the approval of Implanon for marketing in Europe). Because of these inspections, the DMEB concluded that the (1) conduct of the inspected sites had not been

consistent with good clinical practices (GCPs) and (2) reliability of the data from these sites could not be assured. Because of the violations of GCP and errors that were identified, the DMEB recommended that Organon make several changes to the approved Implanon label. Most importantly, however, the DMEB 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.”

Because of the concerns raised by the DMEB inspections, Implanon received an “Approvable Action.” Organon was informed that Approval of Implanon for marketing in the U.S. would require that Organon provide either (1) adequate evidence that the data obtained in Studies 34507 and 34507-CDN was reliable or (2) data from another clinical trial that was conducted in conditions of GCP. The Applicant chose to follow Option No. 1 in the Complete Response (the present submission). Based on the information provided in the Complete Response, this Medical Reviewer cannot conclude that Studies 34507 and 34507-CDN were conducted in accordance with the standards of GCP. Therefore the data from these studies (with the exception of that obtained from a single site in Hungary (Dr. Urbancsek) and the single site in Chile [both of which received satisfactory inspection reports from the FDA’s Division of Scientific Investigation]) could not be considered by this reviewer to be sufficiently reliable to play a pivotal role in supporting the efficacy and safety of Implanon. This conclusion is based on review of the clinical trial Inspection reports conducted by the European regulatory agency (Dutch Medicines Evaluation Board-DMEB) in 2004.

Extent of Subject Exposure to Implanon. Subject exposure data considered by this Medical Reviewer to be probably reliable consists of that obtained from Studies 069001 (U.S.) and 34505 (Thailand) and the 2 sites in Study 34507 that were inspected by the FDA. Data from these studies and sites consisted of 648 subjects who received Implanon and provided 7,520 28-day cycle equivalents during Year 1; 505 subjects who entered treatment Year 2 and provided 5,931 28-day cycle equivalents during Year 2; and 369 subjects who entered treatment Year 3 and provided 2,737 28-day cycle equivalents.

1.3.2 Efficacy

In the original submission, the Applicant provided data from four principal, historically controlled clinical trials that entered approximately 1,117 subjects for either up to 2 or 3 years of treatment. This reviewer has reanalyzed the data after removing subjects from study 34507 (except Hungary [Urbancsek site] and the Chile site) and 34507-CDN. Removing these subjects affected the data in years 1 and 2, but not year 3.

Through Two Years of Use (Excluding Studies 34507 [except Hungary-Urbancsek and Chile). Overall, data in support of the effectiveness of Implanon for the prevention of pregnancy was provided from 7,500 28-day treatment cycles in the first year in the remaining studies/sites. There were 648 subjects remaining in the first year from the four studies: 327 subjects were treated in the U.S. (Study 069001) for 3,584 treatment cycles; 100 subjects were treated in Thailand (Study 34505) for 1,241 treatment cycles; 221 subjects were treated at the Hungary (Urbancsek) and Chile sites for 2,695 treatment cycles. Three conceptions were estimated by the FDA medical reviewer to have occurred (n=2) or may have occurred (n=1) within 7 days of implant removal (2 in the U.S. study; 1 at the Hungary/Urbancsek site). Based on these 3

pregnancies, and 7,520 at risk cycles, the annual Pearl index was calculated to have a point estimate of 0.519 through one year of treatment (including subjects at all ages).

In year 2, 505 subjects were treated resulting in 5,931 treatment cycles. There were no pregnancies reported during year 2.

Year 3 of Use. A total of 215 subjects, from two centers in study 34507 (Chile and Hungary) and one center in Study 34505 (Thailand), entered into the third year of treatment and 195 subjects completed three years of use (90.6% of subjects). There were no reported pregnancies in Year 3 for these studies. For these studies combined, there were 2,844.4 cycles of exposure. The Pearl Index for these subjects was 0 [95% CI: (0, 1.7)]. Among subjects \leq 35 years of age, there were 2,390.5 cycles of exposure. The Pearl Index for these subjects was 0 [95% CI: (0, 2.0)].

No pregnancies were reported to have occurred in any of the supportive clinical pharmacology, special safety, or additional studies. There was a rapid return of fertility after removal of the implant for subjects who desired to become pregnant.

Limitations of the pregnancy data the clinical trial program included some inconsistent pregnancy testing at the time of implant insertion and removal and inconsistency in performing early ultrasounds for all pregnancies occurring near treatment.

Post-Marketing Experience. Since product launch, the Applicant reports that implants have been sold as of 01 Sep 2004, and 836 unplanned medically confirmed pregnancies have been reported in Implanon users. Based on these postmarketing data, a pregnancy rate of 0.051 pregnancies per 100 sold implants can be calculated. In 26 medically confirmed pregnancy cases, a suspected drug interaction was reported. The rate of reported ectopic pregnancy in post marketing data was similar to that seen with other progestin-only contraceptives.

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1.3.3 Safety

Clinical Trial Data

Exposure to Study Drug

See section 1.3.1 above.

Adverse Events

In the overall clinical development program, no deaths or serious adverse events of concern occurred in any studies submitted in either the original submission or the complete response. There was one case of transient ischemic attack in study 34507 but no thromboembolic events in any studies.

In the principal studies of the original submission, bleeding irregularities were the most frequently reported adverse event (occurring in more than 85% of subjects) and was the most common reason for discontinuing Implanon (13%- U.S. Study; 16%-non U.S. Studies).

One or more adverse events were reported in 86% of subjects in the U.S. and 72% of subjects in the non-U.S. principal studies. Serious adverse events were reported in 3% of subjects in the U.S. and 7% of subjects in the non-U.S. principal studies. These statistics did not reveal a trend of under-reporting of adverse events in the European Study 34507 (considered by the DMEB

inspectors). However, 36.1% of subjects in the U.S. Study 69001 discontinued due to an adverse event compared to 28.3% in the European Study 34507.

Laboratory parameters (hematology, blood chemistry, and urinalysis) were assessed in U.S. Study 069001 and in non-U.S. study 34507 (Austria). No clinically meaningful laboratory abnormalities were noted. Parameters of lipid metabolism (studies in the U.S., U.K., and Thailand) did not reveal any adverse effects.

