SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: female condom

Device Trade Name: FC2 Female Condom

Applicant's Name and Address: The Female Health Company (FHC)
515 North State St
Suite 2225
Chicago, IL 60611

Date of Panel Recommendation: December 11, 2008

Premarket Approval Application (PMA) Number: P080002

Date of FDA Notice of Approval: March 10, 2009

Expedited: not applicable

II. INDICATIONS FOR USE

The FC2 Female Condom is indicated for preventing pregnancy, HIV/AIDS, and other sexually transmitted infections (STIs).

III. CONTRAINDICATIONS

none

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the FC2 Female Condom labeling.

V. DEVICE DESCRIPTION

The FC2 Female Condom is a thin and flexible film that is inserted into the vagina before intercourse and acts as a physical barrier between the penis and the vagina. Its purpose is to reduce exposure of the vagina to ejaculate and pre-ejaculate and, thereby, to reduce the risk of pregnancy and sexually transmitted infections compared to unprotected intercourse.

As shown in the image below, the FC2 Female Condom is comprised of a nitrile sheath, a nitrile outer ring, and a polyurethane inner ring. Although not attached to the condom, the inner ring is inside the sheath and aids in insertion.

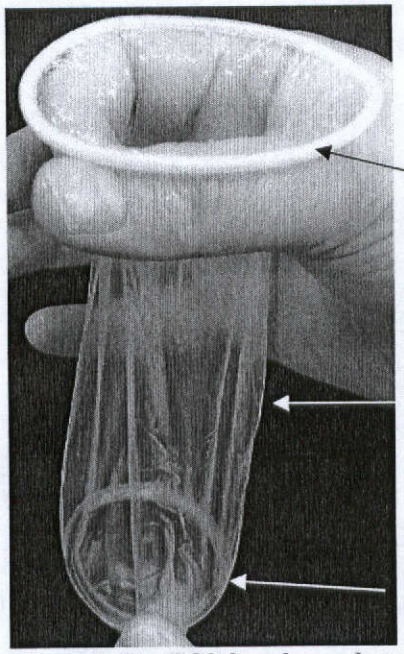

Figure 1. The FC2 female condom.

The FC2 dimensions are described in the table below.

Table 1. The FC2 dimensions.

Dimension	
length (mm)	164-184
width (mm)	76-83
sheath thickness (μm)	65-85
outer ring thickness (mm)	2.9-3.8
outer ring, minimum diameter (mm)	67
inner ring thickness (mm)	4.60-5.10
inner ring diameter (mm)	50.2-50.8

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The male condom is a highly effective alternative to reduce the risk of both pregnancy and STI transmission.

There are several contraceptive alternatives that reduce the risk of pregnancy. These include permanent sterilization, hormone contraceptives, intrauterine devices/contraceptives, cervical caps, diaphragms, and spermicides. These products do not protect against STIs.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets his/her expectations and lifestyle.

VII. MARKETING HISTORY

Between 2006 and the beginning of 2009, the FC2 Female Condoms, has been distributed in 77 countries. Eighty percent of the sales have been distributed to the Global Public Sector in 67 countries: 37 countries in Africa, 11 countries in Asia and 9 countries in Latin America with the remaining countries split between Latin and South America and Australasia. Twenty percent of total sales are for commercial distribution, predominately in Europe: France, Spain and Portugal and the UK.

The FC2 Female Condom has not been withdrawn from marketing anywhere in the world for any issue related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (*e.g.*, complications) associated with the use of the device:

- discomfort,
- burning,
- rash, and
- itching.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

The FC2 is made from a different material and is manufactured differently from its predecessor, the Reality® Female Condom, now referred to as the FC1 Female Condom (FC1). FDA approved the FC1 PMA (P910064) in 1993. Some of the bench tests in this section compare data from the FC2 to the FC1.

