

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

DEVICE GENERIC NAME:	Vaginal Barrier Contraceptive Device
DEVICE TRADE NAME:	<i>Lea's Shield</i> [®]
APPLICANT'S NAME AND ADDRESS:	<i>Yama, Inc.</i> 67-71 East Willow Street Millburn, New Jersey 07041 U.S.A.
DATE OF PANEL RECOMMENDATION	None
PREMARKET APPROVAL APPLICATION (PMA) NUMBER:	P010043
DATE OF NOTICE OF APPROVAL TO THE APPLICANT:	March 14, 2002

II. Indications for Use

The *Lea's Shield*[®] is indicated for use by women of child-bearing age who desire to prevent or postpone pregnancy.

III. Contraindications

Use of the *Lea's Shield*[®] is contraindicated in patients with vaginal, cervical, and/or pelvic infections, and in patients with vaginal or cervical lacerations.

IV. Warnings and Precautions

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

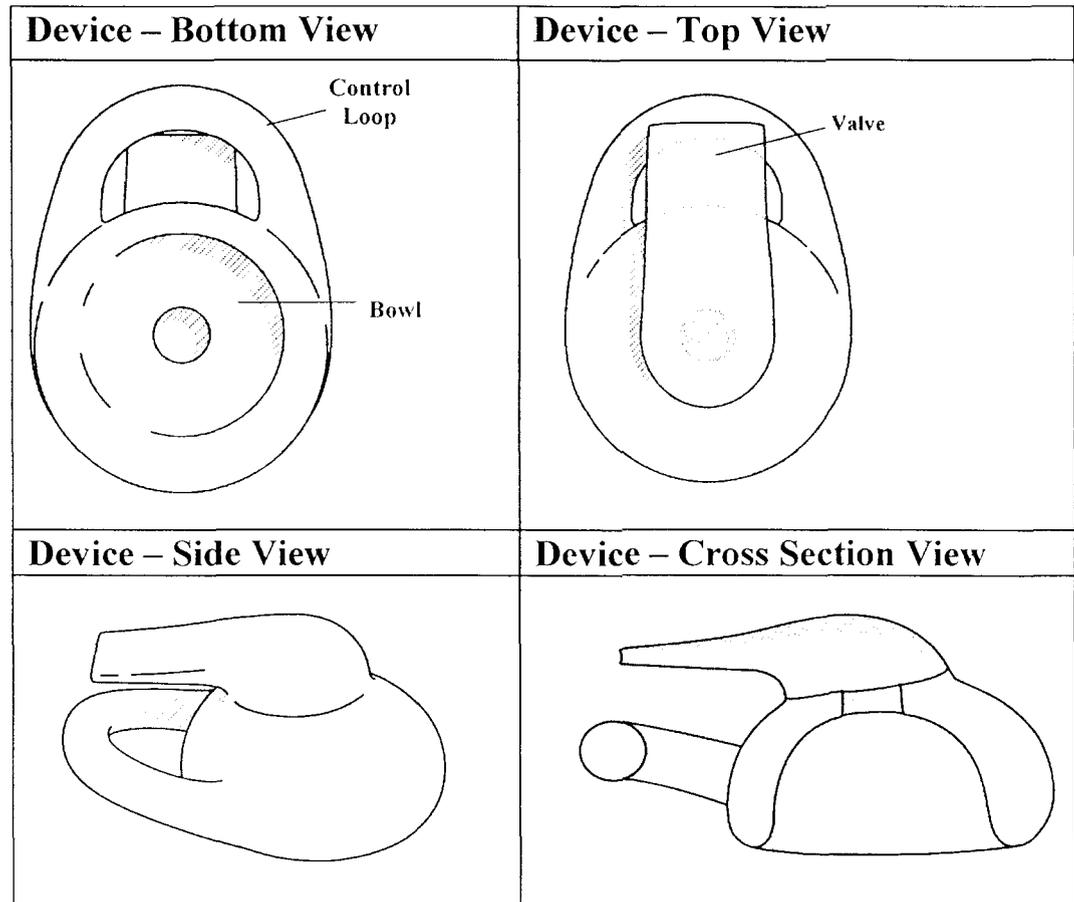
V. Device Description

Lea's Shield[®] is a single-patient-use, reusable, vaginal barrier contraceptive and it is capable of extended wear periods up to 48 hours. The device is composed entirely of medical grade silicone. It is designed to fit the anatomy of the vagina and cover the cervix. It is washable and reusable. It has the following design features:

Cup-shaped Volume Bowl – The *Lea's Shield*[®] device is a cup-shaped bowl, which covers the cervix without being “held” by the cervix like the cervical cap. The volume of *Lea's Shield*[®] is created by the three-dimensional bowl suspended

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

under the cervix by the virtue of a thick posterior lip of the device, which fully occupies the posterior fornix.



The Control Loop – The control loop, which is also an integral part of the *Lea's Shield*[®], is designed to assist removal. The loop is intended to prevent lateral rotation of the device during use.

The Valve – The valve is a thin, flexible elliptical tube leading from the bowl. The primary function of the valve feature of *Lea's Shield*[®] is to vent air during insertion. This creates a surface tension, and a “suction” effect. As the *Lea's Shield*[®] is placed into position, the surrounding tissues exert pressure on the valve and cause it to compress.

VI. Alternative Practices and Procedures

There are several barrier contraceptive devices that are available, including cervical cap, diaphragm, female condom and male condom. Other forms of temporary birth control include oral contraceptives, long acting injections, patches, hormone containing vaginal ring, spermicide and IUDs.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

VII. Marketing History

The *Lea's Shield*[®] was first distributed in Canada in May 1995. The *Lea's Shield*[®] has been marketed in Germany, Switzerland, and Austria, where it was launched in October 1996 under the trade name, "*Lea*[®] *Contraceptivum*."

The device has not been withdrawn from any market for reasons related to safety and effectiveness of the device.

VIII. Potential Adverse Effects:

During the clinical efficacy study, sixty percent of subjects (110/182) reported at least one adverse event involving the urogenital system. Of these, 34.6% (63/182) reported adverse events involving the urogenital system that were possibly or probably related to the *Lea's Shield*[®].

The most commonly reported adverse events related to *Lea's Shield*[®] are listed below:

Adverse Event	Rate
Abnormal bleeding or spotting	6.0%
Male partner pain or discomfort due to the device in the female partner	8.2%
Female partner genital pain or discomfort	6.6%
Urinary tract infection	3.8%
Vaginitis	4.4%
Abnormal Pap test	3.9%

Other less common adverse events included cervicitis, contusion of penis (one case), cervical erosion, and superficial injury of vulva.

The following adverse events were observed during the Microbiology and Colposcopy safety clinical study of 30 patients using *Lea's Shield*[®]: abdominal cramps (20%); dyspareunia (3.3%); burning after intercourse (3.3%); blood in bowl of device at removal (10%); product-related intermenstrual bleeding (3.3%); vaginal pruritis, irritation and/or discharge (10%); and dysuria and /or urinary tract infection (3.3%). The sponsor did not report any serious morbidity associated with these effects; they were of a transient nature. In this study the most common problems experienced with the device by female participants were difficulty with insertion and removal (30%), discomfort (23.3%), and bleeding at device removal (13.3%). Seventy-three percent of the male participants reported that they could either feel the device or experienced pain and/or discomfort associated with it.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

IX. Summary of Pre-Clinical Testing:

A. Silicone History

Lea's Shield[®] is currently manufactured from NuSil Model# MED-4920 silicone. Over the course of its development, the following three silicones were also used to manufacture *Lea's Shield*[®]: Dow Corning Silastic[®], Model #Q7-4840; Wacker Elastosil[®] Model# 3003-20; Bayer Baysilone[®] Model# LSR 4020. (The Dow Corning, Wacker and Bayer silicones have been withdrawn from the market for any female products.) Yama provided data to show that the Wacker, Bayer and Nusil silicones are equivalent to the Dow Corning silicone (silicone used to make device for the efficacy trial) per FDA's "Guidance for Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials".

B. Summary of Physical Testing

The following physical tests were performed on the finished product (manufactured with NuSil silicone) with satisfactory results.

