SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

Device Generic Name	Cervical Cap
Device Trade Name	*FemCap*™
Applicant's Name and Address	*FemCap*™, Inc. 14058 Mira Montana Drive Del Mar, CA 92014
PreMarket Approval (PMA) Application Number	P020041
Date of Panel Recommendation	None
Date of Notice of Approval to Applicant	March 28, 2003

II. Indications for Use

FemCap™ is indicated for use by women of child-bearing age who desire a barrier device to prevent or postpone pregnancy.

III. Contraindications

- The device should not be used in the presence of vaginal, cervical, or pelvic infections.
- The device should not be used in the presence of vaginal or cervical lesions.

IV. Warnings and Precautions

A list of Warnings and Precautions can be found in the device labeling.

V. Device Description

FemCap™ is a single-patient-use, reusable, vaginal contraceptive and is capable of extended wear up to 48 hours. The device is made of medical grade silicone and designed to fit over the cervix. It is washable and reusable. It has the following design features:

- *FemCap*™ comes in three sizes. The inner diameter of the rim determines its size. The small 22 mm *FemCap*™ is intended for women who have never been pregnant. The medium 26 mm device is intended for women who have been pregnant but have not had a vaginal delivery. The large 30 mm, is

intended for women who have previously had a vaginal delivery of a full-term baby.

- *FemCap*™ has a sailor's hat-shaped design to cover the cervix during and following intercourse. The dome of the cap covers the cervix snugly; the brim fits into the vaginal fornices and adheres to the vaginal walls in the upper third of the vagina. The brim is slightly asymmetrical such that one side of it is wider and intended to cover posterior fornix. The groove (or sulcus) between the brim and the dome is intended to collect semen. There is a strap overlying the dome to facilitate removal.

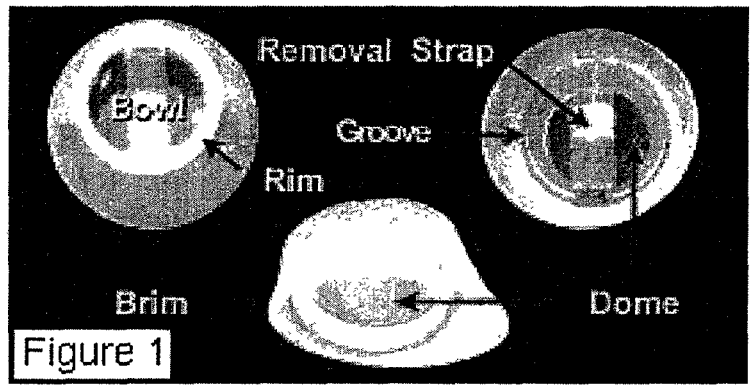

Figure 1

- *FemCap*™ is designed to prevent sperm from entering the cervix. Approximately one-quarter teaspoon of spermicide is applied to the inside dome of the cap, and one-half teaspoon of spermicide is applied to the outside in the groove of the cap. The cap is then inserted into the vagina by folding the longer side of the brim and is inserted so that it fits in the posterior vaginal fornix. The brim flares outward to help secure the position. The groove acts as reservoir for spermicide and a trap for sperm.

VI. Alternative Practices and Procedures

There are several barrier contraceptive devices that are available, including the cervical cap, diaphragm, female condom, Lea's Shield and male condom. Other forms of temporary birth control include oral contraceptives, long-acting injections, patches, hormone-containing vaginal ring, spermicide and intra-uterine devices (IUDs).

VII. Marketing History

FemCap™ received the CE Mark and became commercially available in Europe in July 1999. The device has not been withdrawn from the market for any reason.

VIII. Adverse Events

The Pivotal Safety and Efficacy Study compared *FemCap*™ with spermicide to the diaphragm with spermicide. Some of the most commonly reported adverse events in this study are presented below in Table 1.

Table 1: Pivotal Clinical Study of *FemCap*™[1]

Body System/Symptom	**(N=346) *FemCap*™ with Spermicide**		**(N=396) Diaphragm with Spermicide**	
	N	**%**	**N**	**%**
Bacterial Vaginosis	18	5.2	28	7.1
Blood in Device	31	9.0	16	4.0
Dysmenorrhea	20	5.8	16	4.0
Genital Irritation	15	4.3	23	5.8
Leukorrhea	16	4.6	29	7.3
Menstrual Disorder	16	4.6	23	5.8
UTI	26	7.5	49	12.4
Vaginal Candidiasis	65	18.8	73	18.4
Vaginitis, Etiology Unspecified	34	9.8	48	12.1

[1]Some women in both arms of the study reported more than one type of symptom.