Postmarketing Safety Data

Since the start of marketing of Implanon in 1998, more than _____ units have been sold as of 01 Mar. 2005. Updated postmarketing safety data covering the period from product launch through 1 March 2005 included reports of four deaths (3 deaths due to pulmonary embolus; one death due to bacterial infection). Serious thrombotic/thromboembolic cardiovascular adverse events have consisted of 13 reports of pulmonary emboli, 18 reports of CVAs, and 18 reports of DVTs. Implanon has not been withdrawn from any market because of safety issues. The most common significant postmarketing safety issues has related to adequate training of healthcare providers, a problem that was most prevalent following the initial marketing of the product.

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1.3.4 Dosing Regimen and Administration

After subdermal insertion at the inner side of the upper arm, etonogestrel is slowly released. The initial release rate is approximately 67 µg /day and the release rate over the entire period of three years of use is approximately 41 µg/day. The Applicant selected this release rate because it was the lowest dose that reliably prevented ovulation in Phase 2 clinical trials. The Applicant recommends that Implanon be removed no later than 3 years after implantation and replaced by a new implant. This reviewer, however, believes that the Applicant has not submitted adequate clinical data in Year 3 to support the effectiveness of the product for 3 years of use.

1.3.5 Drug-Drug Interactions

No formal drug interaction studies were conducted.

1.3.6 Special Populations

Ethnicity. There are no separate race or ethnicity considerations about safety or efficacy. The principal U.S. study is the only study that collected data on race. Since the number of non-Caucasian subjects in the U.S. study was small, no formal analyses by race for either efficacy or safety were performed.

Age (Pediatric Population). This product is intended for use only in post-menarchal reproductive-aged women. Hormonal contraceptive drug products are considered safe and effective in post-menarchal adolescent females. No formal studies involving subjects less than 18 years of age have been required by the Division for this class of drug product.

Pregnancy and Renal or Hepatic Impairment. This drug is contraindicated in pregnancy. The pharmacokinetics of Implanon™ has not evaluated in patients with renal or hepatic impairment. Labeling will address this.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Implanon™ (etonogestrel implant) is a progestin-only contraceptive for subdermal use. The 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 (ethylene vinylacetate copolymer with a vinylacetate content of 28%), surrounded by a 60 µm skin

(ethylene vinylacetate copolymer with a vinylacetate content of 14%). Etonogestrel, structurally derived from 19-nortestosterone, is the biologically active metabolite of desogestrel. Using a ready-for-use disposable applicator, the non-biodegradable implant is designed to be inserted subdermally at the inner side of the upper arm. After insertion, ENG is slowly released through the rate-controlling skin.

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2.2 Currently Available Treatment for Indications

Oral contraceptives containing either an estrogen and a progestin or a progestin alone are highly effective and are used by a large percentage of women who wish to prevent pregnancy. All approved oral contraceptives require daily administration of a tablet for at least 21 days during a 28-day period. Failure to adhere to the approved dosing regimens significantly reduces the effectiveness of these products. Highly effective contraceptives that have a dosing regimen other than by daily oral tablet include medicated and inert IUDs, a vaginal ring (NuvaRing), a weekly transdermal patch (OrthoEvra), a 90-day depot injectable progestin (depot medroxyprogesterone acetate), and levonorgestrel containing subdermal implants. The presently approved subdermal contraceptive implants in the U.S. are a 6-rod system (Norplant™) and a 2-rod system (Jadelle™). Neither is currently marketed in the U.S. Approval of this contraceptive implant will give women in the U.S. another option in contraception that they do not currently have.

2.6 Other Relevant Background Information

On Sept 30, 2003, Organon Inc. submitted original NDA 21-529 for Implanon. After the removal of two principal studies because of significant Good Clinical Practice Violations (see below), four historically controlled studies that enrolled 1,117 subjects remained as the principal safety and efficacy studies. Data from approximately 700 additional subjects in 15 other supportive studies also were submitted.

During the first review cycle, NDA 21-529 received an *approvable* decision. The primary issue that precluded approval was irregularities in study conduct identified by European regulatory authorities' (Dutch Medicines Evaluation Board [DMEB] inspections of the clinical trial sites for Study 34507 and Study 34507 CDN) that raised concerns about the quality and accuracy of the data from these studies. These concerns were outlined in the October 11, 2004 letter from the DMEB to European Concerned Member States that was included in the Applicant's October 15, 2004 submission to the NDA.

In the Division's Approvable Letter of October 29, 2004, the Applicant was asked to submit in their complete response (1) the Integrated Inspection Report of the Dutch regulatory authorities (Integrated Inspection Report IGZ 2004-015 entitled "Evaluation of Implanon Non-compliance Issues)," (2) the independent audit report commissioned by Organon, and (3) Organon's response to the DMEB. In addition, Organon was asked to provide a detailed justification of why Study 34507 (including the Canadian component [Study 34507 CDN]) was an adequate and well-controlled trial that provide data sufficient to support (1) a conclusion that Implanon is safe and effective for prevention of pregnancy and (2) accurate product labeling. Alternatively, the Applicant was given the option of conducting another clinical trial.

Other issues listed in the Approvable Letter that would be required for product approval were:

1. Submission of revised product labeling.
2. Submission of an acceptable inspection report of the sterilization facility

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The following information provides the background that led to the inspections by the Dutch Medicines Evaluation Board (DMEB).

1. On March 23, 2004 Organon Inc. informed the Division of Reproductive and Urologic Drug Products (DRUDP) that there were *significant* Good Clinical Practice violations at the Jakarta, Indonesia site (R1001) of Dr. Biran Affandi and the Semarang, Indonesia site (R1007) of Dr. Pramono. During the Applicant's audit visits of the sites in preparation for an upcoming FDA inspection, several instances of misconduct were uncovered. These issues involved two of the principal safety and efficacy studies (Studies 34506 and 34520) submitted in the original NDA. These studies involved the data for 622 Indonesian subjects completing 2 years and 538 subjects completing 3 years. On a subsequent teleconference with the Applicant, there was a mutual agreement to remove these studies and all data from these studies from the analyses supporting the safety and efficacy of Implanon.
2. Organon also informed the DMEB of these findings since the original dossier for Implanon that served as the basis for approval of the drug product throughout Europe had included the data from subjects from these two Indonesian sites. The DMEB/European Regulatory Agency(s) then decided (based on factors not disclosed to the Division) to inspect four European sites not previously inspected by the FDA.
3. Because of these inspections, violations of good clinical practice (GCP) were identified by the European inspectors that resulted in several changes to approved labeling for Implanon. A summary of the most significant violations and the resulting label changes included the following:
 - a. At one or more of the sites, items were identified that might have implications for the quality and validity of the trial data (missing or destroyed source data, record inaccuracies, etc.). It also was concluded that there was an underreporting of the frequency of side effects in some trials (this is more fully discussed in Section 7.2.8 of this review); however, the Inspectors concluded, "there were no indications of fraudulent actions."