- Shore hardness
- compression testing
- loop elastic modulus and loop break strength
- valve elastic modulus and valve break strength
- sample weight testing

C. Summary of Chemical Studies

Nusil MED-4920 is a high-consistency two-part silicone elastomer composed of vinyl-terminated dimethyl polysiloxane and 20% amorphous (non-crystalline) reinforcing silica. The product is catalyzed via a platinum-siloxane complex curing mechanism. The following physical tests were performed with satisfactory results:

- extractables, non-volatile residue
- molecular weight of hexane extracts
- surface characterization by backscatter electron detector

D. Summary of Biological Testing

Biocompatibility testing was performed on the final finished subject device made with NuSil silicone using NAMSA standard protocols with Good Laboratory Practices (GLPs) and in accordance with ISO10993-1. The following table summarizes testing done on *Lea's Shield*[®] made with NuSil silicone:

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Biocompatibility Testing Results – *Lea's Shield*[®]

Test Performed	Extract(s)	Test and Control(s)	Results/Comments
Cytotoxicity (ISO)	ME	Natural rubber (+) Silicon tubing (-)	L-929 cells gave a grade 0-1, no evidence of cell lysis or toxicity.
Sensitization (Maximization)	Saline and CSO*	Saline and CSO (-) DNCB** (+)	No sensitization was observed
Intracutaneous Toxicity (ISO/USP)	Saline and CSO	Saline and CSO (-)	No toxicity observed in either extract
Systemic Toxicity (ISO/USP)	Saline (IV) and CSO (IP)	Saline and CSO	No signs of toxicity
Genotoxicity (Ames)	Saline	Saline (-) 2-aminoanthracene (+) sodium azide (+) 2-Nitrofluorene (+) 9-aminoacridine (+) with and without activation	No genotoxicity in TA98, TA100, TA1535, and TA1537 strains of <i>S. typhimurium</i>
12 weeks Muscle Implantation with histopathology	Test article and negative controls	Implanted in paravertebral muscle of rabbit	Examined macroscopically and microscopically, same as control sites.
Hemolysis (DHEW)	Saline	Saline (-) Water (+)	4.45% hemolysis, considered to be non-hemolytic
Rabbit pyrogen (ISO)	Saline	Saline (-)	<0.5 °C rise in all rabbits non-pyrogenic

*CSO is cotton seed oil

** DNCB is 1-choloro-2, 4-dinitrobenzene

E. Summary of Shelf Life Testing of Yama *Lea's Shield*[®] Molded with NuSil Silicone

Real-time aging studies have been used to establish a shelf life of 2 years.

Ten devices from each of 2 lots made with NuSil silicone passed the following tests after unheated aging for periods of up to 9 and 22 months, respectively:

- visual inspection
- device weight
- dimensions after cyclic compressions
- force of compression during cyclic compression
- force needed for cyclic valve closure
- valve leakage
- Shore hardness
- loop extensibility

Devices made with Wacker silicone were successfully tested following unheated aging for periods of more than 5 years.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

F. Spermicide Interaction Study

The device is intended to be used with spermicide. It is a single-patient, multiple-use device. To determine the effects of the spermicide on the physical properties of the device, accelerated tests were conducted by submerging devices in 20% nonoxynol (N-9) spermicide at 47 °C for 30 days. After such exposure, the devices passed the following tests: hardness testing, cyclic compression, cyclic valve closure, extensibility of the loop, extensibility of the valve, and microscopic surface visualization. There was no statistically significant difference between the test results for the treated and control devices.

G. Device Cleaning Validation:

The cleaning (effectiveness) validation studies of *Lea's Shield*[®] were based on the Association for the Advancement of Medical Instrumentation (AAMI) standards (Technical Information Report No.1, November 1994). NAMSA[™] conducted the validation protocol for the cleaning. The bioburden recovery validation and soiling/cleaning validation test were conducted. The cleaning procedure for *Lea's Shield*[®] was determined to be 99.95 % and 99.98% effective.