FC1- Comparison of Physical Properties, Original and Current Data

Since FDA approved the FC1 in 1993, the applicant improved its manufacturing methods. The table below compares the physical properties of the FC1 Female Condoms manufactured in the early 1990s, around the time of the pivotal study for the FC1 PMA, to the FC1 Female Condoms manufactured more recently. The latter FC1 Female Condoms were used in the preclinical tests described below and served as the control in the FC1-FC2 comparative study described in Section X.

Table 2. Original and current FC1 data.

	Mean Burst Pressure (kPa)	Mean Seam Strength (MPa)	Mean Tensile Strength (cross grain MPa)	Mean Burst Volume (L)
Original FC1	5.5 (n=10)	9.88 (n=20)	42.37 (n=20)	Not known
Current FC1	5.33 (n=20)	20.25 (n=20)	50.55 (n=20)	10.8

In general, the data show that the FC1 Female Condoms used in the FC1-FC2 comparative study have higher physical properties than the FC1s manufactured around the same time as those used in the pivotal study for the FC1 PMA. [i ii]

A. Laboratory Studies

With the exception of airburst testing, the applicant performed the studies below to characterize the FC2. Thus, there are no specifications for these tests.

Viral Penetration Testing

The applicant conducted an *in vitro* viral penetration study to evaluate the physical barrier properties of the female condom. This test challenges condoms by inoculating the inside of each condom with bacteriophage Xφ174 and measures the titre that passes through the condom. This bacteriophage was chosen for the test because it is smaller than the Human Immunodeficiency Virus (HIV), and it is non-pathogenic to humans. After inoculation, condoms were sealed, immersed in sterile simulated serum, pressurized at 60 mm Hg, and held for 30 minutes at 37°C physiologic temperature. Aliquots of the collection fluid were removed after 30 minutes. Any viral particles present in the sample were quantified using standard plaque assay techniques. Appropriate negative, positive, environmental and spike neutralization controls were included.

Results showed that three out of 60 FC2 condoms from three lots failed (5%) while one out of 20 male condoms from one lot failed (5%), and three out of 20 FC1 condoms from one lot failed (15%). These results indicate that the physical barrier properties of the FC2 should provide adequate protection against viral particles.

Compatibility with Personal Lubricants

The applicant tested the FC2 Female Condom to determine whether its physical properties would be adversely affected by additional lubricants. The applicant exposed at least 20 FC2 samples from one lot to three aqueous based lubricants and two petroleum based lubricants. Samples were incubated at 37°C for 30 minutes and subject to airburst testing. In addition, the applicant performed tensile testing to further evaluate aqueous based lubricant compatibility. Please see below for information regarding airburst and tensile testing. Analysis of the results indicates that the FC2 is compatible with aqueous

based lubricants, and the data supporting compatibility with petroleum based lubricants is equivocal.

The applicant justified that the FC2 is compatible with additional silicone-based personal lubricants, explaining that the FC2 is already packaged with a silicone lubricant. The justification included a comparison of data from unlubricated and silicone-lubricated FC2 samples. This data showed that the FC2 is compatible with additional silicone-based personal lubricants. The applicant did not test the FC2 following exposure to a spermicidal lubricant.

Airburst Testing

The applicant measured the airburst volume and pressure of the FC2 Female Condom. This test is done by inflating a condom with air and recording the volume and pressure inside the condom when it bursts. Values for airburst pressure often correlate with intrinsic material strength, while burst volume data often correlate with elasticity. In each case, higher numerical values are preferred over lower values.

The product specifications for the FC1 and the FC2 are below.

Table 3. Airburst specifications.

	FC2	FC1
burst pressure	**3.45 kPa**	**4.80 kPa**
burst volume	**5.0 L**	**4.5 L**

The applicant tested 6,445 FC2s from 25 lots. The mean burst pressure was 5.4 kPa, and the mean burst volume was 11.3 L. Fifty-five condoms, about 0.8%, did not meet the specifications above. This is satisfactory because it is below the 1.5% acceptable quality level, and the values are comparable to the FC1.