- b. Because of the violations of GCP and errors that were identified, the DMEB recommended that Organon make several changes to the approved Implanon label (see Section 4.5).
- c. The DMEB concluded that the most important outcome of the inspections was 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.”

Medical Officer’s Comments

- *The findings of the DMEB raised concerns regarding the quality of the data from clinical trials 34507 and 34507-CND; however, the DMEB did not recommend removal of Implanon from the market and considered an Implanon implant safe and effective for three years of use.*
- *Recommended changes to the label included an increased emphasis on irregular bleeding patterns and a change in the reported Pearl Index to a less specific number (reflecting the confounder of not recording condom use and concerns that all pregnancies occurring during the clinical trial may not have been reported).*

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Medical Officer’s Comments

- *To help the reader understand the issues that (1) impact on the approvability of this NDA and (2) formed the basis for this Medical Reviewer’s recommendation that NDA 21-529 is Approvable, relevant information provided in the original submission as well as information provided in the Complete Response are included in the present review. Data and analyses in this review are identified, for the most part, as based on the original submission, the complete response, or integrated as follows:*
 - **Original Submission** – this includes information and analyses based on the original NDA submission on Sept. 30, 2003, the revised NDA submission (after removal of the Indonesian sites) on May 20, 2004, and all related information requests up to but not including December 13, 2004.
 - **Complete Response** – this includes information and analyses based on the complete response to the Approvable Letter submitted to the FDA on December 13, 2004 and all related subsequent information requests.
 - **Integrated Response** – this includes information and analyses that combine data from both the “Original Submission” and the “Complete Response”.

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4.2 Tables of Clinical Studies

Information Provided in the Original Submission

NDA 21-529 provided data from 1,803 subjects in 19 completed Phase II and III studies plus one ongoing phase II study. Subjects were treated with Implanon for up to 2-5 years in 16 different countries (including studies in Southeast Asia, Europe, North America [U.S. and Canada], and South America). With the exception of Study 34504, all studies were designed to collect pregnancy, vaginal bleeding, and safety data. A listing of the clinical trials included in the original submission is provided in Table 1. After disqualification of Studies 34506 and 34520 (both conducted in Indonesia), 4 clinical trials remained as the “principal safety and efficacy studies” (Studies 69001 [U. S.], 34505 [Thailand], 34507 [Europe/Chile], and 34507 CDN [Canada]).

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Table 1 Listing of Clinical Trial Studies – Original Submission

Principle Safety and Efficacy Studies (4)
069001 (U.S.) – Open label, noncomparative, multicenter, safety and efficacy study of Implanon™ in 330 women age 18-40 for 2 years
34505 (Thailand) – Open label, noncomparative, single center, safety and efficacy study of Implanon™ in 100 women age 18-39 for 2 to 4 years
34507 (Europe/Chile) – Open label, noncomparative, multicenter, safety and efficacy study of Implanon™ in 635 women age 18-40 for 2 to 3 years
34507 CDN (Canada) – Open label, noncomparative, single center, safety and efficacy study of Implanon™ in 52 women age 18-40 for 2 years
Supportive Clinical Pharmacology (4) and Special Safety Studies (6)
34502 (Thailand) – Open label, noncomparative PK/PD study of Implanon™ in 15 women age 20-37 for 2 to 5 years
34504 (UK) – Open label, noncomparative PK/PD leached implant study of Implanon™ in 15 women age 28-37 for 1 to 4 years
34508 (Finland; Sweden) – Open label, randomized, comparative (vs. Norplant™), PK/PD study of Implanon™ in 16 women (16 women- Norplant™ group) age 18-39 for 2 to 3 years
34515 (Singapore) – Open label, single center, absolute bioavailability study of Implanon in 10 women age 27-39 for 2 years
34509 (Finland; Sweden) – Open label, randomized, comparative (vs. Norplant™), hemostasis and liver function study of Implanon™ in 43 women (43 women- Norplant™ group) age 19-40 for 2 years
34510 (Thailand) – Open label, randomized, comparative (vs. Norplant™), lipid metabolism study of 15 women (15women-Norplant™ group) age 19-37 for 2 years
34511 (Singapore) – Open label, randomized, comparative (vs. Norplant™), carbohydrate metabolism, thyroid and adrenal function study of Implanon™ in 40 women (40 women-Norplant™ group) age 19-39 for 2 years
34512 (Finland) – Open label, randomized, comparative (vs. Norplant™), lipid metabolism study of Implanon™ in 40 women (40 women-Norplant™ group) age 19-40 for 2 years
34514 (UK) - Open label, randomized, comparative (vs. Norplant™), endometrium study of Implanon™ in 30 women (30 women in Norplant™ group) age 18-40 for 2 to 3 years
34522 (The Netherlands, Chile, Finland) – Open label, randomized, comparative (vs. IUD), bone mineral density study of Implanon™ in 46 women (30 women-IUD group) age unavailable for 2 years
34523 (Thailand) – randomized, comparative (vs. IUD), lactation and development of infants study of Implanon™ in 42 women (38 women-IUD) age 18-40 for 2 years to 4.5 years
Additional Supportive Studies (5 + 1 ongoing)
34524 (Mexico) – Open label, noncomparative, non randomized, safety and efficacy study of Implanon™ in 58 women age 18-36 for 2 years
34525 (Russia) – Open label noncomparative, non randomized, safety and efficacy study of Implanon™ in 60 women age 18-40 for 1 year
RM01 (China) – Open label, noncomparative PK/PD not good clinical practice study of Implanon™ in 16 women age 26-35 for 2 to 4.5 years
RM02 (China) – Open label, noncomparative, safety and efficacy not good clinical practice study of Implanon™ in 200 women age not available for 2 to 4 years
RM04 (China) – Open label, randomized, comparative (vs. Norplant™) not good clinical practice study of Implanon™ in 100 women (100 women Norplant™ group) age not available for 2 to 4 years
E-1729 Malaysia, Venezuela, Austria, Germany - Ongoing - Open label, noncomparative, multicenter, safety, efficacy study of Implanon™ planned in 211 women for 3 years