The cleaning method developed for the *Lea's Shield*[®] is effective in sanitizing the device between uses. The accepted cleaning method is to use 2 pumps of mild liquid hand washing soap. Manually clean the device for 2 minutes. Rinse the device under running tap water for 1 minute. Visually inspect the device for debris. Repeat cleaning procedure if necessary.

Lea's Shield[®] can be used for up to 6 months. Testing was done to demonstrate that there are no changes to the physical properties of the *Lea's Shield*[®] after being washed 180 times.

X. **Summary of Clinical Studies**

Four types of clinical studies were conducted for *Lea's Shield*[®]: The Phase I Feasibility studies, the Microbiology and Colposcopy Safety Study, the Device Position by MRI Study and the Pivotal (Safety and Efficacy) Trial.

A. Phase I Feasibility Studies

1. Postcoital Studies:

Three postcoital studies of *Lea's Shield*[®] were carried out to determine the effectiveness of the device in blocking sperm from penetrating the cervical mucus. The results of these studies indicated that *Lea's Shield*[®] effectively blocks sperm entering mid-cycle mucus.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Phase I Postcoital Study Without Spermicide - Los Angeles, California (completed in January 1990)

The first postcoital study was performed in ten women at the LAC/USC Women's Hospital in Los Angeles, California. After a screening visit, subjects were instructed to return at mid-cycle to confirm their ovulatory status and the absence of sperm in their cervical mucus. The device was inserted by the clinician and participants were instructed to have intercourse the following morning and return to the clinic three hours later.

No sperm were found in the mucus of five women, a few non-motile sperm were observed in the cervical mucus samples of two women, and the remaining three women had 0.8 or fewer progressively motile sperm per-high field in their mucus sample. (The presence of five or more progressively motile sperm per high – power field is considered a normal postcoital test where fertilization is a possibility.) *Lea's Shield*[®] was found to prevent penetration into cervical mucus of enough progressively motile sperm to substantially reduce the likelihood of pregnancy.

Phase I Postcoital Study Without Spermicide - Paris, France (completed in February 1990)

A second postcoital study of *Lea's Shield*[®] was conducted in ten volunteers at L'Universite Rene Descartes, Paris, France. After a screening visit, the second visit was scheduled for the middle of the volunteer's next cycle. The *Lea's Shield*[®] device was inserted after verification that no sperm were present in the cervix. The third visit took place ten hours after coitus.

No motile sperm were found in any of the mucus samples or in the bowl or valve of any device. A few non-motile sperm were present in the internal or external os of four subjects.

All ten subjects reported that they found *Lea's Shield*[®] to be acceptable. The investigator concluded that 1) the cervix was covered by the device *in situ*; 2) no dislodgment of the device was observed; and 3) *Lea's Shield*[®] used without spermicide appeared to be a barrier to sperm penetration.

Phase I Postcoital Study - Norfolk, Virginia (completed in December 1992)

This study was a comparative study during three test cycles: 1) using a diaphragm with spermicide; 2) *Lea's Shield*[®] with spermicide; and 3) *Lea's Shield*[®] without spermicide.

Ten volunteers completed all 3 test cycles. All volunteers demonstrated more than 5 progressively motile sperm per high-power field in the cervical mucus after intercourse in the baseline cycle, in which intercourse took place without a device.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

No motile sperm were found in the cervical mucus in any cycle in which the *Lea's Shield*[®] or the diaphragm was used with spermicide. No motile sperm were found in the cervical mucus in 9 of 10 cycles in which *Lea's Shield*[®] was used without spermicide. (Only 2 progressively motile sperm were present in the cervical mucus of one volunteer when she used *Lea's Shield*[®] with nonspermicidal lubricant. This volunteer used a smaller device, which is no longer manufactured.) The study provided evidence that the *Lea's Shield*[®] could prevent passage of motile sperm into mid-cycle cervical mucus with or without the use of spermicide.

2. Tolerance Study

The tolerance study assessed changes in the vaginal epithelium and microflora in ten women after wearing *Lea's Shield*[®] for 72 hours.

A total of 17 patients were enrolled. Ten completed the study. Each study participant had a total of three pelvic exams. At the screening exam, subjects underwent Pap smear, and testing for Neisseria gonorrhoea, Chlamydia trachomatis and Staphylococcus aureus. They were also evaluated for clinical evidence of vaginitis.

