

7 INTEGRATED REVIEW OF SAFETY

Data and analyses presented in the “Integrated Review of Safety” 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. Only limited safety analyses, based on eliminating the data from these sites, have been performed.

Information Provided in the Original Submission

7.1.1 Deaths

No deaths were reported in any clinical trial.

7.1.2 Other Serious Adverse Events

Sixty-two (62) out of 1,117 subjects (5.5%) in the 4 trials classified by the Applicant as principal safety studies experienced a total of 83 serious adverse events (SAEs) as shown in Tables 23, 24 and 25 of the Applicant’s revised ISS submitted on 20 May 2004. The system-organ classes with the most SAEs and the number of subjects reporting a SAE associated with the system-organ class (bleeding irregularities excluded) were Gastro- Intestinal System Disorder: 14/1117 (1.3%), Neoplasms: 9/1117 (0.8%), Liver and Biliary System Disorders: 7/1117 (0.6%), and Reproductive Disorders, Female: 6/1117, (0.5%). All individual SAEs occurred with an incidence less than 1%. The most frequently occurring individual SAEs were gastrointestinal disorder not otherwise specified, occurring in seven subjects (0.6%); cholelithiasis, occurring in six subjects (0.5%); and bone disorder, occurring in five subjects (0.4%). Serious adverse events coded as Bone Disorders included four cases of bone fracture and one case of hallux valgus surgery. All other individual SAEs occurred in three or fewer subjects. Twelve (12) of the 83 SAEs were thought to be possibly, probably, or definitely drug-related. These included two cases of ovarian cyst and single cases of gastrointestinal disorders not otherwise specified, breast fibroadenosis, breast neoplasm benign, uterine fibroid, depression, cyst not otherwise specified, cerebrovascular disorder, headache, chest pain, and tachycardia. All subjects recovered with the exception of one subject (Subject 0544 in Study 34507) who had continuing abdominal pain with an unknown outcome.

Medical Officer’s Comments

- *All individual SAEs occurred with an incidence less than 1%. Serious adverse events thought to be related to the study drug all occurred as single cases except for two cases of ovarian cyst. This indicates there were no significant trends that would indicate a drug related adverse event problem that might preclude the approval of Implanon™ for prevention of pregnancy unless there was under-reporting of adverse events.*
- *Of the 62 subjects reporting serious adverse events, 10 participated in U.S. Study 69001 and 52 participated in the non-U.S. studies. In the U.S. and non-U.S. studies, 3% (10 of 330) and 7% (52 of 787) subjects reported a serious adverse event*

- *Because of uncertainty as to the completeness of data reporting from some of the sites in Study 34507 and 34507 CDN, it is possible that there was some underreporting of serious adverse events.*

Serious Adverse Events of Particular interest

Vascular (extracardiac) disorders. In the overall clinical development program for Implanon, four subjects had SAEs that were categorized as vascular disorders. A brief summary of cases follows.

1. Subject 0558 from Study 34507 [N=635, 21 centers in Europe and Chile] suffered from *varicose veins* and was hospitalized for a varicectomy.
2. Subject 0682 from Study 34507 suffered transient loss of vision in the left eye and blurred vision in the right eye. She later had motor problems and paraesthesia of the extremities on the left side that lasted for several hours. The subject was hospitalized for a *suspected transient ischemic attack (TIA)*. The subject recovered from the event, which was judged by the investigator as possibly related to Implanon™ use. The subject discontinued from the study.
3. Subject 0648 from Study 34507 suffered from headache, vomiting, and confusion and was diagnosed with a *rupture of an arteriovenous (AV) left occipital malformation*.
4. Subject 09003 from U.S. Study 069001 experienced chest pains and was diagnosed with bronchospastic disorder, *vasospasm of the arteries*, drug abuse, and allergic reaction.

Medical Officer's Comments

- *Two of these 4 subjects completed the study. Of the 4 vascular related SAEs, only the TIA was judged to be possibly related to Implanon™ use. This reviewer agrees that the TIA may be related to the use of Implanon™, but the symptoms were transient and the woman recovered.*
- *Three of the four serious adverse events were reported to have occurred in Study 34507 and only one was reported to have occurred in U.S. Study 069001.*

Cardiac disorders. In the overall clinical development program for Implanon, one subject had an SAE that was categorized as a cardiovascular disorder. Subject 01014 from the U.S. study experienced repeated episodes of rapid heart rate. She was diagnosed with congenital heart disease, mitral valve prolapse, and paroxysmal atrial tachycardia. The event was judged by the investigator to be unrelated to Implanon use, and the subject continued in the study without further problems.

Medical Officer's Comment

- *In summary, the low report rate of vascular and cardiac thromboembolic events in the clinical studies suggests the risk is not significantly increased over that for nonpregnant individuals not exposed to contraceptives and is lower than the event rate found in similar individuals who use combination hormonal contraceptives or who become pregnant.*

However, it remains unclear whether or not there was under-reporting of these adverse events in Studies 34507 and 34507 CDN, as suggested by the IGZ inspectors.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.2 Adverse Events Associated with Dropouts

Adverse events leading to premature termination were reported for 119 of 330 (36%) subjects in U.S. Trial 069001 and in 204 of 787 (26%) subjects in the non-U.S. trials. Clinical trial adverse events resulting in premature termination in more than 1% of subjects (including bleeding irregularities) were compared between the U.S. study and non-U.S. studies (Europe-34507 (including 34507-CDN) and Thailand-34505). Bleeding irregularities [13.0% U.S. vs. 15.6% non-U.S.], weight increase [3.3% U.S. vs. 2.3% non-U.S.], acne [1.5% U.S. vs. 1.0% non-U.S.], headache [1.2% U.S. vs. 1% non-U.S.], and amenorrhea [0% U.S. vs. 1.5% non-U.S.] were reported at similar rates in both groups. Emotional lability [6.1% U.S. vs. 0.4% non-U.S.], and depression [2.4% U.S. vs. 0.3% non-U.S.] were reported more frequently in the U.S. See Table 9 for a more complete listing of discontinuations due to adverse events.

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Table 9 Number (%) of Subjects Who Discontinued due to an Adverse Event in Principal Safety Studies (System Organ Classes with ≥ 2 Events)

WHO system-organ class	Preferred term	U.S. ^a (N=330)		Europe/ Thailand ^b (N=787)		U.S./Europe/ Thailand (N=1117)	
		n	(%)	n	(%)	n	(%)
Reproductive disorders,		>43	>13	>123	>15.6	>166	>14.9
	Bleeding complaints	43	13	123	15.6	166	14.9
	Amenorrhea	0		12	1.5	12	1.1
	Sexual function abnl.	4	1.2	0		4	0.4
	Dysmenorrhea	2	0.6	0		2	0.2
	Premenstrual tension	2	0.6	0		2	0.2
	Breast pain female	0		3	0.4	3	0.3
Psychiatric disorders		31	9.4	11	1.4	42	3.8
	Emotional lability	20	6.1	3	0.4	23	2.1
	Depression	8	2.4	2	0.3	10	0.9
	Nervousness	3	0.9	2	0.3	5	0.4
	Anxiety	2	0.6	1	0.1	3	0.3
	Libido decreased	0		4	0.5	4	0.4
Metabolic disorders		11	3.3	22	2.8	33	3.0
	Weight increase	11	3.3	18	2.3	29	2.6
	Weight decrease	0		3	0.4	3	0.3
Skin disorders		7	2.1	14	1.8	21	1.9
	Acne	5	1.5	8	1.0	13	1.2
	Alopecia	2	0.6	4	0.5	6	0.5
Nervous system disorders		6	1.8	11	1.4	17	1.5
	Headache	4	1.2	8	1.0	12	1.1
	Paraesthesia	1	0.3	1	0.1	2	0.2
	Dizziness	0		2	0.3	2	0.2
Body as a whole disorders		5	1.5	2	0.3	7	0.6
	Fatigue	2	0.6	0		2	0.2
Application site disorders		3	0.9	1	0.1	4	0.4
	Injection site pain	3	0.9	1	0.1	4	0.4
Neoplasms		2	0.6	1	0.1	3	0.3
	Breast neoplasm (malig.)	1	0.3	0		1	0.1
Gastrointestinal disorders		1	0.3	1	0.1	2	0.2
Vascular disorders		0		2	0.3	2	0.2
	Cerebral hemorrhage	0		1	0.1	1	0.1
	Cerebrovas. disorder	0		1	0.1	1	0.1

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

Medical Officer's Comments

- Adverse events leading to premature termination were reported for 119 of 330 (36%) subjects in U.S. Trial 069001 versus 204 of 787 (26%) subjects in the non-U.S. trials.

- *The most striking difference between the U.S. study and the non-U.S. studies was the higher percentage of subjects discontinuing treatment in the U.S. trial for psychiatric reasons (9.4% versus 1.4%). Emotional problems may have a higher background rate in the U.S., and there may be cultural differences in the terminology used in these “soft” variables.*
- *It is difficult to draw conclusions from the analysis above since there were no trends overall.*

7.1.5 Common Adverse Events

7.1.5.3 Incidence of Common Adverse Events

Table 10 summarizes the number of subjects who used Implanon in the principal safety studies for whom adverse events were reported. Vaginal bleeding related adverse events (except in the category “adverse events leading to discontinuation”) were not included in the Table as an adverse event. One or more adverse events were reported in 86% and 72% of subjects in the U.S. and non-U.S. studies, respectively. Serious adverse events were reported in 3% (10 of 330 subjects) and 7% (52 of 787 subjects) in the U.S. and non-U.S. studies, respectively.

Table 10 Summary of Adverse Events in Principal Safety Studies

	U.S. Study		non-U.S. Studies	
	N	(%)	N	(%)
Total subjects	330	(100)	787	(100)
Any adverse events	282	(86)	569	(72)
Drug related adverse events	198	(60)	396	(50)
Serious adverse events	10	(3)	52	(7)
Adverse events leading to discontinuation *	119	(36)	204	(26)

N = Number of subjects for whom safety data were available or number of subjects reporting the event
 * Includes subjects who discontinued primarily because of menstrual bleeding related adverse events.
 Source: Prepared by Medical Reviewer from revised ISS submitted on 4 May 2004.

Medical Officer’s Comment

- *The was a slightly higher percentage of AEs reported in the U.S. study compared to the non-U.S. studies [86% vs. 72%]; conversely, there was a higher percentage of serious AEs reported in the non-U.S. studies compared to the U.S. study [7% vs. 3%].*
- *Despite the discrepancies, there are no identifiable trends suggesting under-reporting of AEs in any studies.*

Clinical trial adverse event occurrences (reported in at least 5 % of subjects, bleeding irregularities not included) were compared between the U.S. study (069001) and the European study (34507). In the European study (Canada not included) there was a higher percentage of subjects reporting breast pain [15.7 vs. 8.5%] abdominal pain [12.6 vs. 2.7%], pharyngitis [11.0 vs. 4.2%], leukorrhea [10.4 vs. 1.5%] and pharyngitis compared to the U.S. study. In the U.S.

study, there was a higher percentage of dysmenorrhea [15.2 vs. 3.1%], emotional lability [14.5 vs. 1.9%], nausea [7.6 vs. 3.1%], depression [10.0 vs. 3.3%] and upper respiratory infection [13.3 vs. 7.9%] compare to the European study. The incidence of headache [23.6% U.S. vs. 17.2% EU], Acne [16.7% U.S. vs. 14.8% EU], vaginitis [17.0% U.S. vs. 15.7% EU], and weight increase [12.7% U.S. vs. 11.8% E.U.] were similar.

Medical Officer’s Comments

- *There were no consistent trends that would suggest a pattern of under-reporting of adverse events in the non-U.S. studies compared to the U.S. study.*

7.2 Adequacy of Patient Exposure and Safety Assessments

Principal Safety Studies

The revised extent of exposure to Implanon in the four principal safety Studies is summarized in Table 11.

Table 11 Extent of Exposure to Implanon in the Principal Studies

Study	Year1		year2		year3		>year3	
	No. of Pts	28-day cycle equivalents						
069001	327	3584	226	2522	136	80		
34505	100	1241	90	1118	77	826	57	678
34507 CDN	52	597	37	436	27	52		
34507 (Hungary/Urbansek and Chile sites only)	221	2695	189	2291	156	1831	112	76
34507 (Hungary/Kovacs and Hungary/Lampe sites only)	81	958	67	853	51	33		
34507 (without Hungary and Chile sites)	333	3812	253	2938	150	167		

Year1=Day 1 to 365; Year2=Day 366 to 730; Year3=Day 731 to 1095; >Year3=Days beyond 1095

Response to information request, 23 May 2005

Medical Officer's Comments

- *The exposure data considered by this reviewer to be probably reliable, adequate, and well-controlled consisted of 648 that entered Year one and completed 7,520 28-day cycle equivalents, 505 subjects that entered Year two and completed 5931 28-day cycle equivalents, and 369 subjects that entered year 3 and completed 2737 28-day cycle equivalents. These numbers are based on the subjects in Studies 69001 (U.S.), 34505*

(Thailand), and two sites in Study 34507 (Hungary (Urbancsek) and Chile) that were inspected by the FDA.

7.2.8 Assessment of Quality and Completeness of Data

- Refer to sections 4.3, 4.5, and 7.2.9.

7.2.9 Additional Submissions, Including Safety Update

The Complete Response included interim reports of three new supporting clinical trials and a periodic safety update with a cut-off date of 1 Sept. 2004.

7.2.9.1 Clinical Trials

The clinical trials for which safety data were provided in the complete response were (Trial 34525 [completed Oct. 2003 – 60 subjects], Trial E-1729 [ongoing – 211 enrolled subjects], and Trial L-1784 [ongoing – 88 enrolled subjects, 120 planned]). Additional information about these trials is provided in Table 12.