The sponsor later added a strap to the *FemCap*™ to facilitate removal of the device. In addition, the brim on the largest size device (30 mm) was slightly enlarged to improve stability. A second, smaller, safety study was performed on the strapped device. The most commonly reported adverse events from the strapped device study are presented below in Table 2.

Table 2: Follow-up Study of Strapped *FemCap*™[1]

	Strapped *FemCap*™ with Spermicide (N=97)			**Unstrapped *FemCap*™ with Spermicide from Pivotal Study (N=358)[2]**		
Adverse Event	Events	Women	%	Events	Women	%
Abdominal or Pelvic Pain	9	6	6.2	0	0	0
Genital Irritation Related to Device	3	3	3.1	14	13	3.6
Blood in Device	11	5	5.2	23	21	5.9
Dysmenorrhea	6	6	6.2	12	10	2.8
Leukorrhea	11	5	5.2	12	12	3.4
UTI	8	7	7.2	20	15	4.2
Vaginal Candidiasis	7	6	6.2	39	33	9.2
Vaginal, Etiology Unspecified	12	9	7.2	28	21	5.9

[1] Some women in both arms of the study reported more than one type of problem.

[2] The reason that the N=358 for First Generation *FemCap*™ in Table 2 differs from the N=346 in Table 1, for what appears to be the same population, is that there were slight differences between the studies in the way rules for inclusion in analysis were implemented. The difference in numbers is due to differences in follow-up (observation time) between the two studies.

Please refer to the clinical section for additional information.

In a separate colposcopy study, there was no evidence of greater cervical/vaginal irritation among women who used the strapped *FemCap*™ compared with those who used the unstrapped *FemCap*™ (7% vs. 6% respectively).

Only the strapped *FemCap*™ will be marketed.

IX. Summary of Preclinical Studies

Over the course of development, the device has been manufactured using the following three types of silicone: Dow Corning Silastic®, Model 7-4810; Wacker Elastosil®, Model#3003-40; and Applied Silicone, Model# LSR-40. The marketed device will be made from Silicone manufactured by Applied Silicone. The Dow Corning and Wacker silicones have been withdrawn from the market for any use in female products. Per FDA's "Guidance for Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials" (June 29, 1993), *FemCap*™, Inc., provided test results to demonstrate that the Wacker and Applied Silicone products are equivalent to the Dow Corning silicone that was used in the pivotal trial.

A. Summary of Physical Testing

The following physical tests were performed on the final finished product (manufactured with Applied Silicone material) with satisfactory results:

- Strap Properties: Measured the tensile strength, the percent elongation, and the break distances of the straps with and without the body of the device.

- Cyclic Fatigue Testing: Samples from different manufacturing conditions withstood 800 cycles of specified frequency, elongation and pull force without breaking.

B. Summary of Chemical Testing

Applied Silicone LSR-40 is the raw material silicone provided by Applied Silicone. LSR-40 is a two-part silicone elastomer composed of a vinyldimethyl-terminated polydimethyl siloxane and amorphous (non-crystalline) reinforcing silica. In addition to showing equivalence to the Dow Corning silicone, the sponsor conducted chemical extractions of the final finished product. Samples extracted with saline had negligible weight losses, and no silicones were identified in the extracts. Samples extracted with methylene chloride had weight losses of 3.6-4.1%, and low levels of silicones were identified in the extracts.

C. Toxicological Studies/Material Safety

Biocompatibility testing was performed on the final finished device made with Applied silicone using standard protocols in accordance with Good Laboratory Practices (GLPs) and in accordance with the FDA medical device biological testing Guidance publication Bluebook Memorandum #G95-1 entitled *Use of International Standardization, ISO-10993-1, Biological Evaluation of Medical Devices Part 1: "Evaluation and Testing"*. T following table summarizes testing done on *FemCap*™ made with Applied silicone.

Table 3: Biocompatibility Tests and Results

Test	Test Result
Cytotoxicity	Not cytotoxic
Pyrogen, Rabbit	Non-Pyrogenic
Acute Systemic Toxicity	No evidence of systemic toxicity
Intracutaneous Toxicity	No evidence of toxicity
6 weeks Muscle Implantation with Histopathology	Microscopic reaction – not significant as compared to the USP negative control implant material, microscopically a non-irritant
Vaginal Irritation, Sub Chronic	Not an irritant
Sensitization, Maximization Test (Guinea pig)	No evidence of sensitization
Genotoxicity, Mouse Bone Marrow Micronucleus	Test article not genotoxic. No evidence of cellular toxicity.
Genotoxicity, Mouse Lymphoma, Mammalian Cell Gene Mutation, In Vitro	Not mutagenic
Genotoxicity, Ames Test	Not mutagenic.