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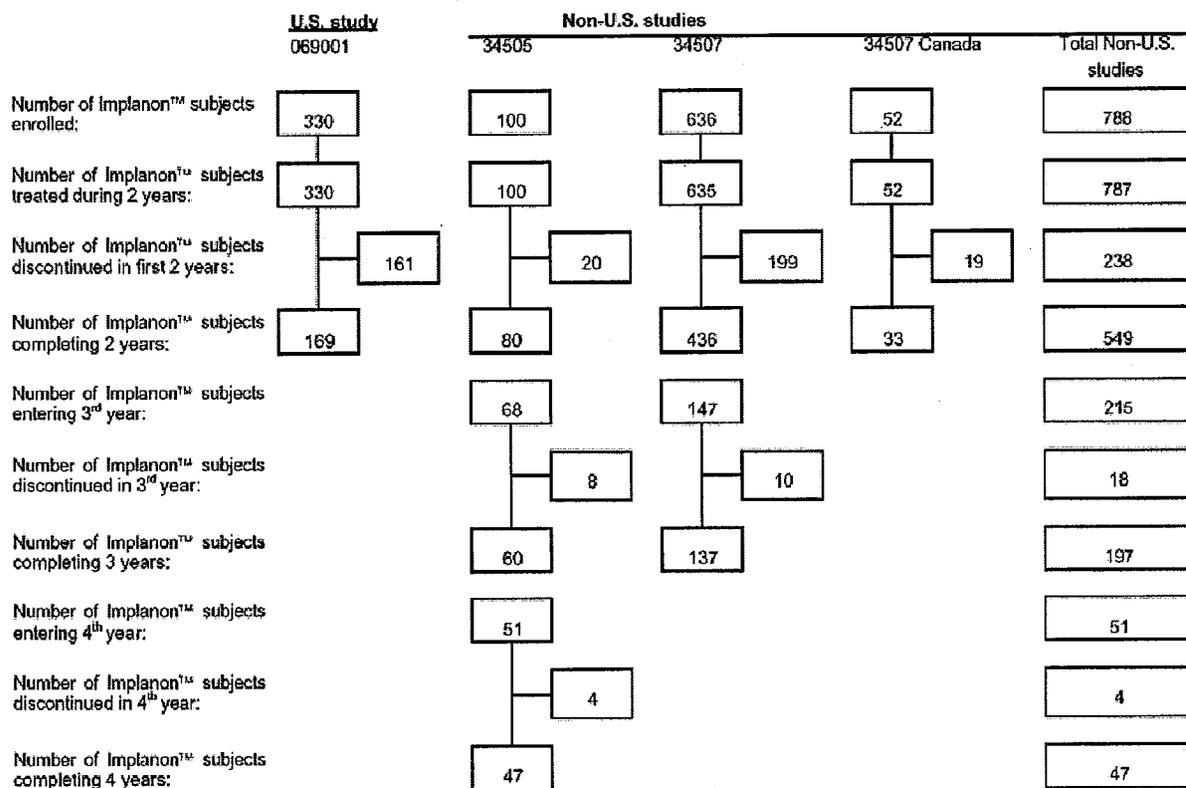
Table 1 Listing of Clinical Trial Studies – Original Submission (cont)

Disqualified Studies (5)
34506 (Indonesia) – Open label, noncomparative, multicenter study of Implanon™ in women age 20-35 for 2 to 4 years
34520 (Indonesia) – Open label, comparative (vs. Norplant™) multicenter, safety, acceptability study of Implanon™ in women age 18-40 for 2 to 3 years
34503 (Indonesia) – Open label noncomparative PK/PD study of Implanon™ in 15 women age 27-34 for 2 to 5 years
34510 (Indonesia; Thailand data included) – Open label, randomized, comparative (vs. Norplant™ and IUD) lipid metabolism study of Implanon™ in 60 women (60 women-Norplant™ group; 45 IUD group) age 19-40 for 2 to 3 years
34514 (Indonesia) Open label, randomized comparative (vs. Norplant™) endometrial histology study in 41 women (40 women-Norplant™ group) age 18-41 for 2 to 3 years

Source: Original NDA 021529; Table 1, ISE, P21, 30 Sep 03.

The disposition of Subjects in the 4 principal safety and efficacy studies is listed in Figure 1.

Figure 1 Disposition of Subjects – Principal Safety and Efficacy Studies – Original Submission



Source: Figure 1, revised ISE, submission of 4 May 2004.

Medical Officer’s Comments

- *Studies 34506 and 34520 (not shown in Figure 1) were originally considered by the Applicant to be principal efficacy and safety studies. The removal of these studies had the*

following impact: these subjects constituted approximately 46% (622/1340) of the total subjects completing 2 years and approximately 73% (538/735) of the total subjects completing 3 years. As a result, only 197 subjects were studied for a full three years.

- *Based on the assessment of 3 study sites from Trials 34507 and the only site in Study 34507 CDN by the Dutch and local regulatory authorities, data from these trials (with the exception of 2 FDA inspected sites) are considered to be of questionable reliability (see Section 4.5).*

4.3 Data Quality and Integrity

This Medical Reviewer has significant concerns regarding the reliability, quality, and integrity of the data submitted by the Applicant in support of NDA 21-529, which arose as a result of inspections conducted by the Applicant (Studies 34520 and 34506 [Indonesia] and Studies 34507 [Europe] and 34507 CDN [Canada]). These concerns resulted in (1) disqualification of all data from Studies 34520 and 34506 and uncertainty as to whether data from Studies 34507 and 34507 CDN could be used to support fully the safety and effectiveness of Implanon. These issues are discussed more extensively in Sections 4.5 and 7.2.9.