Thermal Analysis

The applicant determined the thermal profiles of the FC1 and the FC2 via differential scanning calorimetry (DSC). Heating and cooling scans were performed successively in the temperature range between -100°C and +100°C. The data submitted indicate no unidentifiable or unexpected thermal transitions, such as melting, or phase separation, in either the FC1 or the FC2 material. Thus, it is expected that the performance and properties of the FC2 device will not be adversely affected by the short term exposure to temperatures that the device may encounter during transportation, storage, and use.

Tensile Testing

Tensile testing subjects a condom sample to axial stretching until it breaks. This test method gives three measures of tensile properties:

- tensile strength,
- force-at-break, and
- elongation.

The applicant tested groups of 13 samples from one lot. Specimens that span across the weld seam of the FC1 material were also prepared. In order to quantify any anisotropy in the material properties, mechanical testing was performed along the axial and circumferential directions of the device. Tests were performed at room temperature (23°C), elevated temperature (37°C) and in a simulated physiologically relevant environment where the materials were conditioned with saline solution at 37°C. As expected, elevated temperature and conditioning with saline adversely impacted the mechanical properties.

Table 4. The FC1 and the FC2 tensile data.

Sample	Test Conditions	Direction	Tensile Strength (MPa)	Force at Break (N)	Elongation at Break (%)
FC1 Polyurethane	Tested at 23°C	Length	55.1	10.9	536
		Circum.	49.3	11.3	468
		Across Seam	20.5	4.1	326
	Tested at 37°C	Length	45.6	10.4	658
		Circum.	41.3	9.4	545
		Across Seam	17.7	3.9	383
	1 hour in Saline, tested at 37°C	Length	47.7	9.6	618
		Circum.	46.1	9.2	526
		Across Seam	22.0	4.4	417
FC2 Nitrile	Tested at 23°C	Length	20.4	6.5	408
		Circum.	19.9	6.1	389
	Tested at37°C	Length	17.8	5.8	401
		Circum.	16.2	5.2	396
	1 hour in Saline, tested at 37°C	Length	17.6	5.2	413
		Circum.	15.6	4.8	396

Results show that the FC1 and the FC2 are affected similarly depending on test condition. In general, nitrile (FC2) has lower tensile properties compared to polyurethane (FC1). However, the FC1 has a seam. The tensile properties of the FC1 as measured across the seam were equivalent to or better than the bulk tensile properties of FC2.

Tear Strength

The applicant also measured and compared the force necessary to initiate and propagate a tear in both the FC1 and the FC2 film materials. In this test, a film specimen is subjected to stress accumulation until a tear is initiated. The amount of force required to rupture the specimen can then be determined. Higher tear strength is preferred when evaluating condom materials as this indicates a substance that requires increased force to tear.

The applicant conducted the tear test on 10 FC1 and 10 FC2 samples under the same environmental conditions described for tensile testing, namely 23°C, 37°C, and following 1 hour in saline.

Table 5. FC1 and FC2 tear data.

Sample	Test Condition	Direction	Median Tear Strength (N/mm)
FC1 Polyurethane	Tested at 23°C	Length	75.0
		Circum.	73.1
	Tested at 37°C	Length	72.0
		Circum.	62.8
	1 hour in Saline, tested at 37°C	Length	65.6
		Circum.	56.8
FC2 Nitrile	Tested at 23°C	Length	45.5
		Circum.	43.7
	Tested at 37°C	Length	38.9
		Circum.	38.6
	1 hour in Saline, tested at 37°C	Length	31.8
		Circum.	35.4

As with tensile testing, the FC2 material has lower tear resistance compared to the FC1 material. However, the FC2 does not have a seam. Actual performance during use should be clinically validated.