D. Shelf Life

Accelerated and real-time aging studies was used to establish a shelf life of 3 years. Accelerated studies were done by storing devices at 65° C for 49 days; these conditions were designed to simulate 3 years of real-time aging. Real time studies have been done on devices that were aged for 23 and 34 months. Aged devices were checked against dimensional specifications and subjected to the tensile strength and cyclic fatigue tests described in Section IX. A., "Summary of Physical Testing".

E. Use Life

FemCap™ is intended to be used with spermicide and to be washed between uses; it is a single-patient-use device. Spermicide and multiple-washing studies have been conducted to support a use life of 2 years.

To determine the effects of the spermicide on the physical properties of the device, accelerated tests were conducted by submerging devices in 2% nonoxynol (N-9) spermicide at 45° C for 31 days. To determine the effects of multiple washing, devices were subjected to 365 cycles of washing, drying and immersion

in pH 4 acid to mimic the conditions of vaginal environment. After these exposures, the devices were checked against dimensional specifications and subjected to the tensile strength and cyclic fatigue tests described in Section IX. A."Summary of Physical Testing". *FemCap*™ passed all the pass/fail criteria.

F. Cleaning Validation

The cleaning (effectiveness) validation studies were based on the Association for the Advancement of Medical Instrumentation (AAMI) standards (Technical Information Report No. 1, November 1994). The testing company, NAMSA™, conducted the validation protocol for the cleaning. Bioburden recovery validation and soiling/cleaning validation tests were conducted. The cleaning procedure for *FemCap*™ was determined to be 99.9% effective.

The cleaning method developed is effective in sanitizing the device between uses. The device should be cleaned manually with antimicrobial hand soap, rinsed one minute with tap water, visually inspected for debris, and allowed to air dry. The procedure should be repeated if necessary.

X. Summary of Clinical Studies

To support the safety and effectiveness *FemCap*™, the sponsor provided results from six studies: three Phase I feasibility studies (two with the unstrapped *FemCap*™ and one with the strapped device); a pivotal study of safety and effectiveness (unstrapped *FemCap*™); a colposcopy study (unstrapped *FemCap*™); and two safety and acceptability study (strapped *FemCap*™).

A. Phase I Feasibility Studies

1. Safety and Efficacy Study of unstrapped *FemCap*™

The first clinical trial of the unstrapped *FemCap*™ was a prospective, non-comparative Phase I study of the safety, efficacy and acceptability of the device. Of the 121 women who were enrolled, 106 used unstrapped *FemCap*™ during 1300 cycles of exposure. A cycle was defined as the interval encompassing a menstrual period and days following bleeding to the next menstrual period. Intercourse could occur at any time within this cycle. On average, each participant provided 12.3 cycles for analysis.

Participants in this study were instructed to use the unstrapped *FemCap*™ with one-half teaspoon of 3% nonoxynol-9 spermicidal jelly with each act of intercourse and to leave the *FemCap*™ in place at least 6-8 hours following intercourse. Data were gathered on a single post-coital examination, adverse experiences, contraceptive efficacy and acceptability. The post-coital cervical mucus test, performed on the day following intercourse, failed to reveal any sperm in the cervical mucus.

Five out of 106 women became pregnant. Two of these reportedly believed that the device became dislodged during intercourse. The side effects were reported to be minor.

2. Phase I Study: *FemCap*™ used with and without spermicide in a post-coital study conducted by Contraceptive Research and Development Program (CONRAD)

   An open, randomized, comparative cross-over study of the unstrapped *FemCap*™ (1) with spermicide, (2) without spermicide compared to no device, and (3) to a commercially available contraceptive diaphragm with spermicide. The post-coital study was conducted to evaluate the presence of motile and non-motile sperm in the vagina, especially the cervical canal at mid-cycle.

   The study was designed for each subject to undergo five mid-cycle post-coital tests. Two of the five tests were baseline in which mid-cycle intercourse occurred. The other three tests were mid-cycle tests performed within 2.5 hours of intercourse protected by the *FemCap*™ with KY-Jelly, the *FemCap*™ with nonoxynol-9, or the diaphragm with nonoxynol-9 (N-9). The order of the tests was randomized.