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Table 12 List of Clinical Trial Studies – Complete Response

Study number (number of sites) Country: principal investigator (site number)	Start date End date	Age range (mean) Years	Treatment and dose	Number of subjects/ cycles of exposure	Maximum duration of drug treatment	Location of report	Location of CRF tabs	Location of CRF
Publications	Study design							
NON-U.S. UNCONTROLLED CLINICAL STUDIES								
34525 (2) Russia: Aylamazian, FK (RU 003) Russia: Prilepskaya, V (RU 004) Start: December 2001 End: October 2003 No Publications	Open label noncomparative	19 to > 40 years (30.5)	Implanon: Subdermal implant with initial daily release rate of 67µg	60 / 773.8	1-3 years ^a			
NON-U.S. UNCONTROLLED CLINICAL STUDIES (ongoing)								
E-1729 (12) Malaysia: Tambi, I (MY 002) Venezuela: Martinucci, A (YV 002). Bajares, K (YV 004), Szczedrin, W (YV 006), Somogyi, L (YV 008), Bracho, S (YV 009), Centeno, I (YV 010) Austria: Wenzl, R (A 031) Germany: Brandl, E (D 016), Stietzel, H (D 043), Hoffmann, K (D 054), Zahradnik, H (D 175) Start: May 2001 End: ongoing No Publications	Open label noncomparative multi-center efficacy and safety	≥18 to 40 years ^b (Not Available)	Implanon: Subdermal implant with initial daily release rate of 67µg	211 ^c / Not Available	3 years planned	Not applicable	Not Applicable	Not Applicable
NON-U.S. UNCONTROLLED CLINICAL STUDIES (ongoing)								
L-1784 (37) France: Vaillant P (1); Consille B (2), Pagot, A (4), Bault J-P (5); Madinier V (6); Fournier E (7); Letombe B (8); Manini P (10); Villefranque V (11); Graesslin O (12); Chevilot M (13); Madzou S (16); Agostini A (18); Afak N (19); Pernot C (21); Benezech J-P (24); de Saint-Hilaire P (25); Routiout T (26); Ferry P (27); Le Guevel J-M (28); Camo C (29); Castaing N (30); Rozman M (31); Signon E (33); Engelstein M (34); Dubost-Hocquart C (35); Isoard L (36); Nataf V (38); Laik S (39); Dilman J-C (41) Start: July 2003 End: ongoing No Publications	Open label noncomparative multi-center; effect of mefenamic acid on bleeding irregularities	≥18 years ^b (Not Available)	Implanon: Subdermal implant with initial daily release rate of 67µg Mefenamic acid: If ≥8 days bleeding- spotting or ≥5 days bleeding-spotting with ≥10 days in preceding 30 days: courses of 1000 mg/day p.o. for 5 days, with 20 day spacing between successive courses and a maximum of 6 courses during 6 months	120 ^d / Not Available	3 years Implanon/ 6 month study period with mefenami c acid	Not applicable	Not applicable	Not applicable

^a Subjects were to be studied for 1 year but could continue treatment for 3 years.

^b Based on interim data.

^c Number of subjects is based on monitoring reports.

^d Number of subjects planned.

Source: Safety Update: 13Dec2004

Medical Officer's Comment

- Study 34525 is considered by Organon to be not in compliance with Good Clinical Practices.
- Study E-1729 is not considered a principal study but plans to enroll 211 subjects for 3 years to evaluate safety and efficacy of Implanon

- *Study L-1784 is not considered a principal study but plans to enroll 120 subjects for up to 3 years with a 6-month study to evaluate the effects of mefenamic acid on bleeding irregularities.*

Safety Findings

Deaths and Serious Adverse Events

No deaths were reported for trials 34525, E-1729 or L-1784

No SAEs were reported for trial 34525 or trial L-1784. For trial E-1729, 9 subjects were reported to have experienced an SAE. None of these SAEs were related to thromboembolic disease such as pulmonary embolus, cardiovascular accidents, or strokes. There was one case of major depression with psychotic symptoms. Other non-drug related SAEs included chronic sinusitis, ovarian cyst with torsion, leukoencephalomyelitis, viral infection, allergic dermatitis, Basedow's disease, and two cases of breast cancer.

Dropouts

Trial 34525. Seven (11.7%) of the 60 subjects in Trial 34525 discontinued prematurely. The most common reason was bleeding irregularities (4 subjects). Two subjects were reported to have discontinued this trial due to moderate hypertension (see Table 13)

Table 13 Number (%) of subjects who discontinued by reason for discontinuation in Trial 34525

Primary reason for discontinuation ^a	N=60	
	n	%
Bleeding irregularities	4	6.7
AEs	2	3.3
Other reasons	1	1.7
Total	7	11.7

Data in this table were obtained from the trial report for Trial 34525. Table 3 (R&DRR NL0052700).

^a Reason for discontinuation as specified on the End of Trial form

Source Safety Update 13 Dec. 2004

Trial E-1729. A total of 47 (23.5%) of the 200 subjects were reported to have discontinued from Trial E-1729. Eleven subjects were reported to have discontinued due to AEs/SAEs, 18 subjects were reported to have discontinued due to unacceptable vaginal bleeding, and 18 subjects were reported to have discontinued for other reasons. See Table 14

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Table 14 Number (%) of subjects who discontinued by reason for discontinuation in Trial E-1729

Primary reason for discontinuation ^a	N=200	
	n	%
(S)AEs	11	5.5
Unacceptable vaginal bleeding	18	9.0
Other reasons ^b	18	9.0
Total	47	23.5

^a Discontinuation according to the End of Trial form

^b Subject 0031 discontinued the trial but did not receive trial drug.

Note: Table may include non-verified data.

Source: Safety Update 13 Dec 2004

Trial L-1784. Of the 88 subjects enrolled in trial L-1784, 19 (21.6%) subjects discontinued the trial: 15 (17%) subjects due to bleeding irregularities and four (4.5%) for other reasons (Table 15).

Table 15 Number (%) of subjects who discontinued by reason for discontinuation in Trial L-1784

Reason for discontinuation	Implanon™ + Mefenamic acid (N=88)	
	n	%
(S)AEs	0	0
Bleeding irregularities	15	17.0
Lost to follow-up	0	0
Other reasons	4	4.5
Total	19	21.6

Note: Data were taken from monitoring reports and may include unverified data.

Source: Safety Update 13 Dec 2004

Implant Removal or Insertion Events

For trial 34525, there were no complications associated with implant insertion or removal. Due to the limited data available for Trials E-1729 and L-1784, data on implant site insertion, implant site status, and implant removal have not been examined.

Pregnancies

No pregnancies were reported in these three trials.

Medical Officer's Comments

- *The findings thus far in these studies do not differ substantially from those reported for the principal studies.*

7.2.9.2 Postmarketing Safety Experience

This section provides an overview of the worldwide post-marketing safety data on Implanon. This overview is based on case reports on Implanon which were spontaneously reported to Organon, retrieved from the literature, or obtained via other sources (un-sponsored studies) during the period from 28 August 1998 (international birth date of Implanon) up to 01 September 2004. An exception was deaths and SAEs of special interest, which were reviewed in a more recent safety update with a cutoff date of Mar.1, 2005. Both medically confirmed reports as well as medically unconfirmed reports are included.

7.2.9.2.1 Deaths and other Serious Adverse Events of Special interest

Deaths. Since the introduction of Implanon to the market, five deaths have been reported. Narratives for these cases are presented in the Medical Officer's clinical review of the original submission (dated September 30, 2003). No new deaths have been reported through March 1, 2005.

Other Serious Adverse Events of Special Interest. The numbers and rates of death, pulmonary embolus, cerebrovascular accident, deep vein thrombosis, and myocardial infarction based on postmarketing safety reports worldwide and for Europe only (in number of events per 100,000 woman-years of use) are listed in the table below (cutoff date – March 1, 2005)

Table 16 Event Rates by 100,000 woman-years of use

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

^aThe following countries were included for Europe: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Portugal, Sweden, United Kingdom, Czech Republic, Finland, Malta, Norway, Slovak Republic, Spain, Switzerland, Norway, and Iceland.

^bBoth medically confirmed and medically unconfirmed reports are included.

^cSuperficial venous thrombosis are excluded from this analysis. Cases in which it is unclear whether it involves a deep or superficial thrombosis (e.g. only "thrombosis" was reported) are included.

^dVenous thromboembolic events is the total rate of pulmonary embolus and deep vein thrombosis

Source: Safety Update 18 May 2005

Medical Officer's Comments

- *There have been no significant changes in these rates since the last submission.*
- *The number and types of serious post marketing adverse events reported by the Applicant are compatible with those to be expected with a hormonal contraceptive product that has been used by more than _____ women.*

b(4)

7.2.9.2.2 Insertion Removal Related Events (IRREs)

The international birth date of Implanon is 28 August 1998. The Data Lock Point (DLP) for the periodic report on IRREs for Implanon in the Complete Response was 1 September 2004. The analysis in this report for IRREs covered the Total Period (TP) (28 August 1998 up to 1 September 2004). This TP is subdivided into the <Prior Period (<PP) (28 August 1998 up to 1 September 2003), the Prior Period (PP) (1 September 2003 up to 1 March 2004), and the Analysis Period (AP) (1 March 2004 up to 1 September 2004).

The data analyzed in this report on IRREs focused on the medically confirmed reports, in which the reporter is a health professional and/or a regulatory authority. Since the launch of Implanon in various countries, there have been no post-marketing actions taken by any regulatory agency concerning these issues. There were no suspensions or withdrawals of Implanon in any market.

An Insertion and/or Removal Related Event (IRRE) is defined as:

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

During the TP, Organon received 6,173 medically confirmed reports for Implanon: 1,814 of these medically confirmed reports contain one or more IRREs. In addition, Organon has received 1,905 medically unconfirmed (e.g. consumer) reports, of which 133 contain one or more IRREs. The medically confirmed IRRE reports have been divided by Organon into two groups:

Group 1: IRREs in association with pregnancies

This includes 561 pregnancy reports containing 1,141 IRREs with an average number of 2.0 IRREs/report. Analysis and discussion of Group 1 is included in the postmarketing pregnancies section.

Group 2: IRREs not in association with pregnancies

This includes 1,253 reports containing 3,136 IRREs with an average number of 2.5 IRREs/report.

Compared with the number of IRRE reports received in the PP, there was a slight increase in the total number of reports received in the AP (see Table 17). The number of reports received from France, Switzerland, and the United Kingdom in the AP show an increase compared with the PP. According to the Applicant, as Implanon was launched between 1999 and 2001 in these countries, this increase may be explained by an increase in removal of Implanon because after a

period of three years from market introduction more Implanon rods will be replaced or removed. The increase in the number of reports received from the United Kingdom may be explained by an increase in the sales in the AP. Furthermore, the number of reports received from Germany and the Netherlands show a decrease, which could be explained by a decrease in sales, in both countries, in the AP as compared to the PP.

Table 17 Number of medically confirmed reports for IRREs by country and reporting period.

COUNTRY	Number of Reports*			
	<PP	PP	AP	TP
Australia	81	22	17	120
Austria	15	2	1	18
Belgium	8	5	8	21
Brazil	10	4	1	15
Denmark	11	9	7	27
Finland	0	1	0	1
France	92	35	60	187
Germany	157	40	28	225
Iran, Islamic Republic of	0	1	0	1
Ireland	22	16	15	53
Italy	1	0	0	1
Luxembourg	0	0	1	1
Mexico	1	0	0	1
Netherlands	110	24	18	152
Norway	0	3	9	12
Portugal	3	2	5	10
Slovakia	1	0	0	1
South Korea	1	2	9	12
Sweden	17	10	10	37
Switzerland	29	13	24	66
Turkey	0	0	1	1
United Kingdom	150	57	83	290
Venezuela	0	0	1	1
Total	709	246	298	1253

*Number of reports containing one or more IRREs not associated with pregnancies

Source: Safety Update 13 Dec. 2004

Medical Officer's Comment

- *It is difficult to draw firm conclusions from comparisons of the frequency of reported IRREs between the PP and AP. This is because the number of reports is relatively low. Furthermore, the analysis time period of six months is relatively short and fluctuations in the number of reports (e.g. due to increased awareness secondary to publicity in the media) and in sales may occur. In addition, the reporting of IRREs is not necessarily chronologically related to the sales.*

Insertion Related Events

A subdivision of the IRREs associated with the insertion of Implanon is provided in Table 18.

Table 18 Insertion related events

IRRE	Reporting period			
	PP	AP	AP	TP
IRRE-BLUE ROD INSERTED	1	0	0	1
IRRE-BROKEN OR CUT	35	18	15	68
IRRE-DEEP INSERTION	141	49	68	258
IRRE-DIFFICULT INSERTION	62	15	13	90
IRRE-MULTIPLE INSERT	35	2	8	45
IRRE-NO ROD	39	20	11	70
IRRE-ROD BENT	20	11	8	39
IRRE-WRONG PLACE	17	5	6	28
Total	350	120	129	599

Source Safety Update 13 Dec 2004

Most frequently reported during the TP were ‘*IRRE-deep insertion*’ (258 occasions), ‘*IRRE-difficult insertion*’ (90), ‘*IRRE-no rod*’ (70) and ‘*IRRE-broken or cut*’ (68). The code ‘*IRRE-difficult insertion*’ is used to store all remaining problems concerning a difficult insertion. This IRRE code contains various insertion problems, which could not be placed in another IRRE category. According to the Applicant, failed insertions (‘*IRRE-no rod*’) are most likely the result of not keeping the applicator in such a way that the needle is always pointing upwards after removing the needle shield.

Medical Officer’s Comments

- *There were a greater number of deep insertions (the most common insertion problem) during the analysis period (AP) compared to the previous period (PP). An information request was sent to the Applicant who provided the following information: (1) the increase in the number of reported deep insertions may be explained by an increase in the number of removals of Implanon and consequently the need for localization of the implant; (2) a subsequent periodic report with a data lock point of March 1, 2005 showed a slight decrease to 57 deep insertions.*

Localization related Events

Localization related events are summarized in Table 19. According to the Applicant, difficult localization of the implant may be caused by using an incorrect insertion technique (resulting in e.g. a deep insertion), inserting the rod in the wrong place (for example, abdomen, leg, etc.), or non-insertion of the implant. Additionally, in some cases migration of the implant has been reported as a possible reason for difficult localization.

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Table 19 Localization related events

IRRE	Result	Reporting period			
		PP	PP	AP	TP
IRRE-PALPABLE PRESENCE	YES	54	20	29	103
	NO	322	132	180	634
	DOUBT	9	0	4	13
IRRE-ULTRASOUND PRESENCE	YES	178	52	69	299
	NO	167	66	88	321
	DOUBT	9	5	1	15
IRRE-MRI PRESENCE	YES	30	7	6	43
	NO	41	29	35	105
	DOUBT	3	0	2	5
Total		813	311	414	1538
IRRE-DOUBT PRESENCE	YES	40	22	30	92

In the above mentioned cases doubt means that, e.g. the result of palpation was doubtful and should therefore not be confused with 'IRRE-doubt presence'.

Source: Safety Update 13 Dec 2004

Removal Related Events

A subdivision of the IRREs associated with the removal of Implanon is provided in Table 20. Easy and quick removal of Implanon depends mainly on a correct (subdermal) insertion procedure, but also on knowledge about and some experience with the removal procedure.

Table 20 Removal related events

IRRE	Result	Reporting period			
		PP	PP	AP	TP
IRRE-ENG POSITIVE, ROD NOT FOUND	YES	12	15	30	57
	YES/closed	14	12	18	44
	YES/comed ^{vii}	1	0	0	1
	YES/continued	8	12	8	28
	YES/removed	22	20	11	53
IRRE-MIGRATION	YES	45	15	12	72
IRRE-REMOVAL PROBLEM	YES	143	49	73	265
IRRE-SUR REMOVAL GEN ANESTHESIA	YES	38	11	19	68
IRRE-SURGICAL INTERVENTION	YES	40	10	7	57
Total		323	144	178	645

^{vii} Patient concomitantly used another contraceptive, which cross-reacts with the etonogestrel radio immuno assay
 Source: Safety Update 13 Dec 2004

Examples of 'IRRE-removal problem' are:

- A removal attempt was made but Implanon was not found.
- A larger incision was needed to remove Implanon.
- More time was needed to remove Implanon.