No evidence of trauma to the vaginal walls that were in contact with the device for a period of 72 hours was observed and there were no major changes in the vaginal microflora.

3. Ease of Use Studies

Ease of use studies were conducted among 40 women at three U.S. centers to evaluate whether the instructional materials regarding correct insertion and removal of *Lea's Shield*[®] were comprehensible by users and whether these materials would lead to the correct insertion and removal of the device without prior intervention by health professionals.

Each participant underwent the following: 1) entry physical examination; 2) receipt of instructions about the study; 3) receipt of the Instructions for Use for *Lea's Shield*[®]; 4) insertion of the device without assistance from the study staff; 5) wearing of the device for approximately 1-4 hours; 5) examination by the investigator to check for proper position of the device; and 6) removal of the device according to the Instructions for Use and without the assistance of the study staff. The volunteer subsequently answered a set of standardized questions during an interview regarding her perception and comprehension of the instructions and acceptability of the device. The first *Ease of Use* study was conducted at the Baylor College of Medicine in Houston, Texas.

All but one volunteer indicated that they understood the instructions. One had some questions about instructions for inserting the device. All of the volunteers

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

inserted the device without difficulty. The investigator observed the device to be in the correct position (i.e., covering the cervix) in all ten women. Six out of the ten women said they had some problems during removal and stated that they were not aware of the need to break the suction before attempting to remove the device. In the focus group discussion with these 10 women, it was clear that the Instructions for Use were not sufficiently clear about the need to break the suction and how it should be done.

The following changes in the Instructions for Use were made based on the results of this study:

- A paragraph was added explaining the importance of breaking the suction to ease removal and how to do it. "Twisting mildly" was changed to "twist until you break the suction".
- A warning was added that care should be taken by women with long fingernails to avoid trauma to the vaginal wall.

These changes were incorporated before the initiation of the Ease of Use Study conducted in Sacramento, California.

A second cohort of 10 participants was enrolled in the study at the Valley Center for Women's Health, Sacramento, California. This second cohort, having the advantage of the revised Instructions for Use, removed the *Lea's Shield*[®] with less difficulty than the first cohort. These participants expressed a more favorable impression of the device.

A third cohort of 10 subjects participated at the Feminist Women's Center, Atlanta, Georgia.

All volunteers stated that they understood the written instructions and all ten inserted the device correctly. The investigator found all the devices to be in the correct position (i.e., covering the cervix). No subjects reported problems with insertion or removal.

A fourth Ease of Use study was conducted at the Valley Center for Women's Health, Sacramento, California. All the women in this final cohort successfully inserted and removed *Lea's Shield*[®] without help or additional advice from the study staff.

These studies provided evidence that *Lea's Shield*[®] could be properly inserted and removed by the user after reading the instruction booklet and without the assistance of a health care professional.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

B. Colposcopy and Microbiology Safety Study

Objectives: The purpose of this study was to obtain additional safety data for the *Lea's Shield*[®]. In particular, study objectives were to study the evidence of vaginal and cervical irritation following 8 weeks of *Lea's Shield*[®] use (at least 12 coital acts), changes in the vaginal flora, ectocervical flora and endocervical inflammation.

Endpoints:

- Participant reports of symptoms, findings on pelvic exam, and colposcopic findings after 8 weeks of use.
- Changes in results of the following procedures performed at the Enrollment Visit, and after 8 weeks of *Lea's Shield*[®] use. (After 8 weeks' use, the procedures were performed both immediately after device removal and 24-48 hours after device removal.)
 - Quantitative vaginal and ectocervical cultures for *Staphylococcus aureus*, *E. coli*, *Enterococcus* species, gram-negative rods, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Gardnerella vaginalis*, *Candida albicans*, and H₂O₂-positive and -negative *Lactobacillus*.
 - Testing for vaginal candidiasis and bacterial vaginosis (BV) via wet prep using saline and KOH, pH, and whiff test.
 - Evaluation of Gram stains from vaginal and ectocervical specimens using Nugent's criteria (Hillier, S. and Holmes, K.K. Bacterial vaginosis. In *Sexually Transmitted Diseases*, 1999, 3rd edition, McGraw Hill, 563-586).
 - Evaluation of Gram stains from endocervical specimens for polymorphonuclear leukocytes.
 - The position of the device on exam after it had been in place for 48 hours, during which one act of intercourse had occurred.