4.5 Compliance with Good Clinical Practices

Information Provided in the Original Submission

On January 30, 2004, an inspection assignment was issued by the FDA's Division of Scientific Investigation (DSI) for inspections of three U.S. sites and two non-U.S. sites. The non-U.S. sites and the protocols were Protocol 34520 (Dr. Dewata, Surabaya, Indonesia, Site RI-008, and Dr. Pramono, Semarang, Indonesia, Site RI-007) and Protocol 34506 (Dr. Affandi, Jakarta Pusat, Indonesia, Site RI-001). These non-U.S. sites were selected because of large enrollment, data on three years of use of the study drug, and the low number of reported serious adverse events. Prior to DSI's initiation of inspections, Organon notified the Division and the European Authorities (March 23, 2004) that they had identified significant Good Clinical Practice violations at the Jakarta, Indonesia study site of Dr. Biran Affandi and the Semarang site of Dr. Pramono. Several instances of misconduct were uncovered at these sites that had conducted two of the six studies original classified as the principal safety and efficacy studies in the original NDA submission.

After disqualification of the Indonesian sites, two additional non-U.S. sites (those of Drs. Urbancsek [Hungary] and Croxatto [Chile]) were selected for inspection by DSI because each site had (1) enrolled a large number of subjects and (2) provided the majority of the remaining data supporting three years use of Implanon™. The domestic sites of Drs. Chez, Poindexter, and Funk also were selected for inspection.

A Form 483 was issued for four of the five Investigators: Drs. Funk, Chez, Croxatto, and Urbancsek. DSI issued several citations; however, none of these citations, except possibly that issued to Dr. Chez, was sufficiently critical to raise any concern about the overall quality and validity of the clinical data. The citation for Dr. Chez, however, did not identify any specific instances in which adverse events had been underreported or a possible on-treatment pregnancy had not been reported. The citation identified several instances of protocol deviations including the inclusion of a subject with an exclusionary medical history, multiple follow-up visits with

subjects conducted by telephone rather than in person, and follow-up visits by two subjects that were out of protocol-specified periods.

DSI's final overall assessment of findings and general recommendations were the following: "The data submitted in support of this application by Drs. Funk, Chez, Poindexter, Croxatto, and Urbancsek appear adequate in support of the relevant submission."

Medical Officer's Comment

- *This medical reviewer concurs that the data obtained these sites (and from U.S. Study 69001 overall) are adequate to support the NDA.*

Information Provided in the Complete Response

Upon learning about the violations at the Indonesian sites, the European Mutual Recognition Facilitation Group (MRFG) became concerned since data from these Indonesian sites were part of the dossier submitted for approval in Europe. As a result of the actions to remove the Indonesian sites from the dossier, Organon and the European Regulatory Agency [specifically the Dutch Medicines Evaluation Board – DMEB] initiated three actions that were aimed at further investigating the database for Implanon: (1) DMEB review of internal audits already performed by Organon for studies remaining in the registration file; (2) DMEB [through the Dutch Health Inspectorate, IGZ] requested additional inspections of certain study sites; and (3) Organon conducted additional internal audits of study sites.

First, based on their review of internal audits already performed by Organon, the DMEB concluded that it considered the following sites "not to be compliant with Good Clinical Practice (GCP)":

- Dr. Schwerts, Brussels (Belgium)
- Dr. Colau, Suresnes (France) – [Drs. Schwerts and Colau together accounted for 18/635 subjects enrolled in Study 34507]
- Dr. Vekemans, Brussels (Belgium) – [6/635 subjects enrolled in Study 34507]
- Dr. Prelepskaya, Russia – [all 60 subjects enrolled in study 34525] - data from this site had not been considered to be *either primary or supportive data for the NDA.*

The DMEB requested that the registration dossier be modified such that "the data from these four study sites be deleted from the Implanon database." Organon agreed to this and, in addition, decided to also remove the data from Dr. Newton's site in the United Kingdom [25/635 subjects] from the European database.

In the original NDA submission to the FDA (Sept. 30, 2003), Organon noted in the study report for protocol 34507 that they "considered the study sites of Dr. Schwerts and Dr. Colau to not be GCP compliant." After the removal of the study sites of Drs. Vekemans and Newton, the subject count in the primary studies decreased from 1117 total subjects [26,787 cycles, 2,054.9 woman years] to 1,065 total subjects [25,676.5 cycles, 1,969.7 woman years].

Second, the DMEB – Inspectorate of Health Care [IGZ] in the Netherlands conducted site inspections of four additional European sites that remained in the dossier. The findings of the four site inspections for Study 34507 (based on comments in the review reports) were as follows:

- Dutch site – (Winterswijk, Dr. Beerthuisen: 22 subjects completed 2 yrs) – “ethical issues; poor documentation.”
- Canadian site – (52 subjects screened, 33 completed 2 yrs) – this site “used a different drug batch from the other sites; emphasized the use of condoms; poor documentation, data not robust to be included.”
- UK site – (25 subjects enrolled); in two subjects: “implantation recorded as performed prior to arrival of the product; integrity of data is questionable.”
- German site – (Drs Brandl & Tykal: 84 subjects completed 2 yrs) – “serious AEs reported retrospectively; doubts about authenticity of data in source files – study data is not verifiable from source data; doubtful that these data are suitable to support safety and efficacy.”

The overall conclusions of the DMEB inspection report for study 34507 stated the following:

“Observations with respect to study conduct, collection of adverse events, drug accountability, and monitoring may have implications for the integrity and quality of the trial data”. Specific observations include:

- “Use of additional contraceptives (Condoms) was not recorded by subjects.”
- “Study visits were outside the windows set by the protocol, missed, or conducted by telephone.”
- “Drug accountability was poorly conducted in the trial.”
- “Source data and documents (including bleeding records) kept by the subjects was lacking.”
- “A lack of control over the trials by the company, evident at all levels of the conduct and reporting of the trial, which appeared to be a systems and managerial problem; sites that were declared GMP non-compliant or fraudulent as a result of the audits seemed not to have been reported to the responsible management.”

Third, Organon conducted additional internal audits, the results of which in some cases differed from those of the IGZ. Organon also initiated an independent audit by a contract research organization (CRO) of the German study site in study 34507 [Dr. Tykal and Dr. Brandl]. This action was undertaken because Organon did not agree with the conclusions of the German Federal Institute for Drugs and Medical Devices [BfArM]/Inspectorate of Health Care of the Netherlands (IGZ). b(4)
concluded in its audit report that “... *No evidence could be found which would make the general integrity of the data questionable. The observed findings are in line with acceptable negligence, which is often observed in study conduct. From the documentation checked during the audit, the integrity of the collected data could not be proven to be doubtful...*” Organon stated that they did not formally dispute the conclusions found in the IGZ report because the DMEB did not contest the overall safety and efficacy of Implanon.