During the TP, 'IRRE-ENG positive, rod not found' was reported in 183 occasions. This IRRE code is used to indicate that the result of the patient's serum ENG assay was positive (above LOQ), but the Implanon rod could not be localized (palpation and/or US and/or MRI negative) and hence could not be removed.

Medical Officer's Comments:

- *Because of the greater number of deep insertion in the AP vs. the PP, it was anticipated that there would be more problems with removal; however, these problems were less than anticipated.*

7.2.9.2.3. Post Marketing Pregnancy Reports

Spontaneous reports describing the occurrence of 886 pregnancies in women using Implanon have been reported to Organon's Drug Safety Surveillance Department (DSSD) during the period from market introduction of the implant in August 1998 up to 1 September 2004. After evaluation by the Applicant, a classification is given as to the likely cause of the unintended pregnancy. An overview of the categories that are used for this classification is provided in Table 21. Five groups (with in total 13 subgroups) have been defined to evaluate and classify the pregnancies.

Table 21 Pregnancy analysis groups, which reflect the reasons for the occurrence of a pregnancy in women using Implanon

Groups	Subgroups
1. Presence of pregnancy not confirmed	
	<ul style="list-style-type: none"> • Presence of pregnancy not confirmed
2. No active implant present	
	<ul style="list-style-type: none"> • Implanon not <i>in situ</i> • Blue placebo training rod or other non-active parts inserted
3. Conception took place outside period of Implanon use	
	<ul style="list-style-type: none"> • Already pregnant before insertion of Implanon* • Pregnant after removal of Implanon*
4. Contraceptive method failure	
	<ul style="list-style-type: none"> • Contraceptive method failure
5. Reason for pregnancy cannot be determined with complete certainty	
	<ul style="list-style-type: none"> • Presumed contraceptive method failure • Reporter states that woman was already pregnant, but no confirmation with data on gestational age
Groups	Subgroups
	<ul style="list-style-type: none"> • Conception around date of insertion* • Conception around date of removal* • Doubt about the presence of Implanon • Insufficient data to determine if insertion or removal of Implanon was before or after date of conception • Presence of Implanon has not been investigated

* See Figure 1.

Note: in cases where more than one reason is applicable, the most important reason according to NV Organon is used for the final classification.

Source: Safety Update 13 Dec 2004

In total, pregnancies were described in medically confirmed reports (including 33 ectopic pregnancies). An additional 50 medically unconfirmed reports of pregnancies (i.e. reported by consumers or others, such as lawyers and journalists) were received (including one ectopic pregnancy). The analysis described in this review and provided by the Applicant is focused on the medically confirmed postmarketing pregnancy reports. Additionally, two unintended pregnancies were reported in Implanon clinical trials not sponsored by the Applicant. According to the Applicant, no on-treatment pregnancies have been observed in Implanon sponsored studies (see Section 6.1.4).

Of the medically confirmed reports of pregnancy pregnancies were reported during the <PP, during the PP, and during the AP). The numbers of pregnancies per reporting period classified by Group (i.e., likely cause) is presented in Table 22.

Table 22 Number of pregnancies per group per period

Pregnancies reported for Implanon	Group 1	Group 2	Group 3	Group 4	Group 5	Total
Pregnancies received in the <PP						
Pregnancies received in the PP						
Pregnancies received in the AP						
Pregnancies received in the TP						

b(4)

Source Safety Update 13 Dec 2004

Group four (classified by the Applicant as a “contraceptive Method Failure” includes all pregnancies in which based on the available data the woman conceived while Implanon was *in situ*. In 35 of the pregnancies, an interaction between Implanon and a concomitant drug might have occurred. Twelve of the pregnancies in Group 4 were ectopic pregnancies.

The market use of Implanon during the period of August 1998 up to 1 September 2004, based on the sales in those countries where Implanon is on the market, is estimated by the Applicant to amount to implants. Regarding the total sales, a pregnancy rate of 0.051 pregnancies per 100 sold implants can be calculated, based on post-marketing data. In this number, all reported pregnancies, both medically confirmed and medically unconfirmed, are included. The pregnancy rate for the Applicant’s so-called ‘contraceptive method failure’ group (Group 4 – confirmed pregnancies only) is estimated at 0.0064 medically confirmed pregnancies per 100 sold implants. See Table 23.

b(4)

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Table 23 Pregnancy rates for Implanon based on post-marketing data

	Pregnancy rate per 100 implants	Number of pregnancies [#]
Overall	0.048 (0.051)	
Excluding Group 2*	0.032 (0.034)	
Excluding Group 2* and 3**	0.029 (0.031)	
Group 4***	0.0064 (0.0067)	

b(4)

[#] Number between brackets also include the medically unconfirmed pregnancies

* Group 2: No active implant present

** Group 3: Conception took place outside the period of Implanon use

*** Group 4: Contraceptive method failure

Source: Safety Update 13 Dec 2004

Medical Officer's Comments

- *Unintended pregnancies in women who choose to use Implanon may occur due to reasons other than insufficient contraceptive action. This mainly relates to an incorrect insertion technique, resulting in accidentally not inserting Implanon without realizing this, and to insertions not in agreement with the recommended time frame, leaving the woman insufficiently protected for a certain period.*
- *The Applicant's classifying only medically confirmed (total) reported pregnancies as contraceptive failures cannot be supported. All reported pregnancies (whether due to implantation error by the healthcare provider or true device failure) should be considered as a pregnancy in an Implanon user.*
- *If all medically confirmed pregnancies are considered and all sold devices are assumed to have been implanted (an over estimate of actual use), the pregnancy rate was 0.048 pregnancies per 100 sold implants.*
- *If it is assumed that (1) all sold implants were inserted, (2) the average implant was in place for one year, and (3) only 1 in 50 pregnancies were reported to the applicant, the estimated Pearl Index would be 2.4 pregnancies per 100 woman years of use. Even this "extreme case" value would likely be acceptable for a hormonal contraceptive product based on the estimated "actual or typical use" failure rate of about 5% for combination oral contraceptive users.*

b(4)

Drug Interactions as a cause for method failure.

In 51 medically confirmed pregnancies, a suspected drug interaction was reported. In 40 pregnancies, an interaction may have occurred between Implanon and anti-epileptic drugs.

Medical Officer's Comments

- *Women on treatment with any drugs that may interact with Implanon and reduce its effectiveness should temporarily use a barrier method of contraception in addition to Implanon.*

- *The drugs that interact with Implanon to decrease its' effectiveness should be clearly delineated in the label. (see original review).*

Ectopic Pregnancies

In total, medically confirmed ectopic pregnancies were reported since market introduction of Implanon (since the review of the original NDA submission, 9 more ectopic pregnancies have been reported). Three ectopic pregnancies occurred in Group 2 of the Applicant's classification (see Table 21). In these cases, the etonogestrel level was below the detectable limit of the assay, thus implying that no active implant was in place. In Group 3, one ectopic pregnancy occurred, a report in which a woman became pregnant after the removal of Implanon. In Group 4, 12 ectopic pregnancies occurred for which no reason other than failure of contraceptive action of Implanon could be identified based on the information supplied to NV Organon. In 17 of the reports in Group 5, an ectopic pregnancy was reported in association with Implanon use. Concerning these 17 reports, it should be noted that:

- In 10 cases no information was provided to determine the estimated date of conception accurately, thus it is not clear yet whether the patient had conceived prior to or after Implanon insertion.
- In four cases, the presence of Implanon was not clear.
- In one case, the estimated date of conception was around the date of insertion of Implanon.
- In one case, the reporter stated that the woman was already pregnant before insertion of Implanon.
- In one case, a contraceptive method failure was suspected, but this could not be determined with complete certainty.

Medical Officer's Comments

- *Assuming that all ectopic pregnancies were associated with the use of Implanon, of the medically confirmed pregnancies (or 3.9%) were ectopic. This is about 2-fold higher than the generally reported rate for ectopic pregnancies in women not using contraception (2 ectopic pregnancies per 100 total pregnancies). Although the proportion of reported pregnancies that were ectopic pregnancies was higher in the Implanon users than the historical proportion in a population using no contraception or combination oral contraceptives, it was similar to, or lower than, the proportion seen in women using other progestin-only contraceptives. In addition, the absolute number of ectopic pregnancies was considerably less than would be expected in a population of similar women at risk for pregnancy who used no contraception.*
- *Clinicians/women are more likely to report ectopic pregnancies versus normal pregnancies, thus explaining, in part, the relatively high proportion of pregnancies reported to be ectopic.*
- *The label should alert physicians about the possibility of ectopic pregnancy.*

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

In the clinical development program, no deaths occurred in any study. In these studies, there were no serious cardiovascular adverse events (e.g., no reports of pulmonary embolus, myocardial infarction, or thrombotic intracerebral events). Changes in menstrual bleeding patterns (primarily irregular or unplanned bleeding) were the most frequently reported subject complaint, occurring in more than 85% of subjects. The most common reasons for discontinuing Implanon™ in the principal studies and the percentages of subjects discontinuing because of them were bleeding irregularities (43/330 (13.0%)- U.S. Study; 123/788 (15.6%)-non U.S. Studies). More than 19 % of 1,401 subjects (principal and supportive studies) had a > 10% increase in Body Mass Index from baseline. 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 clinically significant changes.

Since the start of marketing of Implanon in 1998, more than _____ units have been sold as of 01 Sep 2004. Updated postmarketing safety data from product launch through 1 March 2005 included reports of 4 deaths (3 deaths due to pulmonary embolus; one death due to bacterial infection), 13 cases of pulmonary embolus, 18 cases of deep vein thrombosis, 18 cases of cerebrovascular accident, and 2 cases of myocardial infarction. Based on estimated sales, rates for these serious cardiovascular adverse events are not above expected rates. 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 common following the initial marketing of the product.

b(4)

8 ADDITIONAL CLINICAL ISSUES

8.7 Postmarketing Risk Management Plan

Training of Healthcare Providers

The applicant's proposed Risk Management Program regarding insertion and removal of Implanon™ consists of the following elements:

Committees and Development of Local Experts

A Steering Committee will be formed to develop an effective training program and will consist of Organon's "Thought Leader Consultants." The training program will be piloted in five cities in the U.S. to refine it. The 'pilots' will be led by a Steering Committee member and the attendees will become part of the "Implanon Faculty". All attendees will be required to attend a Faculty Development program for training of physicians who will be serving as "Implanon Faculty". The training programs will be lead by these faculty members who will be trained 1 month prior to launch by the Steering Committee members. These faculty members will also become the "Local Implanon Expert" for difficult cases and referrals.

Healthcare Provider Training

Each training session will be a 3-hour program divided into 4 sections:

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

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

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

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

In response to an information request sent to Organon on May 6, 2005, Organon provided the following updated information and clarification regarding the training of health care providers and the risk management program:

- A sample of the training kit with a representative VHS video (the DVD is still under development). The “Training and Demonstration Unit Product” was not yet available; however, European samples were previously sent. The materials and training video were reviewed by the primary reviewing medical officer and project manager and were considered acceptable. Comments will be provided to the applicant.
- Organon stated, “The majority of the program will be devoted to practicing the insertion and removal procedures using the model arm.”
- Organon proposed the following evaluation program to obtain accurate estimates of the rates of various IRRAEs and to implement appropriate remedial actions if necessary:
 - Survey a sample of Health Care Professionals (HCP) who complete the training about their perceptions of the training by means of a questionnaire.
 - A regional Clinical Liaison will be hired by Organon “solely to provide follow-up to the trained HCPs”.
 - “A complete listing of all HCPs trained by Organon on the insertion/removal of Implanon will be available to the US Drug Safety Department of Organon and attempts will be made to match up each reported adverse event with an HCP on this training list. Adverse events and technical complaints will be captured and processed per existing SOP. Additional metrics will include: the training program the HCP attended, name of the faculty who conducted the training, time period since attendance of the program, number of Implanon units distributed, number of other adverse events or IRREs that

can be linked to the HCP, type of other adverse events or IRREs that can be linked to an HCP.”

Medical Officer's Comments

- *The applicant's description of their plan for monitoring Implanon IRREs is lacking in details and therefore, not adequate. Organon should develop a Phase 4 monitoring program in the U.S. for 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.*

Consultation with FDA Office of Drug Safety

A consult was sent to the Office of Drug Safety (ODS) and the following comments were included in their recommendations:

Training Program

- The training should include instructions to: (1) provide a copy of the Patient Package Insert (PPI) to the patient prior to Implanon insertion and (2) use the PPI as a counseling tool by reviewing it with the patient prior to Implanon insertion
- Include a section in the training program to encourage providers to report any insertion and/or removal related events (IRRE) to the sponsor. Include a 1-800 number in the training materials for reporting of IRRE or other types of adverse events.

Medical Officer's Comments

- *The applicant will provide a copy of the PPI and review it prior to insertion.*
- *The applicant will provide a 1-800 number for more information. Whether to report IRREs or other types of adverse events in this manner will be determined later.*

Surveillance/Pharmacovigilance

- The applicant can consider the development of a two-part form: one part would be completed and returned to the sponsor at insertion, and the second part at the time of removal.
- It would be helpful to have sponsor summarize insertion and removal related events reported for U.S. patients as a separate section in their US Periodic Report/Periodic Safety Update Report,
- If possible, attempt to identify (via IRRE reports and surveys) implanters/clinic sites with a relatively high number of IRRE's and provide targeted training to them.

Medical Officer's Comments

- *The periodic safety update reports are currently organized by country.*
- *The sponsor plans to reinforce training at all sites with the use of "clinical liaisons" as needed, to be determined by the clinical site.*
- *Reports of IRREs (if submitted by MedWatch or a separate process) should include the site of the reporter.*

Other Issues Raised by ODS

- “With regard the Sponsor’s Distribution Program—Consider changing the chart sticker at the time of implant to include lot number, location of implant, date of implant, **AND prompt for the physician to record how implantation was confirmed.**”
- DMETS had concerns with including the active drug substance in the Implanon Training and Demonstration Device. They recommend that the “practice implant” not contain active drug substance.