   Eighteen subjects were enrolled; however, only seven completed all five post-coital tests for a total of 43 successfully completed cycles: 20 baseline; 8 *FemCap*™ with KY-jelly; 7 *FemCap*™ with nonoxynol-9; and 8 diaphragm with nonoxynol-9. Two subjects using *FemCap*™ sustained minor cervical lesions: one case of de-epithelialization, and one case of a superficial abrasion. One case of de-epithelialization was noted in a diaphragm cycle. The relationship of these lesions to the contraceptive barrier device is uncertain.

   Specimens of vaginal and cervical mucus were obtained. These were examined microscopically by viewing nine high-powered fields for the presence of non-progressively motile sperm, progressively motile sperm and non-motile sperm.

   There was reduction of all types of sperm in the cervical mucus for both the *FemCap*™ group and the diaphragm group. There was little reduction in any *vaginal* sperm counts with the use of *FemCap*™. The diaphragm, however, showed excellent results for all types of sperm in the *cervix* and for the two types of motile sperm in the vagina. In summary, *FemCap*™ was proven to be safe and, if used with or without spermicide, prevented the sperm entering the mid-cycle cervical mucus.

3. Strapped *FemCap*™ Feasibility Study

The purpose of this study was to evaluate whether the addition of the removal strap would improve user acceptability among women who experienced difficulty inserting or removing the original device.

Forty-seven participants, at 3 centers, were enrolled from the following sources: (a) 18 women discontinued from the Phase III trial of the original *FemCap*™ due to problems with insertion/removal; and (b) 29 women from the Phase III study who had reported similar difficulties but who either withdrew from the study for other reasons or completed the study.

Each participant was seen in one visit during which she was asked to insert and remove a unstrapped and a strapped *FemCap*™ and to complete a questionnaire. Twenty-one percent (10/47) of these subjects reported difficulty inserting, positioning, and/or removing one or both of the devices. In contrast, 72% of these women still had trouble inserting, and/or removing th unstrapped device. Eighty one (81%) of subjects reported that the strap made removal easier.

For the 10 subjects who continued to have trouble with insertion and removal, there was little difference between the devices. That is, these subjects did not find either device easier.

Ease of removal was the aspect liked by most about the strapped device; 85% reported that the strapped device was easier to remove. If both devices were available, 60% of volunteers would choose the strapped device over the unstrapped. In 74% of cases, the clinicians would prescribe the strapped device. Only 13% of the clinicians would prescribe the unstrapped device (13% had no preference).

It was concluded that in a small population of women who experienced difficulty inserting/removing the unstrapped device, most preferred the strapped device, most commonly due to easier removal.

B. Pivotal Safety and Effectiveness Studies

1. Phase III Contraceptive Effectiveness Study

This was a prospective, multi-center, randomized trial comparing safety, effectiveness and acceptability of the unstrapped *FemCap*™ to that of a commercially available diaphragm. Both devices were used with 2% nonoxynol-9 spermicide. The duration of the study was 28 weeks. Eight hundred forty-one (841) subjects were randomized at 10 different centers across the U.S. A subset of 42 subjects underwent colposcopy in one center.

Study Design

Primary Efficacy Endpoint:

- Pregnancy

Primary Safety Endpoints:

- Discontinuation due to medical reasons
- Adverse experiences

Secondary Endpoints:

- Acceptability

    1. Discontinuation due to non-safety device-related reasons
    2. Problems reported at follow-up
    3. Regularity of device use
    4. Responses on participant questionnaire

Inclusion Criteria:

- Ages of 18 to 40, inclusive
- Sexually active (coital frequency at least 6 times/month)
- Stable, mutually monogamous relationship
- Negative pregnancy test at enrollment
- Regular menstrual cycles for past three months, unless recently pregnant or using hormonal contraception as follows:

    1. If recently pregnant, at least 10 weeks since end of last pregnancy. Also, must have had two spontaneous menses 23-38 days apart since end of pregnancy.
    2. If recently used oral contraceptives, must have experienced withdrawal bleed at the end of the last pack and one subsequent spontaneous menses 23-38 days after the withdrawal bleed.
    3. If recently used injectable hormonal contraception, must have been at least nine months after the last injection, with two spontaneous menses 23-38 days apart since the last injection.
    4. If recently used implanted hormonal contraception, must have had at least one spontaneous menses since removal of the implants (withdrawal bleeding occurring within one week of implant removal not considered a menses).