In addition to a number of conferences that Organon had with DMEB regarding the substance and content of the report, Organon provided the DMEB with other comments and information in response to the Integrated Inspection Report. Organon has accepted that there were some GCP violations, protocol deviations, and administrative errors made at some of the study sites. However, Organon had specific objections to the Integrated Inspection Report IGZ that they believe led the inspectors involved to unnecessarily have negative conclusions. Organon listed the following factors that they believe puts the most significant issues raised in the IGZ report into context:

1. "Report IGZ did not take into account all of the information provided by Organon and the investigators to the Dutch Health inspectorate."
2. "The report applies regulatory standards that were not in effect at the time studies were conducted (e.g., requirement for comprehensive monitoring plans; entering of source data directly on case report forms etc.)."
3. "The report places emphasis on the fact that Organon failed to collect and report the potential use of condoms for all sites of study 34507. Organon states that no patients reported that they used condoms but as noted, these data were not formally collected. There was no regulatory guidance in Europe that addressed this point."
4. "The report states that the FDA 483 observations that were issued to the study sites inspected by the FDA are "critical and major" shortcomings, and further suggests that this creates some concern regarding the validity of data from those sites. Organon believes that this characterization relates to the misunderstanding by the European inspectors on how FDA field investigators report deficiencies as part of an inspection. Any potential violation that the inspector observes, regardless of whether it would be considered critical, major or minor, are reported on the 483."

Medical Officer's Comments

- *The conclusions of the contracted-out Organon-hired inspections were more favorable than that of the Integrated Inspection Report (IGZ).*
- *The IGZ indicated there was a possibility of fraudulent activity at one site.*
- *The DMEB never indicated that the inspection reports were in error even after receiving the rebuttal responses from Organon.*
- *This medical reviewer cannot reconcile the divergent opinions between the responses of the study investigators to the criticisms, the government inspectors, Organon, and the European regulatory agencies.*
- *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.*

A second MRFG meeting was held on October 18, 2004 at which members of the EU formulated an official opinion and recommendations for Implanon, based, in part, on the findings reported in the Integrated Inspection Report IGZ 2004-015.

Conclusions of the Mutual Recognition Facilitation Group (MRFG) for Study 34507 based in the October 18, 2004 meeting were:

- “Several inspections revealed observations (some classified as critical) which might have implications for the quality of the study data (e.g. verifiability of data) and their presentation in the final study reports. This may have lead to underreporting of the frequency of side effects in some studies. There were no indications for fraudulent actions.”
- “There is no reason for doubt on the efficacy and safety of Implanon provided it is inserted according to the method presented in the product information. This view is mainly based upon the extensive reporting in the Periodic Safety Update Reports (PSURs).”
- “Organon has to start a Type II variation [equal to an NDA labeling supplement] with the aim to change sections of the Summary of Product Characteristics (SmPC) as proposed by the RMS.”
- “A systems inspection will be performed by the Inspectorate covering all quality control and quality assurance aspects as well as the organization, conduct and reporting of clinical studies for all Organon products. Additionally, an inspection of the systems for safety reporting and Pharmacovigilance will be performed.”

Because of the violations of GCP and errors that were identified, the DMEB recommended that Organon make several changes to the approved Implanon label. Recommended changes are identified below by strike-through (information to be deleted) and underline (information to be added).

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Medical Officer's Comments

- *The DMEB review of Organon audits and its' own independent inspections involved sites that enrolled 216 subjects from study 34507: Organon agreed to remove 52 subjects (Drs. Schwers, Colau, Vekemans, and Prelepskaya [Study 34507]) from the European dossier and the NDA submitted to the FDA. Organon disputes that the three sites from Study 34507 and the single site form Study 34507-CDN inspected by the DMEB (164 subjects) were non- GCP compliant; however, they are also willing to remove these subjects from the NDA. This would result in 1117-52=1065 subjects -- 164= 901subjects left. Organon never gave a detailed*

explanation as to why they thought the European inspectors (IGZ) were in error in their assessments and conclusions.

- *The DMEB stated, “There was no reason to doubt the safety and efficacy of Implanon, provided it is inserted properly. This opinion was based mainly on the extensive reporting in the postmarketing Periodic Safety Update Reports (PSURs)”.*
- *The MRFG issued a formal statement in support of safety and efficacy; however, significant changes in the label were recommended which is of concern to this medical reviewer.*
- *Organon states, “the data could not be proven to be doubtful”.*
- *This reviewer thinks that “data not proven to be doubtful” does not demonstrate that the data are reliable and that they were obtained from adequate, well-controlled trials as required by regulation § 314.125(b)(5) outlined above in Section 1.1. While it may be true that these data are not significantly compromised by the less than optimum conduct of some of the clinical investigators and deficiencies in Organon’s original monitoring processes, this reviewer cannot conclude that the data from Studies 34507 and 34507-CDN are reliable based on information provided by Organon to date.*
- *The FDA is obligated by regulation to depend primarily on clinical trial data for marketing approval of a drug product, and to consider postmarketing data only as supportive. Postmarketing safety data cannot substitute for the absence of sufficient data from adequate and well controlled clinical trials*

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Applicant’s proposed indication is “Implanon is indicated for women for the prevention of pregnancy. Implanon is a long-acting, reversible contraceptive method.”

6.1.4 Efficacy Findings

Data and analyses presented in the “Integrated Review of Efficacy” are based, for the most part, on findings from the four studies considered by the Applicant to be the principal safety and efficacy studies. For the reasons presented earlier in this review (see Sections 4.3 and 4.5), this reviewer has concerns about the reliability of the data from many of the clinical trial sites of Study 34507 and the single clinical trial site in Study 34507-CDN. Although formal analyses based on eliminating the data from these sites have not been performed, the likely impact of eliminating data from these sites is discussed under “Medical Officer’s Comments.”

Information Provided in the Original Submission

Applicant’s Assessment of Contraceptive Effectiveness

Across the four principal efficacy studies, 1,117 women used Implanon for prevention of pregnancy. Total months/cycles of exposure (based on 28 days of use equaling a month or cycle of exposure) was 26,787 cycles or 2,054 woman years (see Table 2) over 4 years of use. Among

these trials, the Applicant reported that four subjects were pregnant at the time that Implanon was inserted and that 32 subjects became pregnant within 1 to 26 weeks of implant removal. The Applicant claimed that no conceptions occurred while Implanon was in situ (i.e., there were no on-treatment pregnancies).