Medical Officer’s Comments

- *Implant insertion should be confirmed by palpation only. If ultrasound or MRI is needed, the HCP should consider removing that implant and inserting another that can be palpated.*
- *The Division does not concur that the training device need not contain the active ingredient. This would require the manufacture of an implant that might not have the physical properties as the to be marketed product. The training device should have the same texture and consistency as the to be marketed product, allowing for replication of the “real” device and facilitating a better training experience.*

9 OVERALL ASSESSMENT

9.1 Conclusions

Adequacy of Clinical Trial Database

During the previous review cycle ending Oct.28, 2004, NDA 21-529 received and approvable action. The applicant was informed that approval was contingent on the following:

- (1) resolution by Organon of the deficiencies identified by the Dutch Medicines Evaluation Board (DMEB) inspectors and (2) the Division’s conclusions that the clinical data submitted in NDA 21-529 are sufficient to (a) support the conclusion that Implanon is safe and effective for the prevention of pregnancy in women and (b) to allow labeling of Implanon that accurately reflects the safety and efficacy profile of Implanon.
- Alternatively, they could conduct another clinical trial to provide safety and efficacy data to support product labeling.

The applicant chose the first option: to attempt to resolve the deficiencies identified by the DMEB.

The exposure data considered by this reviewer to be *probably reliable*, adequate, and well-controlled consisted of: 648 subjects that entered Year 1 and completed 7520 28-day cycle equivalents during Year 1, 505 subjects that entered Year 2 and completed 5931 28-day cycle equivalents during Year 2, 369 subjects that entered Year 3 and completed 2737 28-day cycle equivalents during Year 3. This data is derived from studies 069001 (U.S. - FDA inspected three sites), 34505 (Thailand – not inspected), and 34507 (Europe -- FDA inspected two large sites).

Medical Officer's Comments

- *The WHO guidelines, developed at a February 1987 symposium in Geneva, recommended that "clinical trials be randomized and include at least 1,000 patients over a one-year period for a total of 10,000 cycles." WHO presented its guidelines for review by the FDA Reproductive Health Advisory Committee meeting in 1987. The agency noted, and the committee agreed, that the current FDA guidelines were equivalent to that recommended by WHO, except for the recommendation for randomized studies. FDA Advisory Committee meetings are open, public forums; therefore, these recommendations have been public knowledge since prior to 1987.*
- *The approvals of all other long acting injectable or implantable contraceptive drug products (Norplant, Norplant II [Jadelle], Mirena, and depo-Provera) were based on phase III clinical trials that included > 10,000 28-day cycle equivalents in the first year.*
- *The reliability/integrity of the data in Study 34507 is questionable, based on discrepant reports and opinions from investigators, inspectors, and regulatory agencies. The European regulatory agencies did not challenge or dispute the critical findings of the Dutch and local regulatory inspectors; the DMEB instead relied heavily on postmarketing experience as to the basis for their continued support for the safety and effectiveness of Implanon. The DMEB also recommended significant changes to their Implanon label, which implies doubt about the reliability and adequacy of the clinical trial data.*
- *The Implanon clinical trial exposure data for Year 1 considered by this reviewer to be probably reliable, adequate, and well-controlled consisted of 648 subjects who completed /7520 28-day cycle equivalents (see above).*
- *Implanon studies fall short of the WHO/FDA recommendations for Year 1 by at least 2500 cycles.*
- *This reviewer does not think the deficiencies identified by the Dutch Medicines Evaluation Board, regarding adequacy of reliable data, were adequately resolved by the applicant.*

Efficacy Summary

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 ≤ 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 _____ 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.

b(4)

Safety Summary

Clinical Trial Data

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.

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.

b(4)

9.2 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.

9.3 Recommendation on Postmarketing Actions

9.3.1 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 when inserting or removing Implanon. All attendees will be required to attend a Faculty Development program to become developed as faculty for training other clinicians at their clinical sites. 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, (2) clinical Contact Specialists to review the skills of clinicians, and (3) a Steering Committee to review issues that have arisen and the progress of the training programs, surveys and evaluations

9.3.2 Required Phase 4 Commitments

Organon should develop a Phase 4 monitoring program in the U.S. for 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.

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

Labeling revisions were not finalized because this reviewer recommends that additional clinical data be provided before marketing approval for Implanon is granted.

9.4 Comments to Applicant

“The exposure data considered by the Division to be probably reliable, adequate, and well-controlled consists of 648 subjects/7520 28-day cycle equivalents that entered year one, 505 subjects/5931 28-day cycle equivalents that entered year two, 369 subjects/2737 28-day cycle equivalents that entered year 3, and 169 subjects/754 28-day cycle equivalents that completed 3 or more years. This data is derived from studies 069001 (U.S. - FDA inspected three sites), 34505 (Thailand – not inspected), and 34507 (Europe – FDA inspected two large sites).

You have not provided sufficient clinical trial data from adequate and well-controlled clinical trials in accordance with the requirements for regulation § 314.125 (b) (5) of the Code of Federal Regulations. The Division has required at least 10,000 28-day equivalent treatment cycles in Year 1 for other new contraceptive drug products that have involved a new molecular entity or a new route of delivery. We estimate that you have provided data from only approximately 7,500 28-day equivalent treatment cycles obtained from clinical trials (Studies 069001 and 34505 [subject to FDA inspection]) and 2 clinical trial sites of Study 34507 (those of Dr. Urbancsek

[Budapest] and Dr. Croxatto [Santiago] that are considered by the Division to be “adequate and well controlled.”

In addition, you have provided data from less than 200 women who completed 3 years of treatment.

Approval of Implanon for 2 years of use is contingent on the following:

1. Provision of additional data that consists of 2500 28-day cycle equivalents during the first year of use, that are from adequate and well-controlled studies, and that are considered reliable and of good integrity after inspection by the Division of Scientific Investigation at the FDA. Based on the information that you provided to the Division in a teleconference on June 6, 2005, provision of additional data that will include 2500 28-day cycle equivalents during the first year of use will likely require that you conduct an additional clinical trial.
2. Satisfactory inspection of study 34505 (Thailand) by the FDA.
3. Development of a Phase 4 monitoring program in the U.S. for insertion and removal related adverse events that is acceptable to the FDA.
4. Submission of a final labeling

Approval of Implanon for 3 years of use is contingent on your (1) meeting the recommendations for approval for 2 years of use and (2) providing additional data from an adequate and well-controlled trial(s) for treatment year 3.

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10. APPENDICES

10.3 Executive Summary of Original Review by Primary Medical Reviewer (October 29, 2004)

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1 Recommendation Regarding Approval

1.1.1 Approvability

This reviewer recommends an approvable action for Implanon™ (etonogestrel implant) for the prevention of pregnancy in reproductive age women for three years. Approval is contingent on the following:

- (1) Resolution by Organon of deficiencies identified by the Dutch Medicines Evaluation Board inspectors and the (2) Division's conclusions that the clinical data submitted in NDA 21-529 are sufficient (a) to support the conclusion that Implanon is safe and effective for prevention of pregnancy in women and (b) to allow labeling of Implanon that accurately reflects the safety and efficacy profile of Implanon™.
- A satisfactory inspection report from the Office of Compliance regarding the sterilization facility
- Completion of a final label. b(4)

1.1.2 Basis for Recommendation regarding Approvability (Risk/Benefit Analysis)

Because of potential serious issues concerning (1) the clinical conduct of the Principal Studies supporting the safety and effectiveness of Implanon™ and (2) lack of adequate monitoring and oversight by the Applicant of these studies, the accuracy and adequacy of the data submitted to date in NDA 21-529 to support the safety and effectiveness of Implanon™ for prevention of pregnancy in women cannot be assured. Until these issues are resolved, approval cannot be recommended.

If these issues can be satisfactorily resolved, and the data submitted in NDA 21-529 are deemed to accurately reflect the safety and effectiveness of Implanon™, it can be concluded that Implanon is a safe and highly effective method of contraception that does not compromise future fertility. For most women, the benefits would outweigh the risks.

The benefits of Implanon™ include the following:

- Compliance non-dependant
- Single rod
- Highly effective (< 1% failure rate)

- Rapid onset of action
- Rapid reversibility and return to fertility

The major disadvantages are that a minor surgical procedure is required for use and there is a high rate of frequent/prolonged vaginal bleeding. These bleeding irregularities can be a major nuisance, but do not cause a safety concern.

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

1.2.1 Risk Management Program (Training of Healthcare Providers)

A Steering Committee will be formed to develop a training program. All attendees will be required to attend a Faculty Development program to become trained as faculty for training other clinicians at their clinical sites. Each training session will include clinical information, insertion/removal/localization procedures, hands on training using model arms, and patient counseling. Upon completion of the program, the attendees will receive a model arm, practice kit and a CD-Rom to review the training. 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:

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

Organon should develop a Phase 4 monitoring program in the U.S. for insertion and removal related adverse events

1.2.2 Additional Data to Support 3 Years of Use

It is recommended that the Applicant conduct an additional clinical trial(s), or supply additional confirmatory treatment data obtained through an observational study or registry that would further support the 3-year treatment regimen (effectiveness during treatment Year 3 of a single Implanon implant).

2. SUMMARY OF CLINICAL FINDINGS

2.1 Brief Overview of Clinical Program

2.1.1 Drug

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

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inserted subdermally at the inner side of the upper arm. After insertion, ENG is slowly released through the rate-controlling skin over a period of 3 years.

2.1.2 Design of the Clinical Program

NDA 21-529 provided data from approximately 1803 subjects in 19 completed Phase II and III studies plus one ongoing phase II study, who 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). The clinical development program was designed to evaluate contraceptive efficacy and safety. In addition, dedicated studies on the pharmacokinetics, pharmacodynamics and metabolic safety of Implanon™ were performed.

Four studies were considered to be the principal efficacy and safety studies by this reviewer and the Applicant (Studies 069001, 34505, 34507, and 34507-CDN). All were non-comparative, historical controlled studies. In addition to efficacy and safety, these 4 studies also provide 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 and brief summaries of these studies are provided below.

Study 069001- Study 069001 (United States) was an open-label, non-comparative, historically controlled multicenter (16 centers) efficacy and safety study in healthy female subjects. The duration of treatment was up to 24 months. Subsets of Study 069001 evaluated pharmacologic parameters, ophthalmological variables, lipid metabolism, carbohydrate metabolism, and endometrial morphology. Three hundred and thirty (330) subjects were enrolled and treated for a total of 6,198 cycles (based on 28-day cycles and equivalent to 474 women-years of use). One hundred sixty one (161) subjects discontinued in the first 2 years (49% of 330 subjects), and 169 subjects completed 2 years (51%, 169 of 330 subjects).

Study 34505- Study 34505 (Thailand) was an open-label, single-center, non-comparative, historically controlled efficacy and safety study. The duration of treatment was 24 months with an option for a 1 year or 2 year extension period. Upon removal of the implant, subjects were monitored for a 3-month follow-up period. One hundred (100) subjects were enrolled and treated for a total of 3,836 cycles (equivalent to 296 women-years of use). Eighty (80) subjects completed 2 years; 68 subjects extended for 3 years, and 60 completed the 3rd year; 51 subjects extended for 4 years and 47 completed the 4th year. In total, 32 subjects (32% of 100 subjects) discontinued Study 34505, of which, eight were lost to follow-up.

Study 34507- Study 34507 (Europe and Chile) was an open-label, multicenter (21 sites) non-comparative, historically controlled efficacy and safety study. Study 34507 was conducted primarily in Europe (Germany, Belgium, France, Netherlands, Sweden, Hungary, and Austria) but did have a single study site in South America (Chile). The treatment duration was up to 24 months. Study centers in Santiago, Chile and Budapest, Hungary extended the treatment duration to up to 3 years. Upon removal of the implant, subjects were monitored for a 3-month follow-up period. Six hundred and thirty-six subjects (636) were enrolled in Study 34507; 635 subjects received the implant. Four hundred thirty-six (436) subjects completed 2 years, 199 subjects discontinued in the first 2 years; 147 subjects extended for 3 years. 10 subjects

discontinued during year three, and 137 subjects completed 3 years. A total of 205 subjects discontinued the study and 4 subjects were lost to follow-up,

Study 34507 CDN- Study 34507 CDN was an open-label, single-center, non-comparative efficacy and safety study. The duration of treatment was up to 24 months. Fifty-two (52) subjects were enrolled and received an implant, 19 subjects discontinued (36.5%, 19 of 52 subjects), and 33 subjects completed 2 years (63.5% of 52 subjects) of treatment.

Four studies specifically addressed the pharmacokinetics (PK) and pharmacodynamics (PD) of Implanon™, in particular examining ovulation inhibition and plasma levels of etonogestrel (Studies 34502, 34508, and 34515). In addition, one 2-year study (Study 34504) was performed with a “leached” implant to provide information on the in vivo release of Implanon in the 2nd year of use.

A further six studies explored specific safety parameters, particularly for effects on hemostasis (Study 34509), lipid metabolism (Studies 34510, 34512), carbohydrate metabolism, adrenal and thyroid function (Study 34511), bone mineral density (BMD) parameters (Study 34522) and the effects of Implanon™ on lactation and development of infants (Studies 34523).

Data from five additional studies that were performed in China, Russia, and Mexico were also submitted and considered by the Applicant as additional information in support of the claim of preventing pregnancy.

Five studies conducted in Indonesia (not included in the 19 studies) were disqualified because of significant Good Clinical Practice violations. The Applicant had classified two of the five studies as principal safety and efficacy studies and enrolled 649 subjects.

2.2 Efficacy

Principal Efficacy Studies.

The Applicant submitted data from four adequate and historically controlled clinical trials (principal studies 069001-U.S., 34505-Thailand, 34507-Europe, and 34507 CDN-Canada) to support the efficacy of Implanon for the prevention of pregnancy for up to 3 years. These 4 clinical trials had similar inclusion/exclusion criteria and enrolled 1117 reproductive aged, healthy female subjects.

The table below summarizes the annual Pearl Index and annual exposure to Implanon for subjects ≤ 35 years old.

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Annual Pearl Index and Annual Exposure to Implanon™ (Subjects ≤ 35 years old at entry)

Parameter	Year 1	Year 2	Year 3
Pearl Index	0.5	0	0
95% CI	(0.1, 1.2)	(0, 0.5)	(0, 1.8)
Woman Years of Use	886	691	202

Source: Response to Information Request, 9 SEP 04

Through Two Years of Use. Overall, the total number of 28-day cycle equivalents was 22,695 with 1,746 woman-years of exposure. Conception for four pregnancies were estimated by the FDA medical reviewer to have occurred (n=3) or may have occurred (n=1) within 7 days of implant removal. Based on these four pregnancies, the cumulative Pearl index for women ≤ 35 years of age was calculated to be 0.27 (95% CI: 0.08 to 0.69) through two years of treatment. This value is well within an acceptable pregnancy rate reported with other methods of hormonal contraception.

Third Year 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 218.8 woman-years of exposure equivalent to 2,844.4 cycles of exposure. The Pearl index for these subjects was 0 [95% CI: (0, 1.7)]. Among women ≤ 35 years of age there were 183.9 woman-years of exposure equivalent to 2,391 cycles of exposure. The Pearl index for these subjects was 0 [95% CI: (0, 2.0)]. Although the total number of subjects studied in Year 3 was less than that which is usually requested for a contraceptive product, the upper bound of the 95% CI of 2.0 for women ≤ 35 years supports the effectiveness of Implanon throughout 3 years of use.