- Not actively desiring pregnancy for 28 weeks and willing to accept an unknown risk of pregnancy

- Willing to be randomly assigned to either *FemCap*™ or diaphragm and to use that method as her only means of contraception during her participation in the study
- Planning to reside in area for at least 28 weeks after enrolling in the study
- Willing and able to comply with study procedures and to return to the clinic for scheduled follow-up visits

Exclusion Criteria:

- History suggestive of infertility, defined as

    1. known history of a fertility problem or sterilization;
    2. previous pelvic surgery, ectopic pregnancy, or antibiotic treatment for PID, unless participant had an intrauterine pregnancy afterwards;
    3. abnormalities on pelvic exam at enrollment that might impair fertility; or
    4. known history of endometriosis unless participant had an intrauterine pregnancy afterwards.

- Currently breastfeeding unless participant had 2 menses 23-38 days apart before enrolling
- Known sensitivity or allergy to silicone, latex, or spermicide
- History of toxic shock syndrome
- History of 2 or more urinary tract infections requiring treatment during the year preceding enrollment
- At high risk for HIV or other sexually transmitted diseases
- Signs or symptoms of current cervicitis, endometriosis or PID
- Contraindication to pregnancy
- Vaginal or cervical anatomic abnormality identified by examination and precluding proper fit of either device
- Unable to insert, position, and/or remove device
- Other conditions that, in the opinion of the investigator, would constitute contraindications to participation in the study or would compromise ability to comply with the study protocol, such as any major chronic illness including cancer, serious autoimmune disease or a major psychiatric disorder, e.g., schizophrenia
- Currently participating in any other study or previous participation in this study
- UTI, yeast infection, trichomonas, or bacterial vaginosis that could not be resolved within 14 days after enrollment
- Positive gonorrhea or Chlamydia test at enrollment

- Abnormalities on admission Pap smear other than inflammation, infection, or atypical squamous cells of undetermined significance (ASCUS)

In addition, the participant's partner must have had (by report)

- no history of sensitivity or allergy to silicone, latex or spermicide;
- no known fertility problem or vasectomy; and
- no known risk for STDs including HIV.

Two randomization lists were prepared at each study site, one for women with female barrier experience (diaphragm, Lea's Shield, *FemCap*™, cervical cap, female condom, or vaginal sponge) and the other for those without experience with female barrier contraceptives. Subjects were evaluated at enrollment, 2 weeks, 6 weeks, 12 weeks, 20 weeks (telephone contact only), and 28 weeks. Subjects recorded menses, intercourse, type of contraception, and problems (medical and non-medical) before, during or after use with the device in daily diaries. Urine pregnancy tests were performed at each visit. Questionnaires were given to subjects and their partners at the 2-week visit and at the final visit.

Subjects using *FemCap*™ were instructed not to have intercourse during menses. If they elected to have intercourse while menstruating, they were advised to use condoms instead of *FemCap*™. Subjects assigned to the diaphragm were told to follow instructions for use for the diaphragm regarding use of the device during menses, i.e., removing the device as soon as possible after intercourse (within 6 hours) to reduce the risk of Toxic Shock Syndrome.

For subjects assigned to use *FemCap*™ with spermicide, obstetrical history dictated the size of *FemCap*™ to be used. Nulligravid subjects received the smallest or 22 mm *FemCap*™, subjects who had been pregnant but had delivered abdominally or who had pregnancy termination received the 26 mm device, and subjects who had delivered vaginally received the 30 mm device.

At the 2-week visit, subjects were asked to demonstrate correct insertion and removal. Additional instructions were offered if the subject was experiencing difficulty. If after additional instruction the subject still could not insert and remove the device correctly, she was discontinued from the study. A subject was considered to have completed the study if she used the assigned device for 28 weeks after enrollment. At the final visit, the following were performed:

- Review of diary
- Interview
- Examination and laboratory tests as in other follow-up visits, including Pap smear and urine pregnancy test
- Return of devices

A total of 841 subjects were enrolled in the pivotal Contraceptive Safety and Effectiveness Study. A total of 419 subjects were randomized to *FemCap*™ and 422 were randomized to the diaphragm. Of these, 40 *FemCap*™ and 3 diaphragm subjects could not insert or remove the device and were excluded from the study. Another 29 *FemCap*™ subjects and 21 diaphragm subjects were also discontinued at baseline or lost to follow-up. Seven hundred forty-one subjects comprised the per-protocol population, 350 *FemCap*™ and 398 diaphragm subjects.