Table 2 Summary of Subject Exposure and Reported Pregnancies (Principal Studies)

Study	Total No. of women	Total exposure (28-day cycle equivalents)	Total exposure (women-yrs)	No. of Pretreatment pregnancy	No. of On-Treatment pregnancy	No. of post-treatment pregnancy	Pearl Index (95% CI) *
U.S. Study							
069001	330	6,186	475	0	0	11	0 (0, 0.77)
Non-U.S. Studies							
34505	100	3,863	296	0	0	6	0 (0, 0.12)
34507	635	15,653	1,200	4	0	24	0 (0, 0.31)
34507 CDN	52	1,085	83	0	0	2	0 (0, 4.27)
<i>Total</i>	<i>787</i>	<i>20,601</i>	<i>1,579</i>	<i>4</i>	<i>0</i>	<i>32</i>	<i>0 (0, 0.23)</i>
U.S. and Non-U.S. Studies Combined							
Total	1,117	26,787	2,054	4	0	43	0 (0, 0.18)

*: two-sided 95% confidence intervals computed by FDA statistician.
 Source: Modified from Tables 14, 16, and 17 from revised ISE, submitted 4 May 2004

The annual Pearl Index values and the annual exposure to Implanon for subjects < 36 years of age in the four principal efficacy studies are listed in Table 3. Cumulative Pearl Index values and annual exposures to Implanon in subjects < 36 years of age (principal efficacy studies) are listed in Table 4.

Table 3 Annual Pearl Index Values and Annual Exposures to Implanon in Subjects <36 Years of Age (principal Efficacy Studies)

Annual Pearl Index and Annual Exposure to Implanon (subjects < 36 years old at entry)			
Parameter	Year 1	Year 2	Year 3
Pearl Index	0.00	0.00	0.00
95% CI	(0, 0.4163)	(0, 0.5336)	(0, 1.8218)
Woman Years	886.186	691.274	202.482
Cycle Equivalents*	11552.071	9011.25	2639.5

* based on 28 day cycle equivalents
 Year 1: duration 1-365, Year 2: duration 366-730, Year 3: duration 731-1095
 Studies 69001, 34505, 34507, and 34507 CDN
 Source: Applicant's submission of 12 October 2004 – table 13b

Table 4 Cumulative pearl index Values and Annual Exposures to Implanon in Subjects < 36 Years of Age (Principal Efficacy Studies)

Cumulative Pearl Index and Annual Exposure to Implanon (subjects < 36 years old at entry)			
Parameter	Through Year 1	Through Year 2	Through Year 3
Pearl Index	0.00	0.00	0.00
95% CI	(0, 0.4163)	(0, 0.2338)	(0, 0.2072)
Woman Years	886.186	1577.46	1779.942
Cycle Equivalents*	11552.071	20563.321	23202.821

* based on 28 day cycle equivalents
 Year 1: duration 1-365, Year 2: duration 366-730, Year 3: duration 731-1095
 Studies: 69001, 34505, 34507, and 34507 CDN
 Source: Applicant's submission of 12 October 2004 – table 14b

Medical Officer's Comments

- *In general, the Division requires that a new contraceptive drug product be studied in at least 10,000 28-day cycle equivalents in the first year. If the data were reliable, total number of subjects (1,117) and the number of cycles per year (year-1 [11,552], year-2 [9,011]) would be adequate to assess the effectiveness of Implanon for 2 years.*

FDA Reviewer's Initial Assessment of Contraceptive Effectiveness (assumes data from the four principal studies are valid)

Across the 4 principal studies, 4 pregnancies (2 in the U.S. study and one each in Studies 34507 and 34507-CDN) were considered by this Medical Officer to have occurred either within 7 days of removal of Implanon (n=3) or may have occurred within this period (n=1). These pregnancies were classified by this Medical Officer as on-treatment pregnancies (i.e., a method failure). All four of these pregnancies also occurred within the first year of use. If these pregnancies are considered "method failures," the annual Pearl Index would be higher for Year 1 of use (see Table 5) and the values for the cumulative Pearl Index would be increased in Years 1-3 (see Table 6)

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Table 5 Annual Pearl Index Values and Annual Exposures to Implanon in Subjects < 36 Years of Age (Principal Efficacy Studies)

Annual Pearl Index and Annual Exposure to Implanon (subjects < 36 years old at entry)			
Parameter	Year 1	Year 2	Year 3
Pearl Index	0.45137	0	0
95% CI	(0.123, 1.1557)	(0, 0.5336)	(0, 1.8218)
Woman Years	886.186	691.274	202.482
Cycle Equivalents*	11552.071	9011.25	2639.5

* based on 28 day cycle equivalents
 Year 1: duration 1-365, Year 2: duration 366-730, Year 3: duration 731-1095
 Studies: 69001, 34505, 34507, and 34507 CDN
 Source: Applicant's submission of 12 October 2004 – table 15b

Table 6 Cumulative Pearl Index Values and Annual Exposures to Implanon in Subjects < 36 Years of age (Principal Efficacy Studies)

Cumulative Pearl Index and Annual Exposure to Implanon (subjects < 36 years old at entry)			
Parameter	Through Year 1	Through Year 2	Through Year 3
Pearl Index	0.45137	0.25357	0.22473
95% CI	(0.123, 1.1557)	(0.0691, 0.6492)	(0.0612, 0.5754)
Woman Years	886.186	1577.46	1779.942
Cycle Equivalents*	11552.071	20563.321	23202.821

* based on 28 day cycle equivalents
 Year 1: duration 1-365, Year 2: duration 366-730, Year 3: duration 731-1095
 Studies: 69001, 34505, 34507, and 34507 CDN
 Source: Applicant's submission of 12 October 2004 – table 15d