Supportive Studies

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.

2.3.2 Safety

Exposure to Study Drug

Principal Studies. A total of 1117 subjects were exposed to Implanon in the principal safety studies for a total of 26,787 cycles and 2,054 woman-years. Of these, 549 subjects completed 2 years, 197 subjects completed 3 years and 47 subjects completed 4 years.

Principal and Clinical Pharmacology Studies Combined. The mean duration of exposure to Implanon™ for the subjects in studies conducted in U.S./Europe/Singapore/Thailand was 685.8 days with a total exposure for 1,411 subjects of 2,649.2 woman years or 34,557 cycles. Most subjects in this population were exposed for 1 to <3 years (63.6%). A total of 1,112 subjects (78.8%) were exposed to Implanon™ for at least one year, and 214 subjects (15.2%) were exposed to Implanon™ for at least 3 years.

General Safety Findings in Clinical Trials

Deaths

In the clinical development program, no deaths were reported to have occurred in any study.

Discontinuations in the Principal Safety Studies:

A total of 323 out of 1117 (29%) of subjects in the principal safety studies discontinued due to an adverse event. Regional differences were observed, such that the incidence of discontinuations due to AEs was generally higher in the U.S. compared to Europe/Canada/Thailand. A total of 119 out of 330 (36%) subjects in the U.S. study discontinued due to AEs. In the studies conducted in Europe/Thailand, 204 out of 787 subjects (26%) discontinued due to AEs

The most frequently reported reasons for discontinuation (>1%) were bleeding irregularities (n=166, 14.9% subjects), weight increase (n=29, 2.6% subjects), emotional lability (n=23, 2.1% subjects), acne (n=13, 1.2% subjects), headache (n=12, 1.1% subjects), and amenorrhea (n=12, 1.1% subjects).

A total of 161 out of 330 subjects (48.8%) discontinued from U.S. Study 069001. The most common reason for discontinuation was adverse experience, with 119 subjects (36.1%) discontinuing primarily for this reason. Of these subjects discontinuing for an adverse experience, 43 subjects (13.0% of enrolled subjects) discontinued because of adverse menstrual experiences (bleeding irregularities) as the primary reason, and 76 subjects (23.0% of enrolled subjects) discontinued with other adverse experiences being the primary reason.

Adverse Events in the Principal Safety Studies

Serious Adverse Events. Sixty-two (62) out of 1117 subjects (5.5%) in the principal safety studies conducted in U.S./Europe/Thailand had a total of 83 serious adverse events (SAEs). Twelve (12) of the 83 SAEs were thought to be possibly, probably, or definitely drug-related. These included two cases of ovarian cyst and single cases of gastrointestinal disorders not otherwise specified, breast fibroadenosis, breast neoplasm benign, uterine fibroid, depression, cyst not otherwise specified, cerebrovascular disorder (a case of A-V malformation), headache, chest pain, and tachycardia.

Treatment-related Adverse Events. Within the population of subjects from the 4 principal safety studies (U.S./Europe/Thailand), the system-organ classes with the highest incidence of treatment related AEs were: Reproductive Disorders, Female, (212/1117 subjects or 19%); skin and appendages disorders (192/1117 subjects or 17.2%); CNS disorders (164/1117 subjects or 14.6%); and Psychiatric disorders (159/1117 subjects or 14.2%).

Individual drug-related adverse events (*other than uterine (vaginal) bleeding*) in this population and the percentage of subjects reporting them included acne (14.3%), headache (12.6%), weight increase (11.0%), breast pain (10.0%), emotional lability (5.4%), and dysmenorrhea (4.8%)

The overall vaginal bleeding pattern associated with Implanon™ ranged from amenorrhea to heavy bleeding and was primarily unpredictable. In the principal and clinical pharmacology non-comparative studies combined, Implanon™-treated subjects (completers and non-completers combined) experienced a mean of 18.36 bleeding-spotting days per 90-day reference period.

The hematology parameters measured in the US Study 069001 and Study 34507 (Austrian site only) did not show a clinically significant lowering of hemoglobin.

Systolic and diastolic blood pressure posed no safety concerns any studies; however, a gradual increase in body mass index over time was noted. The number of subjects with a >10% increase in body mass index from baseline at least once during treatment was 59 out of 330 (18.3%) in the U.S study, and 268 out of 1401 (19.1%) in the non U.S. Principal and Clinical Pharmacology Studies.

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. The mean Bone Mineral Density (BMD) parameters were not adversely affected by the use of Implanon.

Summary statistics for implant insertion times in the clinical trials showed a mean insertion time of 84.3 seconds and a mean removal time of 244.1 seconds; a total of 15 subjects (1.1%) experienced complications at implant insertion and 27 subjects (2.0%) experienced complications at implant removal.

2.3.3 Safety Issues of Particular Concern

Thromboembolic Adverse Events. No cases of pulmonary embolus or myocardial infarction, one case of an intracranial hemorrhage associated with a congenital vascular malformation, and one case of DVT were reported among a total of 1803 subjects who participated in the clinical trials.

Insertion/Removal Adverse Events. Since the market introduction of Implanon™, Organon has received over 450 complaints of insertion and removal problems. Problems with insertion of Implanon™ are thought to be the major factor that contributed to unintended pregnancies. The consequence of improper insertion also resulted in removal difficulties. These have included 'non-palpable Implanon™', 'otherwise difficult localization of Implanon™', 'broken Implanon™', 'difficult removal of Implanon™', and 'loss of implants'.

Organon has submitted a Risk Management Program regarding healthcare provider training in insertion and removal of Implanon™. This program is similar to those used with other implants..

2.3.4 Serious Postmarketing Safety Reports

On September 9, 2004, Organon submitted a cumulative listing of all selected postmarketing events from August 1998 – September 1, 2004. The number of implants sold during this period was approximately [redacted]. Rates of death, pulmonary embolus, cerebrovascular accident, deep vein thrombosis and myocardial infarction worldwide, and for Europe only (in number of events per 100,000 woman-years of use) are outlined in the Table that follows:

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Cumulative Listing-of Selected Serious Postmarketing Adverse Events

	Number of events worldwide	Number of events Europe ^a only	Worldwide rates (events per 100,000 woman-years of use) ^b	Europe ^a only rates (events per 100,000 woman-years of use) ^b
Death	5	3	0.15	0.17
Pulmonary embolus	10	7	0.31	0.41
Deep vein thrombosis ^c	18	14	0.55	0.82
(Venous thromboembolic events (VTE)) ^d	(28)	(21)	(0.86)	(1.22)
Cerebrovascular accident (CVA)	14	12	0.43	0.70
Myocardial infarction	1	1	0.03	0.06

^aThe following countries were included for Europe: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Portugal, Sweden, United Kingdom, Czech Republic, Finland, Malta, Norway, Slovak Republic, Spain, Switzerland, Norway and Iceland.

^bBoth medically confirmed and medically unconfirmed reports are included.

^cSuperficial venous thrombosis is excluded from this analysis. Cases in which it is unclear whether it involves a deep or superficial thrombosis (e.g. only "thrombosis" was reported) are included.

^dVenous thromboembolic events is the total rate of pulmonary embolus and deep vein thrombosis.

Source: Response to information request, 9Sep04

2.3.5 Overall Assessment of the Safety Profile for Implanon

Based on the safety data from the clinical trials for Implanon supported by the applicant submitted in NDA 21-529 and post marketing safety reports, the safety profile of Implanon is acceptable for a highly effective contraceptive drug product. The most common adverse event, irregular uterine (vaginal) bleeding does not pose a safety concern.

2.4 Dosing

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, etonogestrel is slowly released over a period of 3 years. The initial release rate is approximately 67 µg/day and the release rate over the entire period of three years 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. Implanon must be removed no later than 3 years after implantation and replaced by a new Implanon implant.

2.5 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. Two of the four in-treatment pregnancies in the clinical development program occurred in the U.S.: both subjects were Caucasian.

Age (Pediatric Population). The product is intended for use only in reproductive age women. A separate pediatric program is not required. Hormonal contraceptive drug products are considered safe and effective in post-menarchal females. No formal studies involving subjects less than 18 years of age have been required by the Division for this class of drug products. This product is not intended for pre-menarchal use.

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

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this page is the manifestation of the electronic signature.**

/s/

Barbara D. Wesley
6/9/05 04:08:37 PM
MEDICAL OFFICER

Scott Monroe
6/14/05 02:07:21 PM
MEDICAL OFFICER

I concur with Dr. Wesley's recommendation that Implanon receive an
"Approvable Action."

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

CLINICAL TEAM LEADER MEMORANDUM

NDA	NDA 21-529
Type of Application	Original NDA
Applicant	Organon USA, Inc. West Orange, New Jersey
Proprietary Drug Name	Implanon™
Established Drug Name	Etonogestrel implant
Indication	Prevention of pregnancy in women
Route of administration	Subdermal implant
Dosage Form	Subdermal implant (non-biodegradable)
Dosage Strength	68 mg of etonogestrel per implant
Dosing Regimen	A single implant to be replaced or removed at or before 36 months after insertion
CDER Receipt Date	September 30, 2003
PDUFA Goal Date	October 29, 2004 (Based on 3-month extension)
Date of Memorandum	October 29, 2004
Reviewers	Scott E. Monroe, MD Clinical Team Leader, DRUDP

RECOMMENDATIONS

Recommendation Regarding Approvability

This reviewer recommends that Implanon (etonogestrel implant) for the prevention of pregnancy in women not be approved until either (1) the 2 issues listed below are satisfactorily addressed or (2) additional clinical trial data in support of the safety and efficacy of Implanon are provided.

The 2 issues that need to be satisfactorily addressed are the following:

- Resolution by the Applicant of (1) the deficiencies/irregularities concerning the conduct of Study 34507 (including the Canadian component) and (2) concerns about the quality of the data from Study 34507. These issues and concerns were identified as a consequence of the Dutch Medicines Evaluation Board/EMEA inspections of clinical trial sites for Study 34507.

October 29, 2004

- A determination by the Division that the clinical data submitted in NDA 21-529 are sufficient (1) to support the conclusion that Implanon is safe and effective for prevention of pregnancy in women and (2) to allow labeling that will accurately reflect the safety and efficacy profile of Implanon.

Additional tasks that need to be completed prior to approval are:

- A satisfactory inspection report from the Office of Compliance regarding the sterilization facility
- Completion of a final label.

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Basis for Recommendation Regarding Approvability (Risk/Benefit Analysis)

The accuracy and adequacy of the data submitted to date in NDA 21-529 cannot be assured because of potentially serious issues concerning (1) the clinical conduct of the principal studies supporting the safety and effectiveness of Implanon and (2) lack of adequate monitoring and oversight by the Applicant of the these studies. Approval cannot be recommended until these issues are resolved,.

It can be concluded that Implanon is a safe and highly effective method of contraception that does not compromise future fertility if these issues can be satisfactorily resolved and the data submitted in NDA 21-529 are deemed to accurately reflect the safety and effectiveness of Implanon. For most women, the benefits would outweigh the risks.

The benefits of Implanon include the following:

- No patient compliance issues once the implant is inserted
- A single rod instead of 2 rods (Jadelle) or 6 rods (Norplant)
- Highly effective (< 1% failure rate)
- Rapid reversibility and return to fertility post removal

The major disadvantages of Implanon are that a minor surgical procedure is required for removal and there is a high rate of frequent/prolonged vaginal bleeding. These bleeding irregularities can be a major nuisance and a common cause for discontinuation of the method, but do not appear to pose a safety concern.

There are no preclinical toxicology deficiencies, chemistry-manufacturing-control deficiencies (other than the need for inspection of the sterilization facility listed above), or biopharmaceutical deficiencies.

Recommendation on Risk Management Steps and/or Phase 4 Studies

Risk Management Steps. The Applicant will need an effective training program for healthcare providers regarding proper insertion/removal of the implant since insertion/removal of Implanon has continued to be problematic in markets where the product is presently approved. The Applicant has proposed such a program, but it could be improved (e.g., providing for actual insertion/removal of the implant under supervision). The Applicant also should implement a Phase 4 monitoring program for Implanon-related insertion/removal adverse events to ensure that the training program is meeting its objectives.

Phase 4 Studies. This Medical Officer recommends that the Applicant provide additional clinical data confirming the effectiveness of Implanon during Year 3 of use, particularly in

obese women. Data confirming the effectiveness of Implanon during Year 3 of use may be obtained as a Phase 4 commitment if the Applicant is able to resolve satisfactorily the concerns regarding the quality and validity of the data submitted in support of NDA 21-529 without the need for additional new clinical data.

INTRODUCTION AND BACKGROUND

Limitations of this TL Memorandum

This memorandum will focus on those issues that were identified during the review of NDA 21-529 as significant factors in making a recommendation/decision regarding the approvability of Implanon for prevention of pregnancy in women. In addition, any areas where this reviewer disagrees with the recommendation(s)/interpretations of the primary Medical Reviewer also will be addressed.

It also should be noted that the descriptions of the efficacy and safety findings from the clinical trials, as well as the interpretations of the clinical significance of these findings, has been based on the assumption that the data provided in this Application are accurate. The conclusions put forth in this Memorandum regarding the effectiveness and safety of a single Implanon rod to prevent pregnancy for up to 3 years cannot be supported and may not be valid if it is subsequently determined that the validity of the data submitted in NDA 21-529 cannot be reasonably assured.

Primary Medical Review

The primary Medical Reviewer, Dr. Barbara Wesley, with the assistance of Medical Officers Daniel Davis, Phill Price, and Theresa van der Vlugt, has conducted a comprehensive review of the clinical data submitted in support of NDA 21-529. Based on her review of the efficacy and safety data, Dr. Wesley "recommends an approvable action for Implanon™ (etonogestrel implant) for the prevention of pregnancy in reproductive age women for three years." I concur that Implanon should not be approved for marketing for the prevention of pregnancy at this time.

Available Hormonal Contraceptive Options In the U.S.

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 regimen significantly reduces the effectiveness of these products. Highly effective hormonal contraceptives that have a dosing regimen other than by daily oral tablet include medicated and inert IUDs, a 21-day 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.

Implanon

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

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68 mg of etonogestrel dispersed in a polymeric matrix of (ethylene vinylacetate copolymer with a vinylacetate content of 28%), surrounded by a 60 µm skin of (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, etonogestrel is slowly released through the rate-controlling skin over a period of 3 years.

Progestin-only based contraceptives can be used by women who are unable to tolerate estrogen or by women for whom estrogen is contraindicated. The major disadvantages of progestin-only contraception are unpredictable menstrual bleeding changes such as short cycles, spotting, breakthrough bleeding, and less frequently, amenorrhea. These menstrual cycle changes often are the cause of early discontinuation of progestin-only contraceptives because of the lack of acceptability by the user.