Table 4: Patient Accountability

Number of Patients	*FemCap*™ with Spermicide	Diaphragm® with Spermicide
Per-Protocol Population	350	398
Nulligravid	81	98
Non-Vaginal Delivery	78	110
Vaginal Delivery	191	190
Discontinued	123	103
Protocol Violation	24	21
Pregnancy	39	27
Device-Related Reason	21	8
Non-Device Related Reason	20	25
Medical Reasons	19	22
Loss-to-Follow-Up	13	17
Completed 6-Month Study without Becoming Pregnant	214	278

In both device groups, the mean age was 29 years. Between 70-72% of subjects were Caucasian. Black women accounted for 19-22% of subjects. Hispanic women accounted for 5-7% of subjects. Between 59-65% of subjects in both groups had prior experience using female barrier contraceptives. The percentage was slightly higher among *FemCap*™ users, but not by more than four percentage points.

Effectiveness Results:

The 6-month unadjusted gross cumulative pregnancy probabilities per 100 women in the per-protocol population were 13.5% for *FemCap*™ users and 7.9% for the diaphragm users. The upper limit of the 95% confidence interval for the 6-month cumulative pregnancy probability for the *FemCap*™ user was 17.8%. The 12-month pregnancy probability of 22.8% with *FemCap*™ is a projected probability with an upper limit for the 95% confidence interval for 12 months of 30%.

Out of the 69 nulligravid subjects in this study who used the small *FemCap*™, 4 became pregnant for an 8.1% 6-month cumulative Kaplan-Meier pregnancy probability. Of the 61 parous subjects who did not have a vaginal delivery and used the medium sized *FemCap*™, 4 became pregnant for an 8.2% 6-month cumulative Kaplan-Meier pregnancy probability. In contrast, of the 184 subjects who had a vaginal delivery and used the large *FemCap*™, 28 became pregnant for a 17.3% 6-month cumulative Kaplan-Meier pregnancy probability.

The Table 5 shows pregnancy probabilities from different studies and various types of contraceptives compared to the *FemCap*™.

Table 5: Pregnancy Rates

Contraceptive Method	**6-month Pregnancy Rate**	**12-month Pregnancy Rate**
Surgical Sterilization Injectable Hormones IUDs	Less than 1%	Less than 1%
Hormone Pills Vaginal Ring	1-2%	1-2%
Male Condom	7%	11%[1]
Contraceptive Diaphragm	8%	17%
Cervical Cap	11%	17%
Female Condom	13%	21%[1]
Lea's Shield	9%	15%[1]
FemCap™ (All Sizes)	(13.5%)	(23%)[1]
22 mm, nulligravid	8.1%	14%[1]
26 mm, parous (non-vaginal)	8.2%	14%[1]
30 mm, parous (vaginal)	17.3%	29%[1]

[1] These 1-year rates are projected since most barrier studies today are conducted as 6-month studies.

Acceptability:

FemCap™ users most commonly reported dislodgement, difficulty inserting the device, and difficulty removing the device. Diaphragm users most commonly reported vaginal symptoms, difficulty inserting, and inconvenience. *FemCap*™ users reported dislodgement for 1.85% of coital acts. Although significantly more *FemCap*™ users reported dislodgement or movement, the pregnancy probabilities of these women were not different from pregnancy probabilities of *FemCap*™ users who did not complain of dislodgment or movement.

Pap Smear Results:

Comparison of Pap smear between baseline and 12 weeks and baseline and discontinuation visit did not reveal significant differences between the two device groups. Because women with abnormal Pap smears were not enrolled into the study, the numbers of subjects with abnormal smears were small at both the 12 weeks and discontinuation visits. There were a greater percentage of "Unsatisfactory" smears (absence of endocervical cells) in the *FemCap*™ group at discontinuation compared to the diaphragm group, 3.8% versus 0.8% respectively.

2. Colposcopy Sub-Study:

Forty-two subjects from the pivotal study were enrolled in single center "nested" colposcopy study. Half of these subjects used the unstrapped *FemCap*™ with spermicide, and the other half used the diaphragm with spermicide.

These colposcopy sub-study subjects underwent colposcopy four times: at enrollment, and at the 2-, 6-, and 28-week visits. Any vaginal or cervical abnormality on colposcopy at enrollment excluded a subject from participation. At the 2-week visit, 4 *FemCap*™ subjects and 3 diaphragm subjects had lesions. At the 6-week visit, 4 *FemCap*™ users had lesions and 2 diaphragm users had lesions. At the 28-week visit, 3 subjects in both groups had lesions.