Study Design: Open-label, single arm study.

Number of participants: 30

Number of centers: One (Magee-Womens Hospital in Pittsburgh, PA).

Fewer subjects were colonized with *Lactobacillus* at the 8-week and final visits compared with the enrollment visit. Statistically significantly more women were colonized with *E. coli*, *Enterococcus* species, and anaerobic Gram (-) rods at the

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

8-week and final visit compared with the enrollment visit. Furthermore, the average number of colony-forming units of these three bacteria increased between enrollment and the 8-week and final visits.

Specifically, at enrollment 10% of subjects were colonized by anaerobic Gram (-) rods in the vagina. By the final visit, 52% were colonized. Only 5% of subjects had vaginal colonization by *Enterococcus* at enrollment. This increased to 33% at the final visit. No *E. coli* were identified at enrollment among participants. By the final visit, 43% of participants had vaginal colonization of *E. coli*.

There was also an increase in colony-forming units (CFU) of vaginal bacteria at the final visit compared to the enrollment visit. The number of CFUs of anaerobic Gram (-) rods in the vagina increased almost three orders of magnitude from $[5.1 \times 10^4]$ to $[1.9 \times 10^7]$. *Enterococcus* species increased from $[4.0 \times 10^4]$ to $[2.3 \times 10^7]$ over this time. Finally, the count of *E. coli* went from none to $[1.8 \times 10^8]$ between enrollment and the final visit.

The effect of the *Lea's Shield*® on the tissue of the vulva, vaginal fornices, vaginal walls and cervix were evaluated by analysis of new colposcopic findings seen at follow up. These product-related abnormal findings were primarily erythema and peeling of the superficial epithelium. There was one case of scaling of the labia majora and grossly apparent vulvar edema, and a case of petechiae (disrupted blood vessel) in two subjects who were discontinued from the study. There were no reports of deep epithelial disruption.

Seventy percent of the above cases involved cervical epithelium, 20% involved the vaginal fornices and 15% involved the external genitalia.

In summary, there were effects on the epithelium of the cervix, vagina and vulva caused by the use of the device. There were no reports of any serious morbidity associated with these effects. The effects of long term, chronic use of the device on these tissues cannot be answered in a study of this design.

C. Study to Confirm Device Position by MRI

Objectives: To evaluate device position by MRI at baseline, immediately after self-insertion and after one-hour of wear. Two women participated in this study. One parous and one nulligravida.

Results:

The following adverse events were reported: 1) dysuria after removing the device; and 2) pelvic cramping after removing the device.

The MRIs demonstrated that the cervix was centered in the device immediately after insertion and after ambulation. The posterior rim of the device filled the

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

posterior fornix. There was a small (2mm) gap between the bowl of the device and the tip of the cervix. The valve appeared to be sealed.

D. Pivotal Clinical Study

Objective:

The purpose of this study (originally a Phase II feasibility study) was to evaluate the contraceptive effectiveness, safety and acceptability of the *Lea's Shield*[®] when used with either spermicide or non-spermicidal lubricant.

Endpoints:

- 6-month life table pregnancy rates for users of the device with spermicidal lubricant and with non-spermicidal lubricant.
- Safety as demonstrated by adverse events, changes in physical and pelvic exams, and Pap smears.
- Acceptability

Study design:

This multicenter study had two treatment groups. One group was randomized to the *Lea's Shield*[®] with lubricant containing the spermicide 3% nonoxynol-9. The other group was randomized to *Lea's Shield*[®] with a non-spermicidal lubricant. The gels were provided in plain tubes. The sponsor, investigator and subjects were blinded to the contents of each tube.