Currently, one etonogestrel product containing etonogestrel is approved and marketed in the U.S. for the prevention of pregnancy: NuvaRing® (Organon USA) is a combination contraceptive vaginal ring containing etonogestrel and ethinyl estradiol (EE) designed to release on average 0.120 mg/day of etonogestrel and 0.015 mg/day of EE over a 3-week period.

MAJOR APPROVABILITY ISSUES

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) 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 five of the studies submitted in the original NDA. Affected studies included "principal" Studies 34506 and 34520; pharmacodynamic Study 34503, lipid metabolism Study 34510 (Indonesia site only), and endometrial histology Study 34514. These studies involved the data for 720 Indonesian subjects. On a subsequent teleconference with the Applicant, there was a mutual agreement to remove these studies and all related data from the analyses supporting the safety and efficacy of Implanon.

Organon also informed the Dutch Medicines Evaluation Board (DMEB) of these findings since the original dossier for Implanon that served as the basis for approval of the drug product in throughout Europe had include the data from 720 subjects from these 2 Indonesian sites. The DMEB/European Regulatory Agency(s) then decided to inspect 4 European sites not already inspected by the FDA. As a result of these inspections, violations of good clinical practice (GCP) were identified 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:

1. 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.). Some of the violations were classified as "critical." It also was concluded that there was an underreporting of the frequency of side effects in some trials.

Of importance, the Inspectors concluded that “there were no indications of fraudulent actions.”

2. Because of the violations of GCP and errors that were identified, the DMEB recommended that Organon make several changes to the approved Implanon label. Changes are identified by strike-through and underline.

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3. It was agreed that there are no reasons for doubts about the efficacy and safety of the product provided it is inserted in the appropriate manner. This conclusion was based on the large postmarketing experience and extensive monitoring and reporting.

Medical Officer’s Comments

- *Removal of Studies 34506 and 34520 has had a significant impact on the adequacy of the data submitted in support of this NDA since both were considered by the Applicant to be principal efficacy and safety studies. In additional, both studies provided more efficacy and safety data for a third year of use than data that was provided by the 3 other centers.*
- *Although the DMEB did not recommend removal of Implanon from the market, their findings and the label changes that they recommended, raised significant concerns about the quality of the data from clinical trials 34507 and 34507-CDN.*
- *Approval of Implanon for marketing for the indication of prevention of pregnancy in women cannot be recommended until either (1) these concerns about the quality of the clinical trial data are resolved or (2) the Applicant submits additional clinical data obtained under conditions of GCP that support the safety and effectiveness of Implanon.*

OVERVIEW OF THE SCOPE OF THE CLINICAL DATA

NDA 21-529 provided data from approximately 1,800 subjects, in 19 completed Phase II and III studies, who were treated with Implanon for up to 2-5 years. Studies were conducted in at least 16 different countries and included North America and South America, Europe, and Southeast Asia.

Four studies that enrolled a total of 1,117 subjects were considered to be the principal efficacy and safety studies by the Applicant and the FDA reviewers (Studies 069001 [U.S.], 34507 [Europe/Chile], 34507-CDN [Canada], and 34505 [Thailand]). All were non-comparative, historical controlled studies. In addition to contraceptive effectiveness and overall safety, these 4 studies also provided data on the pharmacokinetics (PK) of

etonogestrel (subsets of Studies 069001 and 34507) and special safety including the impact of the use of Implanon on serum lipids, carbohydrate metabolism, ophthalmological safety, and endometrial histology (subsets of Study 069001).

Of these 4 studies, Studies 069001 and 34507-CDN provide evidence of efficacy during 2 years of use. At 3 of the centers in the other 2 clinical trials, 2-4 year efficacy data were obtained. For study 34507, the duration of treatment of subjects at 2 centers (those in Hungary and Chile) was extended to 3 years. Study 34505 (Thailand) provided efficacy data for up to 4 years of use.

Subjects in the principal safety and efficacy studies had to be healthy females who were sexually active and of childbearing potential between 18 and 40 years of age. The subjects had to have normal menstrual cycles with a cycle length of 24-35 days, an intra-individual cycle length variation of plus or minus 3 days, and could not be breast-feeding. Body weight was to be between 80% and 130% of ideal weight. Subjects had to be willing to return to the clinic for the scheduled visits, to fill in the diary card with information on bleeding, and to give written informed consent. The use of any contraceptive drug or device other than the study medication was not permitted. *However, the use of condoms for the prophylaxis of sexually transmitted diseases was permitted.*

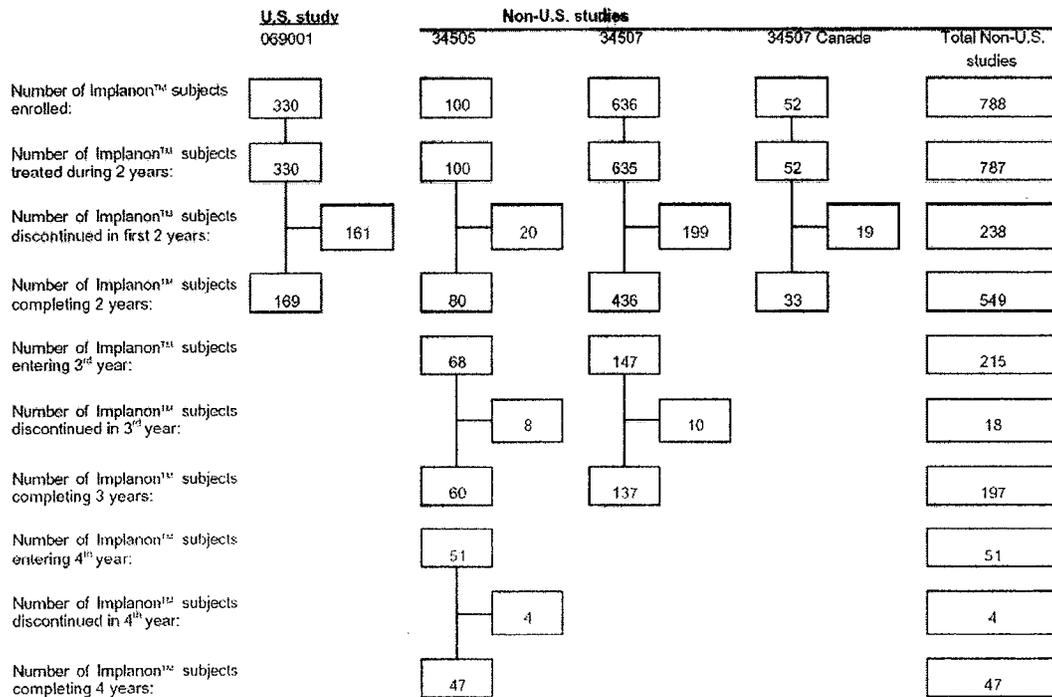
Additional supportive safety and efficacy data of varying quality was provided from the Phase 2 supportive clinical pharmacology studies.

DISPOSITION OF SUBJECTS IN PRINCIPAL STUDIES

Figure 1 lists the disposition of subjects in the principal clinical studies, including the number of subjects enrolled in each study, number of subjects who received Implanon, number of subjects who discontinued prematurely from each study, and the number of subjects who completed each study.

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Figure 1 Disposition of Subjects – Principal Safety and Efficacy Studies



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

The extent of exposure to Implanon was expressed both in terms of woman-years of use and total number of 28-day cycles. The duration of treatment and extent of exposure to Implanon for the U.S. and non-U.S. principal studies are listed in Table 1.

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Table 1 Duration of Treatment and Extent of Exposure in the Principal Studies

Study	Duration of treatment (Number of subjects)			Extent of exposure	
	0-2 Yrs	2-3 Yrs	3-4 Yrs	Cycles (28-days)	Woman-yrs
U.S. study					
069001	327 ^a	-	-	6,198	475
Non-U.S. studies					
34505	100	68		3,863	296
34507	635	147	-	15,653	1,200
34507 CDN	52	-	-	1,085	83
Total: Non-U.S. studies -	787	215	51	20,601	1,579
Total (U.S. + Non-U.S.)	1114	215	51	26,799	2,054

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

Source: Table 14, amended ISE, submitted on 4 May 2004,

EFFICACY

Applicant's Summary of Contraceptive Effectiveness

Across the 4 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). Among these trials, the Applicant reported that 4 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 4 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
 Adequate and well controlled studies: 069001,34505,34507, 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
 Adequate and well controlled studies: 069001,34505,34507, and 34507 CDN.

Source: Applicant's submission of 12 October 2004, Table 14b.

Medical Officer's Comments

- *As a general policy, the Division requires that 200 women use a new contraceptive drug product for at least one year and that the drug product be investigated in at least 10,000 28-day treatment cycles. The total number of treatment cycle equivalents (i.e., months at risk for pregnancy) in this submission is adequate to assess the effectiveness of Implanon.*

Across the 4 principal studies, 4 pregnancies (2 in the U.S. study) were considered by the primary Medical Reviewer 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 the primary Medical Reviewer as on-treatment pregnancies (i.e., a method failure). All 4 of these pregnancies also occurred within 365 days of implant insertion. If these pregnancies are considered to be “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)

Table 5 Annual Pearl Index Values and Annual Exposures to Implanon in Subjects < 36 Years of Age (Principal Efficacy Studies) (Primary Medical Reviewer Interpretation of Pregnancy Data)

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
 Adequate and well controlled studies: 069001,34505,34507, 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) (Primary Medical Reviewer Interpretation of Pregnancy Data)

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
 Adequate and well controlled studies: 069001,34505,34507, and 34507 CDN.

Source: Applicant's submission of 12 October 2004, Table 15d.

Medical Officer's Comments

- *This Medical Officer does not believe that the 3 pregnancies that were estimated as occurring within 5-7 days post removal of Implanon, and perhaps the pregnancy that might have occurred within 14 days after implant removal, should be considered as*

method failures. Since progestin-only contraceptives do not consistently inhibit ovulation and are dependent on other mechanisms such as alterations of cervical mucous to prevent conception, it is to be expected that conception can occur within a few days of removal of a progestin containing implant. This is different from the situation following discontinuation of a combination oral contraceptive (COC) since COCs are intended to inhibit ovulation. A conception within 14 days after discontinuation of a COC would therefore constitute a likely method failure.

- *Assuming that the data provided in the Application are valid, it is not important if these 3 or 4 pregnancies are considered a method failure. The values for the annual and cumulative Pearl Index and the upper bounds for the 95% CIs for these values (Table 5 and Table 6), even if these 3 or 4 pregnancies are considered to be method failures, are well within the range for other hormonal contraceptive products approved by the Division.*
- *A limitation of these studies is that the use of backup contraception (i.e., condoms) presumably for protection against sexually transmitted diseases was not recorded in subject diaries. Although most, if not all, recently conducted contraceptive trials allow for the use condoms, this information is usually recorded in subject diaries. This allows the statistician to adjust (i.e., reduce) the number of "at risk" cycles in the calculation of the Pearl Index and the 95% CIs. This adjustment could not be done in the present trial. In other contraceptive clinical trials up to 20% of cycles have been eliminated because of the use of condoms. One can assume that the frequency of use of condoms in the Implanon clinical trials was similar. Although such an adjustment was not made for the Pearl Index values provided by the Applicant, the resulting Pearl Index values would still have shown that Implanon was highly effective during Year 1 and Year 2 of use.*

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)].

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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 (195/2535) studied in treatment Year 3 was less than that submitted to support 3 years of effectiveness for previously approved implantable contraceptive products (e.g., Norplant and Jadelle). However, when the < 36 year old group (the most fertile group) was analyzed considering only women who completed Year 3 of use with Implanon, the Pearl Index was calculated to be 0 with an upper limit of the 95% confidence interval of 2.23. Based on the upper bound, this would be sufficient evidence to support approval for a third year of use for a single Implanon implant, assuming that the data were highly reliable.*
- *Even if the data represented in Table 7 are assessed as being highly reliable, it is still recommended that the Applicant conduct an additional clinical trial, or supply confirmatory treatment data, in a Phase IV commitment, to provide additional support for the 3-year treatment regimen. Such information is particularly important for obese women since PK data for etonogestrel indicate that plasma levels are lower in women with higher body mass index (BMI) values. Labeling should reflect this observation.*

During the review of NDA 21-529, the Applicant was asked to submit an updated 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 (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 unable to provide information about the time of conception for 60% of the reported pregnancies. However, for those pregnancies for which data were available, the greatest number occurred in the first year of use, which may be related to problems that occurred with insertion. There was no observed increase in the rate of pregnancies in Years 2 or 3. These data support the clinical trial data indicating that Implanon continues to be effective throughout a third year of use.*

Overall Conclusion Regarding the Efficacy of Implanon

- Assuming that the data submitted in NDA 21-529 accurately reflect the events of the clinical trial, a single Implanon implant, when inserted correctly, has been shown to be highly effective for the prevention of pregnancy for 2 years.
- Although the data presented in the NDA also support the effectiveness of a single Implanon implant through 3 years of use, the number of subjects and treatment cycles in Year 3 were small (< 200 women who completed 3 years of treatment). Therefore, if there was a failure to identify only one or 2 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.

SAFETY PROFILE OF IMPLANON

As stated earlier, the descriptions of the safety findings from the clinical trials as well as this Medical Officer's interpretations of the clinical significance of these findings has been based on the assumption that the data provided in the Applicant's submission are accurate. The conclusions that follow regarding the safety of Implanon for prevention of pregnancy cannot be supported and may not be valid if it is subsequently determined that the validity of the data in NDA 21-529 cannot be reasonably assured.

Post Marketing Experience and Reports of Serious Adverse Events

In this Memorandum, a comprehensive review of the safety findings for Implanon based on the safety data in NDA 21-529 will not be provided. Rather, this Memorandum will focus upon those safety issues and adverse events that are likely to be of most concern to a woman using Implanon for prevention of pregnancy and to her healthcare provider. The primary medical review of NDA 21-529 by Dr. Wesley provides a comprehensive review of the overall safety profile of Implanon based on (1) the information provided in NDA 21-529 and (2) postmarketing safety reports.

According to the Applicant, since the approval of Implanon for marketing in 1998, total worldwide sales have been _____ units of which _____ units have been sold in Europe (Table 9). Based on the assumption that all units sold have been implanted and an estimate of the average time that an implant remains in place before removal, the Applicant has calculated that total exposure in terms of woman-years of use has been 3,250,896 women-years worldwide as of September 2004 (Table 10).

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Table 9 World wide and European Sales of Implanon since Initial Approval and through September 2004

Sales	< Sep02	Sep02 -Sep03	Sep03 -Sep04	Overall
World wide				
Europe ^a only				

^aThe following countries were included for Europe: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Portugal, Sweden, United Kingdom, Czech Republic, Finland, Malta, Norway, Slovak Republic, Spain, Switzerland, Norway and Iceland.