In summary, 29 lesions were seen in the *FemCap*™ group and 18 in the diaphragm group. Of these, 28 in the *FemCap*™ group were on the cervix and 14 in the diaphragm group were on the cervix. Of the cervical lesions, there was a difference between the two groups in that 40% of the *FemCap*™ lesions were within the transformation zone (TZ) and 86% of the diaphragm cervical lesions were in the TZ.

Approximately 40% of the lesions in both groups were classified as aceto-white (non-condyloma) lesions. All of these were squamous metaplasia, a normal finding. Of the other lesions in *FemCap*™ group: 5 (17%) were classified as ecchymosis; 4 (14%) as abrasive; 2 (7%) each as petechia hemorrhage, edema, and lehkoplakia; and 1 (3%) each as fibrosis and irritation.

3. Safety and Acceptability Study of Strapped *FemCap*™:

Purpose: To compare the strapped *FemCap*™ device with the unstrapped *FemCap*™ with respect to safety and acceptability.

A prospective, non-randomized, single-arm study with a historical control was conducted (the *FemCap*™ with spermicide arm of the pivotal Study of Safety

and Effectiveness of the unstrapped *FemCap*™). One hundred-twenty subjects were enrolled and fitted with the strapped *FemCap*™. There were more Caucasian subjects (85%) in this study compared to African American subjects (11%).

Primary Endpoints:

- Safety and acceptability of the strapped *FemCap*™

Secondary Endpoints:

- Removal difficulty
- Dislodgement
- Participant genital pain or discomfort
- Adverse Events
- Cervical/vaginal irritation
- Acceptability

Participants were given diaries in which to record: dates of intercourse and menses; whether the device was used correctly; other contraceptive devices used; and partner problems. Each subject underwent 3 colposcopies: (1) at enrollment; (2) at 2 weeks; and (3) at 8 weeks into the study.

Removal Difficulty:

Of the 120 subjects enrolled in this study, 20 were discontinued due to inability to insert or remove the device. One subject was discontinued because she could not be fitted successfully. Two were lost to follow-up. Therefore, the treated population for this study was 97 subjects.

At the enrollment visit, 12% of the subjects were unable to remove the strapped *FemCap*™. These subjects were discontinued from the study. This was greater than the 8% in the pivotal study who were not able to remove the unstrapped *FemCap*™ at enrollment.

The degree of difficulty in removal is provided in Table 6.

Table 6: Device Removal Problems

Problem with removal	**Strapped *FemCap*™ (120)**	**Unstrapped *FemCap*™ (419)**
Severe Problem	14 (12%)	34 (8%)
Moderate Problem	29 (24%)	148 (35%)
Slight Problem	21 (18%)	71 (17%)
No Problem	56 (47%)	166 (40%)

Improvements in the above categories for the strapped device were not statistically significant.

Device Dislodgement:

The correct position of the *FemCap*™ is covering the cervix such that the entire rim of device is seated within the posterior fornix. When the *FemCap*™ is no longer in this position, it is considered "dislodged". Device dislodgment negates contraceptive efficacy. The rate of device dislodgements, though slightly higher in the strapped group compared to the diaphragm, was not significantly different between the two groups.

Pain/Discomfort/Device "Awareness":

Emphasis given to these questions in the strapped device study, compared to the pivotal study which tested the unstrapped device, might have heightened participants' awareness of, memory of, or willingness to report device problems compared to the pivotal study.

Two women discontinued the study because their male partners complained of discomfort from the device. Neither of these two men reported any visible penile injury. The complaints associated with the devices are provided in Table 7.

Table 7: Complaints

Complaint	Strapped *FemCap*™		Unstrapped *FemCap*™	
	N	%	N	%
Female Partner				
Pain/Discomfort	26/97	26.8	42/348	12.1
Awareness of Device	16/97	16.5	63/348	18.1
Male partner				
Pain/Discomfort	*	31.3	13/336	3.9
Awareness of Device	*	34.4	128/336	38.1

*Actual numbers not available

Cervical/Vaginal Irritation:

Three colposcopic evaluations were performed on each subject: at the enrollment (i.e., baseline) and at 2- and 8-week visits. This corresponded to visits among the Colposcopy Sub-Study subjects. The findings for cervical and vaginal lesions are provided in Table 8.