Number of participants: 300

Number of centers: 6

Entry criteria:

Inclusion Criteria

- 18 to 40 years of age
- in good general health as evidenced by history, physical examination, and screening laboratory tests
- sexually active in an ongoing relationship and at risk of pregnancy
- willing to use *Lea's Shield*[®] with or without spermicide, as the sole means of contraception for six months
- having regular menses, or at least one menstrual period since termination of last pregnancy or since termination of hormonal contraception
- willing to undergo the specified pelvic examinations, Papanicolaou smears, and pregnancy tests
- agree to return for follow-up examinations
- freely consent to the study and sign the volunteer Consent Form

18

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Exclusion Criteria

- currently pregnant, as confirmed by a pregnancy test at admission, or if the couple desire pregnancy within the next twelve months (as this may inordinately influence user effectiveness)
- gynecological abnormalities that produce distortion of the vaginal-cervical anatomy that would interfere with use of *Lea's Shield*[®]
- evidence of vaginal, cervical, or upper genital infections
- history of sensitivity/allergy to nonoxynol-9 spermicide, KY jelly, or silicone
- history of Toxic Shock Syndrome
- dysplasia or evidence of *A. israelii* infection (Bethesda Classification System) on Papanicolaou smear
- clinical evidence of urinary tract infection or history of two or more UTIs per year
- history of infertility
- alcohol or drug abuse
- medical or psychological contraindications to pregnancy
- breastfeeding
- prior tubal ligation
- subject is unable to properly insert or remove device
- clinical evidence of pelvic inflammatory disease (PID) or history of recurrent PID
- sexual partner's sensitivity/allergy to nonoxynol-9, KY jelly, or silicone
- sexual partner's history of infertility

Study procedures:

At admission, each volunteer underwent a complete physical exam including pelvic exam, Pap smear, urine pregnancy testing, urinalysis, and hematocrit. Each woman was given written instructions and shown how to insert the *Lea's Shield*[®] and was asked to demonstrate her ability to insert and remove it. She was also given a diary card in which to record coitus, use of the device and any other contraceptive method, menses, and problems. Routine follow-up visits were scheduled at one week, one month, three months, and six months after admission. At each scheduled visit, the volunteer underwent a pelvic exam, demonstrated her ability to insert the device, reviewed her coital diary with the clinician, and discussed any problems. Pap smears were performed at the three- and six-month visits.

Protocol amendment leading to discontinuation of the small device:

The original protocol specified that 300 women would enter the study and would be assigned to use one of two devices, a smaller *Lea's Shield*[®] with a 45 mm diameter and a larger *Lea's Shield*[®] with a 55 mm diameter with- or without spermicide based on random assignment. The particular device each

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

woman used was based on her obstetric history: the 55 mm device was assigned to women who had ever had a vaginal delivery, while the 45 mm device was assigned to women who were nulliparous, or who had been pregnant but had experienced only Cesarean section deliveries or spontaneous or induced abortions.

On October 30, 1992, a protocol amendment went into effect, which called for 1) volunteers who were using the smaller device to be discontinued from the study, and 2) all women subsequently enrolled to be assigned to the larger device, regardless of obstetrical history. This change was based on interim Pearl rates observed during the study which showed a higher than expected pregnancy rate, although without statistical significance, among users of the smaller device. Use of spermicide or non-spermicidal lubricant was still determined by random assignment. A total of 182 women were assigned to the large device.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Patient Population

Demographic features did not differ substantially across populations or between spermicide users or non-spermicide users. Eighty-four percent of volunteers were parous. Spermicide users were slightly older than non-spermicide users. Two-thirds of the volunteers reported frequent barrier use in the past.

One hundred forty-six (146) patients contributed to the efficacy population. Seventy-nine (79) of these used spermicide and 67 used non-spermicidal lubricant. Of the efficacy population, 106 (73%) completed six months of relying on the device for contraception without becoming pregnant: 59 spermicide users and 47 non-spermicide users.