Medical Officer's Comments

- *Whether to count the three pregnancies that were estimated to occur within 7 days post removal of Implanon and the one pregnancy that may have occurred within this timeframe as "on-treatment" pregnancies is controversial. The Applicant claims that inhibition of ovulation is the primary mechanism of action for Implanon; this argument would support counting pregnancies in a similar fashion as combination oral contraceptives (COC) since COCs act primarily by inhibiting ovulation. A conception within 14 days after discontinuation of a COC would be considered a likely method failure. However, progestin-only contraceptives in general do not consistently inhibit ovulation and are dependent on other mechanisms such as alterations of cervical mucus to prevent conception. As such, it can be expected that conception could occur within a few days of removal of a progestin containing implant.*

- *If one were to assume that the data from the four studies classified as principal safety and efficacy studies are valid, it would not be important if these four pregnancies were considered a method failure. The values for the annual and cumulative Pearl Index and the upper bounds for the 95% CIs for these values (see Table 5 and Table 6) when the 4 pregnancies are considered method failures are still well within the range for other hormonal contraceptive products approved by the Division.*
- *A limitation of these studies is that the use of condoms for protection against sexually transmitted diseases was not recorded in subject diaries, which has been done in most other contraceptive trials for recently approved hormonal contraceptive products. In these other contraceptive trials, up to 20% of cycles have been eliminated because of the use of condoms. This adjustment could not be done in the trials submitted in support of Implanon.*
- *The most significant limitation is whether the data from Studies 34507 (with the exception of that from the two sites inspected by the FDA) and 34507-CDN can be considered sufficiently reliable to support the effectiveness of Implanon (see Sections 4.3 and 4.5).*

Effectiveness of Implanon during Year 3 of Use

After disqualification of the clinical data from the Indonesian Centers and therefore disqualification of Studies 34506 and 34520, the number of treatment cycles in Year 3 and the number of subjects who used Implanon for 3 years were significantly reduced. To assess the effectiveness of Implanon during Treatment Year 3, the FDA statistician was asked to calculate the Pearl Index and 95 % CIs based on only subjects who completed treatment Year 3. These calculations are summarized in Table 7.

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 pregnancies in these 195 subjects or in those subjects who did not complete Year 3. Overall, in the 3-year completers, there were 2,535 cycles of exposure of which 2,132 were in women < 36 years of age. The Pearl Index for all subjects during Year 3 was 0 [95% CI: (0, 1.87)]. The Pearl Index for subjects < 36 years of age at entry was 0 [95% CI: (0, 2.23)].

Table 7 Exposure and Pearl Index Values Based on Treatment Year 3 (Study Days 731-1095) (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	2535	0	0	1.87
< 36 year old	164	2132	0	0	2.23
≥ 36 year old	31	403	0	0	11.23

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 studied (195/2535) in treatment Year 3 was low even if all data (except that from Indonesia) were included. Other previously approved implantable contraceptive products had more subjects and cycle (e.g., the number of subjects/cycles submitted for support of the effectiveness of Jadelle in the third year was 492 women-years/6,396 cycles). When the <36 year old group (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 of the 95% confidence interval of 2.23. Based on the upper bound, this might support approval for a third year of use for Implanon if the reliability was assessed to be very high.*

Information Provided in the Complete Response

Data from three additional clinical trials (one complete [34525] and 2 ongoing trials [L-1784, E1729]) were submitted in the Complete Response (See Section 7.2.9). None of these trials were considered by either the Applicant or the medical reviewer to be principal safety and efficacy studies. There were no pregnancies reported in Studies 34525, E1729, or L1784.

Medical Officer’s Comment

- *These studies, if determined to be adequate and well controlled trials, could provide additional support for approval of Implanon.*

Effectiveness of Implanon Based on Postmarketing Data

Information Provided in the Original Submission

During the review of original NDA 21-529, the Applicant was asked to submit a summary of reported postmarketing pregnancies and to summarize the data based on the estimated date of conception for each of the pregnancies relative to months after insertion of the implant. Information on 486 medically confirmed pregnancies was submitted (see Table 8).

Table 8 Number of Reported Postmarketing Pregnancies Based on time of Conception post Insertion of Implanon

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 04.

Medical Officer's Comment

- *The Applicant was able to provide information about the time of conception for only 40% of reported pregnancies. For those pregnancies for which data were available, the greatest number occurred in the first year of use, which may be related to problems with insertion. There was no observed increase in the rate of pregnancies in Years 2 or 3.*

Information Provided in the Complete Response

Refer to Section 7.2.9.2

6.1.6 Efficacy Conclusions

- If the data provided in the four principal studies submitted in support of NDA 21-529 are reliable, a single Implanon implant, when inserted correctly, appears to be highly effective for the prevention of pregnancy for at least 2 years.
- *A limitation of these studies is that the use of condoms for protection against sexually transmitted diseases was not recorded in subject diaries, which has been done in most other contraceptive trials for recently approved hormonal contraceptive products. In these other contraceptive trials, up to 20% of cycles have been eliminated because of the use of condoms. This adjustment could not be done in the trials submitted in support of Implanon.*
- *The most significant limitation is whether the data from Studies 34507 (with the exception of that from the two sites inspected by the FDA) and 34507-CDN can be considered sufficiently reliable to support the effectiveness of Implanon (see Sections 4.3 and 4.5).*
- The number of subjects and treatment cycles in Year 3 were small (< 200 women who completed 3 years of treatment) and approximately 2,500 28-day cycle equivalents. Therefore, if there was a failure to identify only one or two pregnancies in Year 3 (none were reported by the Applicant), this would have significantly increased the Pearl Index value. Thus, the true effectiveness of a single Implanon implant in Treatment Year 3 may be less than that suggested by the data submitted in NDA 21-529.
- Based on the inspection report submitted by the DMEB regarding Clinical Trial 34507 and Clinical Trial 34507 CDN, the data from these 2 trials ((other than that from the Budapest site of Dr. Urbancsek and the single site in Chile) is not considered by this Medical Reviewer to have been obtained from adequate and well controlled clinical trials and thus may not be "highly reliable." In the absence of these data, the Applicant has not met the usual criteria of the Division for 10,000 28-day cycle equivalents of data during the first year of contraceptive use.
- Elimination of data from Clinical Trial 34507 and Clinical Trial 34507 CDN (other than that from the two FDA inspected sites in Trial 34507) in assessing the effectiveness of Implanon would not significantly affect the point estimate for the Pearl index. The two pregnancies reported to have possibly occurred in these clinical trials would be eliminated from the estimate of the Pearl index, but the upper limit of the 95% confidence interval for the Index would increase because of the reduced sample size.