Source: Applicant's submission of 11 Oct 2004.

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Table 10 World wide and European Estimates of Women-Years of Exposure to Implanon since Initial Approval and through September 2004

Exposure (best estimate)	< Sep02			Sep02 -Sep03		Sep03 -Sep04	Overall
	1st yr (90%) ^a	2nd yr (80%) ^a	3rd yr (75%) ^c	1st yr (90%) ^d	2nd yr (80%) ^e	1st yr (90%) ^f	
World wide	782,293	695,371	651,911	384,737	341,989	394,695	3,250,896
Europe ^a only	404,696	359,730	337,247	208,202	185,068	221,354	1,716,295

^aFinals 90% of sales from <September 2002

Source: Applicant's submission of 11 Oct 2004.

The number and estimated rates (in number of events per 100,000 woman-years of use) for postmarketing reports of deaths and serious thrombotic and thromboembolic adverse events in users of Implanon are listed in Table 11. The data reflect all reports received by the Applicant since the start of marketing of Implanon in 1998 through September 2004.

Of the 5 reported deaths, 3 were secondary to a pulmonary embolus, one was secondary to sepsis, and one occurred in a neonate.

Table 11 Postmarketing Reports of Deaths and Serious Thrombotic and Thromboembolic Adverse Events (Number and Rate of Events)

	Number of events worldwide	Number of events Europe ^a only	Worldwide rates (events per 100,000 woman-years of use) ^b	Europe ^a only rates (events per 100,000 woman-years of use) ^b
Death	5	3	0.15	0.17
Pulmonary embolus	10	7	0.31	0.41
Deep vein thrombosis ^c	18	14	0.55	0.82
(Venous thromboembolic events (VTE)) ^d	(28)	(21)	(0.86)	(1.22)
Cerebrovascular accident (CVA)	14	12	0.43	0.70
Myocardial infarction	1	1	0.03	0.06

^aThe following countries were included for Europe: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Portugal, Sweden, United Kingdom, Czech Republic, Finland, Malta, Norway, Slovak Republic, Spain, Switzerland, Norway and Iceland

^bBoth medically confirmed and medically unconfirmed reports are included

^cSuperficial venous thrombosis is excluded from this analysis. Cases in which it is unclear whether it involves a deep or superficial thrombosis (e.g. only "thrombosis" was reported) are included.

^dVenous thromboembolic events is the total rate of pulmonary embolus and deep vein thrombosis.

Source: Applicant's submission of 11 Oct 2004.

Medical Officer's Comments

- *The rates per 100,000 women-years of use for deaths and serious thrombotic and thromboembolic adverse events in users of Implanon do not appear to be excessive.*

However, it is difficult to assess the true significance of these rates because of uncertainty as to the proportion of the events that have been reported to the Applicant.

REPORTED SAFETY FINDINGS FROM IMPLANON CLINICAL TRIALS

Extent of Safety Data

The extent of exposure to Implanon in the 4 principal safety studies is summarized in Table 12. A total of 1,114 subjects were exposed to Implanon in these studies, representing a total of 26,787 treatment cycles or 2,054 woman-years of use. The mean duration of exposure was 673 days. Approximately 597 subjects were exposed to Implanon for 2 or more years. Across the 4 principal safety studies and the supportive clinical pharmacology studies, a total of 1,411 subjects were exposed to Implanon, representing 34,557 treatment cycles or 2,649 women-years of use.

Table 12 Extent of Exposure to Implanon in the Principal Safety Studies

	Implanon™		
	US ^a	Europe/Thailand ^b	Total: US/Europe/ Thailand
	(N=327)	(N=787)	(N=1114)
Mean +/- SD	529.7 +/- 256.2	732.9 +/- 357.1	673.3 +/- 343.3
Median	721	736	733
Total exposure			
Woman-years	474.2	1579.2	2053.5
Number of 28-day cycles	6186.2	20600.5	26786.7
Number of subjects exposed by duration			
< 1 year	101 (30.9%)	151 (19.2%)	252 (22.6%)
1 to < 2 years	90 (27.5%)	175 (22.2%)	265 (23.8%)
2 to < 3 years	136 (41.6%)	292 (37.1%)	428 (38.4%)
3 to < 4 years	0	131 (16.6%)	131 (11.8%)
≥ 4 years	0	38 (4.8%)	38 (3.4%)

^a Study 069001. Extent of exposure was calculated from 327 subjects in Study 069001 (3 subjects had no postbaseline assessments).

^b Studies 34505, 34507, and 34507 CDN.

Source: Table 21, revised ISS, submission of 4 Oct 2004.

Medical Officer's Comments

- *The extent of exposure would be adequate to assess the safety profile of Implanon for prevention of pregnancy.*

Reasons for Discontinuation

The reasons for subject discontinuation by general category and the number (%) of subjects in each category for the 4 principal safety studies are listed in Table 13. A total of 421 out of 1,117 subjects (37.3%) prematurely discontinued using Implanon. There was a numerically greater percentage of subjects who discontinued prematurely because of an adverse event in the U.S. study (36.1%) compared to that in the non-U.S. studies (25.9%). The most

frequently reported single adverse event leading to premature discontinuation was bleeding complaints.

U.S. Study 069001. A total of 161 out of 330 subjects (49%) discontinued prematurely. The most common reason for discontinuation was an adverse event, with 119 subjects (36.1%) discontinuing primarily for this reason. Of these, 43 subjects (13.0%) discontinued primarily because of menstrual bleeding complaints, and 76 subjects (23.0%) discontinued primarily because of other adverse experiences.

Non- U.S. Studies (Studies 34505, 34507, and 34507 CDN). A total of 260 Implanon-treated subjects (33.0%) discontinued prematurely from these studies. The most common reason for discontinuation was an adverse event (204 subjects [25.9%]). Among adverse events, bleeding complaints were the most common reason with 123 subjects (15.6% of total subjects) discontinuing primarily for this reason.

Table 13 Primary Reasons for Subject Discontinuation in Principal Safety Studies

Study	Number (%) of Subjects			
	69001	34505	34507	34507 CDN
Number subjects randomized	330	100	636	52
Completed Study	169 ((51%)	68 (78%)	427 (67%)	33 (63%)
Discontinued Prematurely	161 (49%)	32 (32%)	209 (33%)	19 (37%)
Adverse Event	119 (36.1%)	12 (12%)	180 (28.3%)	12 (23.1%)
Amenorrhea	-*	1 (1%)	11 (1.7%)	-
Bleeding complaints	43 (13%)	6 (6%)	110 (17.3%)	7 (13.5%)
Other adverse events	76 (23%)	5 (5%)	59 (9.3%)	5 (9.6%)
Lost to follow-up	-	8 (8%)	4 (0.6%)	1 (1.9%)
Protocol violation	4 (1.2%)	-	-	-
Unwilling to continue	8 (2.4%)	-	-	-
Intercurrent illness	1 (0.3%)	-	-	-
Other reasons	29 (9%)	12 (12%)	25 (3.9%)	6 (11.5%)

*: No data available

Source: Protocol 069001 (Table 4), Protocol 34505 Table 5), Protocol 34507 (Table 6), & Protocol 34507 CDN (Table 6).

Deaths

There were no reported deaths in the clinical development program for Implanon.

Overview of Adverse Events

Table 14 summarizes the number of subjects who used Implanon in the principal safety studies for whom adverse events were reported. With the exception of the category “adverse events leading to discontinuation,” menstrual bleeding related adverse events were not included in the Table as an adverse event. One or more adverse events were reported in 86% and 72% of subjects in the U.S. and non-U.S. studies, respectively. Serious adverse events

were reported in 3% (10 of 330 subjects) and 7% (52 of 787 subjects) in the U.S. and non-U.S. studies, respectively.

Table 14 Summary of Adverse Events in Principal Safety Studies

	U.S. Study		non-U.S. Studies	
	N	(%)	N	(%)
Total subjects	330	(100)	787	(100)
Any adverse events	282	(86)	569	(72)
Drug related adverse events	198	(60)	396	(50)
Serious adverse events	10	(3)	52	(7)
Adverse events leading to discontinuation *	119	(36)	204	(26)

N = Number of subjects for whom safety data were available or number of subjects reporting the event

* Includes subjects who discontinued primarily because of menstrual bleeding related adverse events.

Source: Prepared by Medical Reviewer from revised ISS submitted on 4 May 2004.

The most frequently reported adverse events (other than uterine/vaginal bleeding), reported in $\geq 5\%$ of the 1,117 subjects in the 4 principal safety studies, were: headache (19.9%), acne (15.2%), vaginitis (14.5%), breast pain, female (12.25%), weight increase (11.6%), upper respiratory tract infection (9.6%), abdominal pain (9.4%), pharyngitis (7.8%), leukorrhea (7.3%), dysmenorrhea (6.9%), influenza-like symptoms (6.0%), emotional lability (5.7%), nausea (5.2%), and depression (5.0%).

Medical Officer's Comments

- *The adverse events reported to occur most frequently in the principal safety studies are commonly reported in clinical trials of hormonal drug product, and do not raise any safety concerns.*
- *Menstrual bleeding disorders are discussed later in this Memorandum.*

Discontinuations Secondary to Adverse Events

A total of 323 out of 1,117 (28.9%) of subjects in the principal safety studies discontinued due to an adverse event. The most frequently reported reasons for discontinuation (based on preferred terms) were bleeding irregularities (n=166, 14.9% subjects), weight increase (n=29, 2.6% subjects), emotional lability (n=23, 2.1% subjects), acne (n=13, 1.2% subjects), headache (n=12, 1.1% subjects), and amenorrhea (n=12, 1.1% subjects). The numbers (%) of subjects who discontinued due to an adverse experience classified by WHO system-organ class and preferred term in the principal safety studies are listed in Table 15.

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Table 15 Number (%) of Subjects who Discontinued due to an Adverse Event in Principal Safety Studies (System Organ Class with ≥ 2 Events)

WHO system-organ class	Preferred term	U.S. ^a (N=330)		Europe/ Thailand ^b (N=787)		U.S./Europe/ Thailand (N=1117)	
		n	(%)	n	(%)	n	(%)
Reproductive disorders,		>43	>13	>123	>15.6	>166	>14.9
	Bleeding complaints	43	13	123	15.6	166	14.9
	Amenorrhea	0		12	1.5	12	1.1
	Sexual function abnl.	4	1.2	0		4	0.4
	Dysmenorrhea	2	0.6	0		2	0.2
	Premenstrual tension	2	0.6	0		2	0.2
	Breast pain female	0		3	0.4	3	0.3
Psychiatric disorders		31	9.4	11	1.4	42	3.8
	Emotional lability	20	6.1	3	0.4	23	2.1
	Depression	8	2.4	2	0.3	10	0.9
	Nervousness	3	0.9	2	0.3	5	0.4
	Anxiety	2	0.6	1	0.1	3	0.3
	Libido decreased	0		4	0.5	4	0.4
Metabolic disorders		11	3.3	22	2.8	33	3.0
	Weight increase	11	3.3	18	2.3	29	2.6
	Weight decrease	0		3	0.4	3	0.3
Skin disorders		7	2.1	14	1.8	21	1.9
	Acne	5	1.5	8	1.0	13	1.2
	Alopecia	2	0.6	4	0.5	6	0.5
Nervous system disorders		6	1.8	11	1.4	17	1.5
	Headache	4	1.2	8	1.0	12	1.1
	Paraesthesia	1	0.3	1	0.1	2	0.2
	Dizziness	0		2	0.3	2	0.2
Body as a whole disorders		5	1.5	2	0.3	7	0.6
	Fatigue	2	0.6	0		2	0.2
Application site disorders		3	0.9	1	0.1	4	0.4
	Injection site pain	3	0.9	1	0.1	4	0.4
Neoplasms		2	0.6	1	0.1	3	0.3
	Breast neoplasm (malign.)	1	0.3	0		1	0.1
Gastrointestinal disorders		1	0.3	1	0.1	2	0.2
Vascular disorders		0		2	0.3	2	0.2
	Cerebral hemorrhage	0		1	0.1	1	0.1
	Cerebrovas. disorder	0		1	0.1	1	0.1

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

Medical Officer’s Comments

- *The percentages of subjects who discontinued prematurely for bleeding complaints were similar in both the U.S. (13%) and non-U.S. (15.6%) studies. Bleeding complaints do not appear to represent a safety issues, but rather are an important factor in a subject’s deciding to discontinue using Implanon.*
- *For most categories (based on WHO system-organ class) the percentages of subjects discontinuing because of an adverse event were similar in the U.S. and non-U.S. studies. An exception was the category “psychiatric disorders” for which 9.4% of U.S. subjects and 1.4 % of non-U.S. subjects discontinued prematurely. Emotional lability and depression (8.5 % of U.S. subjects) are well known complications of progestin-only contraceptives.*

ADVERSE EVENTS OF SPECIAL CONCERN OR INTEREST

Thrombotic and Thromboembolic Adverse Events

According to the Applicant's submission of September 9, 2004, among all of the clinical trials with Implanon, there were no cases of pulmonary embolus or myocardial infarction, one case of thrombosis in a lower extremity, one case of an intracranial hemorrhage in a woman with an intracranial vascular malformation, and one case of a women with transient neurological symptoms, possibly secondary to transient ischemic attacks.

Medical Officer's Comments

- *The number of serious thrombotic and/or thromboembolic adverse events in the Implanon clinical trials based on total exposure to the drug product was low. Whether this was a true reflection of the study findings or due to under reporting of adverse events cannot be ascertained at this time.*

Uterine (Vaginal) Bleeding

To evaluate the effects of Implanon™ on the menstrual cycle all subjects in the clinical trials were given diary cards to record daily occurrences of vaginal bleeding, spotting, and the absence of bleeding or spotting. Data were analyzed using a reference period (RP) analyses during which bleeding variables evaluated and analyzed over consecutive 90-day reference periods. Each 90-day treatment segment represented one reference period, starting with the day of implant insertion as the first day of the first reference period. Data from a subset of the total treated population who appeared to reliably complete their dairy cards during a specific reference period (referred to as the Reference-Period-Analyses Group) were used by the Applicant to conduct the reference period analyses that are summarized in Table 16 and Table 17.

The mean and median number of bleeding-spotting days in all subjects who used Implanon and those subjects who terminated prematurely because of bleeding complaints are listed by reference period in Table 16. For each of the references periods shown in the table, the mean/median number of bleeding-spotting days in the subjects who discontinued prematurely because of bleeding-related complaints was approximately 2-fold greater than in the total population. Beginning with reference period 2, the mean number of bleeding spotting days per reference period ranged from 17.15 to 20.27 in the all subjects group and from 31.96 to 42.45 in the subjects who discontinued prematurely because of bleeding complaints.