Number of Study Subjects	<i>Lea's Shield</i> [®] with Spermicide	<i>Lea's Shield</i> [®] without Spermicide
Intent-to-Treat Population*	90	92
<i>Nulliparous</i>	17	13
<i>Parous</i>	73	79
Discontinued...	31	45
<i>Pregnant at Enrollment</i>	0	3
<i>Protocol Violation</i>	9	10
<i>Device-related, personal reason</i>	7	6
<i>Non-device related, personal reason</i>	2	1
<i>Medical reasons</i>	1	2
<i>Desired pregnancy</i>	1	0
<i>Unable to contact subject</i>	5	13
<i>Undesired Pregnancy</i>	6	10
Completed Study (6-months, continuous use)	59	47
Efficacy Population**	79	67

* Treated population- of 185 women enrolled, 182 contributed at least some follow up data (3 were pregnant at enrollment).

** Efficacy population – of the 182 treated women, 146 women contributed some efficacy data, although not all of these completed 6 months continuous use.

Results

Primary Endpoint: Pregnancy Rates

The unadjusted 6 month gross cumulative pregnancy rates per 100 women in the Efficacy Population was 8.7 (confidence interval (CI), 0.9 - 16.6) for spermicide users. The failure rate was higher for the study population that did not use spermicide. The upper limit of

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

the 95% confidence interval for the six-month cumulative pregnancy rate was 16.6. The projected 12-month unadjusted cumulative pregnancy rate was 15.0 (CI, 2.0 - 28.0).

None of the nulliparous subjects in this study became pregnant. However, the study was too small to conclude that nulliparous women have a lower risk of pregnancy using the *Lea's Shield*[®] than parous women.

Secondary Endpoint: Device Acceptability

Acceptability data included in the PMA was reported on 98.3% (179/182) of the Treated Population in the Pivotal Study. 13.4% (24/182) reported difficulty with insertion of the *Lea's Shield*[®] and 11.1% (20/182) reported difficulty with removal; 11% (20/182) reported that the device rotated during use; and 12.8% (23/182) reported that their partner could feel the device during intercourse.

Relative Contraceptive Efficacy

The following table shows pregnancy rates from different studies and various types of contraceptives compared to the *Lea's Shield*[®]. These rates are based on clinical trial data that the Food and Drug Administration (FDA) has reviewed. Pregnancy rates among users of *Lea's Shield*[®] with spermicide compared favorably with pregnancy rates reported in studies of other barrier methods

Contraceptive Method	Pregnancy Rate After 6 months, Typical Use from Clinical Trials	Pregnancy Rate After 12 months ¹ , Typical Use from Clinical Trials
<ul style="list-style-type: none"> ▶ Surgical Sterilization ▶ Injectable Hormones ▶ IUDs ▶ Implantable Hormones 	Less than 1	Less than 1
Hormone pills, vaginal ring	1-2	1-2
Male condom	7	12 ¹
Contraceptive Diaphragm	8	17
Cervical Cap	11	17
Female condom	13	21 ¹
<i>Lea's Shield</i> [®]	8.7	15 ¹

¹ Most barrier studies today are conducted as 6-month studies. 1-year rates are projected.

Adverse Events

See section VIII, page 3

22

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

XI. 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 the PMA substantially duplicates information previously reviewed by the panel.

XII. CDRH Decision

In 1995, Yama submitted a PMA for this device (P950025). On October 21, 1996, FDA's Obstetrics and Gynecology Devices Panel reviewed that PMA and recommended that it be found 'not approvable'. The Panel stated that there was not enough contraceptive effectiveness data and that more women should be entered into the study. . The Panel also recommended that Yama conduct a small clinical study to evaluate the *in situ* effects of the *Lea's Shield*[®] on vaginal microflora. FDA agreed with the Panel recommendation and sent Yama a "not approvable" letter on November 8, 1996.

On October 4, 1999, FDA convened the Obstetrics and Gynecology Devices Panel to reevaluate the FDA's PMA approach for vaginal barrier contraceptive devices. The Panel encouraged FDA to require less burdensome PMA studies for these devices, because the need for precise failure rates should be balanced against the need for more contraceptive options. FDA concurred with this recommendation.

Based on this decision, the applicant resubmitted the PMA with additional safety data from 1) a colposcopy/microbiology study and 2) an MRI study to demonstrate how the device is seated in the vagina after insertion. 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 14, 2002.

XIII. Approval Specifications

Directions for Use: See labeling

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

Post-approval Requirements and Restrictions: See approval order.

23