Table 8: Cervical and Vaginal Lesions

	Strapped Device			Unstrapped Device		
	Baseline N=97	2-Weeks N=93	8-Weeks N=85	Baseline N=20	2-Weeks N=18	8-Weeks N=19
Cervix	26	48	42	8	6	6
Vagina	9	9	16	0	0	1

The most common adverse events are provided in Table 9.

Table 9: Most Common Adverse Events

	Strapped Device			Unstrapped Device		
	Baseline N=97	2-Weeks N=93	8-Weeks N=85	Baseline N=20	2-Weeks N=18	8-Weeks N=19
Petechiae	17 (13.4%)	27 (22.6%)	27 (12.9%)	1 (5.0%)	0 (0.0%)	1 (5.3%)
Erythema	4 (4.1%)	7 (7.5%)	13 (11.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
De-Epithelialization	1 (1.0%)	9 (7.5%)	3 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Female Subject Acceptability Outcomes: Strapped vs. Unstrapped Device

The Table 10 summarizes key device acceptability responses at the two-week follow-up on female subject questionnaires.

Table 10: Female Subject Acceptability Outcomes

Outcome	Strapped *FemCap*™ N	%	Unstrapped *FemCap*™ N	%
General Opinion				
Liked a Lot	26/93	28.0	98/329	29.8
Liked Somewhat	35/93	37.6	154/329	46.8
Problems	45/92	48.9	121/327	37.0
How Likely to Use Device Alone				
	29/93	31.2	98/329	29.8
Probably	35/93	37.6	165/329	50.2
Definitely				
Recommend to a Friend	76/91	83.5	280/321	87.3

Male Partner Acceptability Outcomes: Strapped vs. Unstrapped Device

The general opinion of the male partners at the two-week follow up was approximately the same for the strapped and unstrapped devices. For example, those whose partners used the strapped *FemCap*™ liked the device somewhat or a lot (45.8%) compared with the unstrapped device (49.5%). However, 62.2% of men whose partners used the strapped *FemCap*™ were aware of the device, whereas only 50.2% of those whose partners used the unstrapped *FemCap*™ were aware of the device. As discussed (see Pain/Discomfort/Device Awareness), this difference might be the result of study bias.

Strapped *FemCap*™ male partners reported 20.7% problems and unstrapped *FemCap*™ male partners reported 15.5%. Sixty-four percent (64%) of strapped *FemCap*™ male partners would recommend it to a friend and 72.7% of unstrapped device partners would recommend it to a friend.

The addition of the removal strap had no overall effect on safety and effectiveness of the *FemCap*™.

XI. Conclusions Drawn From Studies

The 12-month pregnancy probability of 22.8% with *FemCap*™ is a projected probability with an upper limit for 95% confidence for 12 months of 30%. There was a difference in the chance of pregnancy depending on whether or not a woman had given birth vaginally and on the size of *FemCap*™ she used.

For women who had never had a vaginal delivery and who used the small or medium *FemCap*™, the 6-month chance of pregnancy was about 8.2%. If a woman had given birth vaginally and used the large *FemCap*™ the chance of pregnancy at 6-months was 17.3%.

Women with a history of vaginal delivery will require special counseling to ensure that they understand that they have a much higher risk of pregnancy than women who are nulliparous or who have had an abdominal delivery. This should be accomplished through labeling.

The pivotal trial demonstrated that *FemCap*™ is an effective barrier contraceptive device and does not raise any significant clinical safety issues. Only the strapped device will be marketed. *FemCap*™ is a prescription device.

XII. Panel Recommendation

In accordance with the provisions of section 515(C)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA application was not referred to the Obstetrics and Gynecology Devices Panel, an FDA advisory committee, for review and recommendation because the information in this PMA substantially duplicates information previously reviewed by the panel at previous meetings on vaginal barrier contraceptive devices.

XIII. CDRH Decision

FDA reviewed the preclinical and clinical data and determined that the device is reasonably safe and effective for its intended use. FDA conducted an inspection of the applicant's manufacturing facility and determined the facility was in compliance with applicable requirements of the Quality Systems Regulation (21 CFR 820). FDA issued an approval order for the application on March 28, 2003.

XIV. Approval Specifications

Directions for Use: See Labeling (Physicians and Patient Labeling)

Hazards to Health from Use of Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events sections of the labeling.

Post-Approval Requirements and Restrictions: There are no post approval study requirements for *FemCap*™.