Medical Officer's Comments

- *Assuming that a woman normally has 4-7 days of bleeding/spotting per monthly menstrual cycle, she would be expected to have 12-21 days of bleeding-spotting in a 90-day reference period. This is similar to the number of bleeding-spotting days observed in the "all subjects" group.*

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Table 16 Number Of Bleeding-Spotting Days: All Subjects and Subjects Who Terminated Prematurely for Bleeding Complaints – Principal Safety And Efficacy Studies

RP	All Subjects				Subjects who Discontinued Prematurely			
	N	Mean	SD	Median	N	Mean	SD	Median
1	985	29.60	22.00	25.00	131	48.95	21.75	51.00
2	878	20.27	20.14	15.00	83	42.45	24.02	42.00
3	816	17.86	17.91	14.00	63	39.95	23.80	38.00
4	777	17.33	16.36	14.00	42	37.81	22.82	41.00
5	724	17.15	15.30	14.00	25	31.96	21.49	33.00
6	694	17.42	15.11	15.00	15	33.93	20.10	33.00
7	659	17.55	15.19	15.00	4	39.50	25.59	33.00

Source: Applicant's submission of 12 October 2004, Tables 7a and 7b.

Bleeding pattern indices for all subjects and those that discontinued Implanon use prematurely because of bleeding complaints are summarized by percentages of reference periods with a particular bleeding pattern in Table 17. The percentages of reference periods with frequent bleeding or prolonged bleeding in subjects who discontinued because of bleeding complaints were 2-3 fold higher in these subjects compared to values in the all subjects group.

Table 17 Bleeding Pattern Indices: All Subjects and Subjects Who Discontinued Prematurely Because of Bleeding Complaints – Principal Safety And Efficacy Studies

Bleeding pattern indices	All Subjects		Subjects Who Terminated Prematurely	
	N=957		N=100	
	Number of RP	%	Number of RP	%
Amenorrhea	3889	19.3	256	6.6
Infrequent bleeding	3889	32.6	256	30.1
Frequent bleeding	3889	7.5	256	13.3
Prolonged bleeding	3889	17.9	256	46.9

%=Percentage of pattern index occurrence.

RP = 90-day reference period.

Source: Applicant's submission of 12 October 2004, Tables 8a and 8b.

Menstrual bleeding patterns in a subset of subjects using Implanon who discontinued primarily due to bleeding irregularities or amenorrhea are summarized in Table 18. Among these women, "frequent irregular bleeding" and prolonged menstrual flow were the most common patterns of bleeding.

Table 18 Menstrual Bleeding Patterns in a Subset of Implanon Treated Subjects Who Discontinued Primarily Due to Bleeding Irregularities or Amenorrhea

Study Location	Reason for discontinuation	Specific bleeding pattern	Implanon™ n (%)
Europe and N. America (n = 1070)	Amenorrhea		17 (1.6%)
	Bleeding irregularities	Frequent irregular bleeding	103 (9.6%)
		Heavy menstrual flow	9 (0.8%)
		Prolonged menstrual flow	46 (4.3 %)
		Spotting	29 (2.7%)
		Other bleeding problems	7 (0.7%)
Total bleeding irregularities and amenorrhea			211 (19.7%)

Source: NDA 21-529, Integrated Summary of Efficacy, Modified from Table 37, page 0106

Medical Officer’s Comments

- *It is well accepted that progestin-only contraception is associated with disruption of bleeding patterns, especially during the first year of use. The daily impact of the progestin on the endometrium in association with variable suppression of endogenous estrogen contributes to the formation of an unstable endometrium. In addition, the absence of cyclic administration does not allow for predictable vaginal withdrawal bleeding. Consequently, the resulting relatively unstable endometrium sheds at unpredictable intervals.*
- *Overall, the vaginal bleeding associated with the use of Implanon™ is characterized by an unpredictable bleeding pattern.*
- *A review of hematology parameters from U.S. Study 069001 by the primary FDA Medical Reviewer (Dr. Wesley) did not identify any subjects who had a clinically significant low hemoglobin value post baseline. She concluded that: “ the irregular/prolonged bleeding seen in women using Implanon for prevention of pregnancy negatively impacts on the acceptability of the treatment. However, it does not appear to be a safety issue based on a lack of clinically significant changes in blood indices.”*

Implanon Insertion and Removal Issues

Implanon insertion complications were reported for 14 subjects (1.3%, 14 of 1,117 subjects). Insertion complications included reports of implant stayed in needle, slight bleeding and compression, hematoma, and difficult insertion. Removal complications were reported for 25 subjects (2.3%, 25 of 1,117 subjects). Removal complications included reports of portion of implant rod broken off, implant could not be palpated, removal difficult due to deep insertion, adherences, and difficult to find.

Medical Officer’s Comments

- *Implant removal problems have been a significant problem associated with the use of Norplant. Although no direct comparisons to Norplant were made in the principal safety studies, it appears that the incidence of removal complications with Implanon is likely to*

be lower, if only because Implanon is a single rod, compared to the 6-rod Norplant system.

- *The incidence of removal problems with Implanon in the clinical trials does not present a safety concern. It should be noted, however, that these results are reported for clinical investigators who were likely to have been well trained by the Applicant in insertion and removal techniques. They may not represent insertion and removal complications that are likely to be encountered in general use.*
- *Based on post marketing safety reports, insertion and removal complications have been a concern. Although the percentage of women reported to have become pregnant while using Implanon has been low based on postmarketing safety reports, a high percentage of these pregnancies are thought to have resulted from improper insertions.*
- *Similarly, there have been postmarketing reports of removal problems. These have included reports of inability to palpate the implant, requiring either ultrasonography or MRI for localization. In rare instances, in women with measurable serum levels of etonogestrel, healthcare providers have not been able to locate an implant by any available technique. The Applicant stated that the incidence of significant insertion/removal problems has been reduced with improved healthcare training.*
- *The Applicant has provided a description of the proposed training program for U.S. healthcare providers, but it could be improved (e.g., providing for actual insertion/removal of the implant under supervision). The Applicant also should implement a Phase 4 monitoring program for Implanon-related insertion/removal adverse events to ensure that the training program is meeting its objectives.*
- *The present Implanon implant is not radio-opaque although the Applicant stated that they are exploring the possibility of developing a radio-opaque implant. The Applicant should be encouraged to develop such an implant.*

Changes in Body Weight and Body Mass Index (BMI)

Weight increase was one of the most frequently reported adverse events (11.6%, 123 of 1,117 subjects) in Implanon-treated subjects in the principal safety and efficacy studies. In these studies, a total of 29 subjects (2.6%, 29 of 1117 subjects) discontinued due to a complaint of weight increase. Table 19 lists the number (%) of subjects in a range of weight change categories in women who used Implanon for up to 3 years. Considering only those subjects who used Implanon for 11 to 22 months, 10% of subjects lost more than 5 pounds compared to 45% of subjects who gained more than 5 pounds. The percentages were similar for subjects who used Implanon for 22.5 to 34 months.

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Table 19 Number and % of Subjects in Each Weight Change Category for Implanon Users

Change in weight							
(Pounds)	(kg)		(%)		(%)		(%)
<-5.0	< -2.27	16	(10.2%)	81	(15.7%)	16	(10.6%)
-5.0 to -2.5	-2.27 to -1.13	6	(3.82%)	35	(6.77%)	6	(3.97%)
-2.4 to 0.0	-1.09 to 0	25	(15.9%)	74	(14.3%)	10	(6.62%)
0.1 to 2.5	0.04 to 1.13	15	(9.55%)	41	(7.93%)	16	(10.6%)
2.6 to 5.0	1.18 to 2.27	24	(15.3%)	62	(12.0%)	18	(11.9%)
5.1 to 7.5	2.24 to 3.40	11	(7.01%)	58	(11.2%)	21	(13.9%)
7.6 to 10.0	3.25 to 4.54	15	(9.55%)	51	(9.86%)	17	(11.3%)
>10.0	> 4.54	45	(28.7%)	115	(22.2%)	47	(31.1%)

* Year1-Subjects completing at least 11 months and not greater or equal to 22.5 months

* Year2-Subjects completing at least 22.5 months and not greater or equal to 34 months

* Year3-Subjects completing at least 34 months and not greater or equal to 46 months

Source: Response 10 of Applicant's submission of 11 October 2004.

Medical Officer's Comments

- *When change in weight was assessed in terms of change in BMI, the Applicant reported that 216 out of 1,105 subjects (19.5%) in the principal safety and efficacy studies had an increase in body mass index of > 10% from baseline at one or more assessments after starting to use Implanon.*
- *Weight gain is a common complaint in women who use hormonal contraception. This complaint is most common in women who use depot medroxyprogesterone acetate (DMPA). The change in weight in Implanon users appears to be less than that reported in users of DMPA.*

SUMMARY OF SAFETY FINDINGS

Assuming that the information provided by the Applicant in NDA 21-529, accurately reflects the findings from the clinical trials with Implanon, the Application contains sufficient exposure data to assess the likely safety profile of the drug product for the indication of prevention of pregnancy in women. A total of 1,114 subjects were exposed to Implanon in the 4 principal safety, representing a total of 26,787 treatment cycles or 2,054 woman-years of use. In addition, postmarketing safety data, based on global sales of units were provided. b(4)

Postmarketing safety reports provided by the Applicant included 3 deaths secondary to pulmonary embolus, 10 cases of non-fatal pulmonary embolus, 14 cases of cerebral vascular accident, and one case of myocardial infarction. The rates per 100,000 women-years of use for deaths and serious thrombotic/thromboembolic adverse events in users of Implanon do not appear to be excessive. However, it is difficult to assess the true significance of these rates because of uncertainty as to the proportion of the events that have been reported to the Applicant.

According to the Applicant's submission of September 9, 2004, among all of the clinical trials with Implanon, there were: no deaths, cases of pulmonary embolus or myocardial infarction; one case of thrombosis in a lower extremity; one case of an intracranial hemorrhage in a woman with an intracranial vascular malformation; and one case of a women with transient neurological symptoms, possibly secondary to transient ischemic attacks.

A total of 323 out of 1,117 (28.9%) of subjects in the principal safety studies discontinued due to an adverse event. The most frequently reported reasons for discontinuation (based on preferred terms) were bleeding irregularities (n=166, 14.9% subjects), weight increase (n=29, 2.6% subjects), emotional lability (n=23, 2.1% subjects), acne (n=13, 1.2% subjects), headache (n=12, 1.1% subjects), and amenorrhea (n=12, 1.1% subjects). Labeling should accurately reflect the incidence and severity of these adverse events.

Difficulties or complications related to the insertion or removal of Implanon were reported to have occurred in a small number of subjects in the clinical trials. Adequate training of healthcare personal will be important to reduce the incidence of these insertion/removal complications should Implanon be approved for general clinical use.

In summary, the safety profile of Implanon, based on information provided in NDA 21-529, would be acceptable for a highly effective hormonal contraceptive drug product. However, this conclusion must be tempered by concerns regarding the quality of the data submitted in the principal safety studies and the statement by European regulators (following their inspection of 4 clinical study centers from Trial 34507) that adverse events were under reported.

OVERALL BENEFIT / RISK ASSESSMENT

Based on the information provided by the Applicant in NDA 21-529, a single Implanon implant, when inserted properly, is highly effective for prevention of pregnancy for at least 2 years and possibly 3 years. In addition, there were no safety signals that would preclude approval of Implanon if (1) the drug were properly labeled as to expected adverse events and (2) healthcare providers were adequately trained in Implanon insertion and removal techniques. However, approval of Implanon for prevention of pregnancy in women cannot be recommended at this time because of concerns regarding the quality of the clinical data submitted in support of this Application.

LABELING ISSUES

Labeling negotiations were suspended after it was recognized that Implanon would not be approved during this review cycle.

RECOMMENDATIONS OF NON-MEDICAL DISCIPLINES AND DIVISIONS

Toxicology and Preclinical Pharmacology

The primary Toxicology Reviewer (Dr. Krishan Raheja) stated the following in his conclusions and recommendations for his review of NDA 21-529:

Conclusions

“Essentially all preclinical study data was referred to that submitted for 3-KDSG/EE for

contraception indication for the approval of NDA 21-187. Since Implanon is to be used for the same indication, Pharmacology considers no toxicological concerns."

General Toxicology Issues

"None"

Recommendations

"Pharmacology recommends approval of NDA 21-529."

CMC and Product Microbiology

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

Recommendation and Conclusion on Approvability

"From Chemistry, Manufacturing and Controls point of view, NDA 21-529 remains approvable pending the satisfactory inspection report from the Office of Compliance."

Basis for Approvability or Not-Approval Recommendation

"The sterilization facility was not ready for inspection. Therefore, the facility could not be inspected. Based on that the Office of Compliance has given an "Withheld" recommendation. Since sterility is an important parameter dealing with product safety, it is recommended that the application remains approvable pending satisfactory inspection report from the Office of Compliance."

b(4)

Phase 4 commitments

None were recommended.

The Microbiology Reviewer recommended approval of the drug product "on the basis of product quality microbiology."

Clinical Pharmacology and Biopharmaceutics

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

"The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-529 submitted on September 30th, 2003. The overall Human Pharmacokinetic Section is acceptable. Labeling comments outlined in the labeling section have been conveyed to the sponsor. An addendum will be added to this review when agreement on labeling is reached. The effect of body mass index will be addressed in the label."

Statistics

The FDA Statistical Reviewer (Moh Jee Ng) recalculated the values (and 95% CIs) for the Pearl Indices. Although there were small differences, in some cases, between the values obtained by the FDA statistician and those provided by the Applicant, none of the differences were material.

Medical Officer's Comment

- This Medical Officer concurs with the recommendations and/or findings of the toxicology and preclinical pharmacology, chemistry, microbiology, statistical, and clinical pharmacology and biopharmaceutics primary reviewers.*

Division of Scientific Investigation (DSI)

The FDA's Division of Scientific Investigation conducted on-site audits of 3 domestic clinical sites (those of Drs. Chez, Poindexter, and Funk) and 2 foreign sites. The foreign sites of Dr. Urbancsek and Croxatto were selected for inspection as these were 2 of the 3 sites with data on 3 years use of Implanon.

A Form 483 was issued for 4 of the 5 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 concerns 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 2 subjects that were out of protocol-specified time frames.

DSI's the 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. For Drs. Croxatto and Urbancsek this assessment is based upon preliminary reviews.”

Office of Drug Safety/Division of Medication Errors and Technical Support (DMETS)

The safety evaluator from DMETS made the following recommendation: “*DMETS has no objections to the use of the proprietary name, Implanon™.*”

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

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

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

DSRCS made specific and detailed recommendations regarding the format and simplification of language for the Patient Package Insert. All recommendations will be considered in the Division's revision of the Patient Package Insert.

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Scott Monroe
10/29/04 04:51:30 PM
MEDICAL OFFICER

Donna Griebel
10/29/04 05:01:46 PM
MEDICAL OFFICER

I have read Dr. Monroe's review and concur with
his assessment and recommendation that this NDA is
approvable.