Preclinical Testing Conclusions

Preclincial testing indicates the following:

- The FC2 is an effective barrier to viral particles.
- The FC2 is compatible with silicone and water based lubricants although petroleum based lubricant information is equivocal.
- The FC2 is thicker than the FC1 and has no seam, and the FC2 nitrile material has lower physical properties. However, it is difficult to predict in-use performance based solely on physical properties. This underscores the importance of an acceptable clinical study.

B. Animal Studies

The applicant tested the FC2 Female Condom for material safety. FDA recommends that such testing conform to methods described in the International Organization for Standardization standard, ISO 10993, Biological Evaluation of Medical Devices. Part 1 of this standard provides a framework for determining which tests should be conducted, based on the nature of the contact between the device and its user. Using the definitions of Part 1, the human contact potential posed by the FC2 is characterized as short term, mucosal contact, with the potential for repeat use contact. FDA determined that the following tests be conducted:

- cytotoxicity,
- sensitization,
- irritation,
- acute systemic toxicity,
- genotoxicity, and
- implantation (90 day).

The applicant conducted all of the above testing, and a brief summary of the biocompatibility testing is below. These test results show that the FC2 materials did not cause cell lysis in excess of that observed for natural rubber latex condoms. In addition, FDA found that there were acceptable results regarding sensitization, irritation, systemic toxicity, genotoxicity, and muscle implantation.

Cytotoxicity - ISO Elution Method: The applicant provided two cytotoxicity studies for the FC2 Female Condom. In the first study, undiluted and 1:2 diluted extracts of the device were shown to be cytotoxic, while dilutions of 1:4 and greater showed no cytotoxic effects. In the second study, undiluted, 1:2, and 1:4 diluted extracts of the device were shown to be cytotoxic, while dilutions of 1:8 and greater showed no cytotoxic effects. The company adequately justified the cytotoxic potential of their proposed device in comparison to results from commercially available natural rubber latex condoms and results from other FC2 Female Condom testing (e.g., biocompatibility testing , in-use testing).

Sensitization- ISO Maximization Sensitization Study (saline extract) and Mouse Local Lymph Node Assay (cottonseed oil extract): The applicant adequately justified why different test methods were used for the saline and oil extracts. Testing showed no evidence of sensitization from saline or cottonseed oil extracts of the FC2 Female Condom materials.

Irritation - ISO Vaginal Irritation Study: The applicant provided two irritation studies for the FC2 Female Condom. Results from both studies showed the saline and cottonseed oil extracts to be non-irritants to the vaginal mucosa tissue of rabbits. However, the extracts used in these studies were extracted for 24 hours at 37°C. The applicant was asked to justify the use of these extraction conditions on a device that had the potential

for repeat use. The applicant adequately justified the use of the extractions conditions followed for this study.

Systemic Toxicity- USP and ISO Systemic Toxicity Study: Testing showed no evidence of mortality or systemic toxicity from saline or oil extracts of FC2 Female Condom materials.

Genotoxicity - Bacterial Reverse Mutation Assay: Testing using saline and 95% ethanol extracts in the presence and absence of S9 activation showed the FC2 Female Condom materials to be non-inhibitory to growth of tester strains and non-mutagenic to *Salmonella typhimurium* (strains TA98, TA100, TA1535, and TA1537) and *Escherichia coli* (strain WP2*uvrA)*.

Genotoxicity – Mouse Peripheral Blood Micronucleus Study: Testing using saline and sesame oil extracts showed that the FC2 Female Condom materials did not induce toxicity or mutagenic effects in mice.

Genotoxicity - Mouse Lymphoma Assay: Results of this study showed that RPMI culture medium and 95% ethanol extract dilutions tested were non-mutagenic to the mammalian cell line tested.

Implantation – Six and Twelve-Week Rabbit Muscle Implantation- ISO Muscle Implantation Study in the Rabbit: Testing showed no significant difference between the control and test materials. The conclusion from this test is that the FC2 Female Condom Materials did not elicit any toxic effects on muscle tissue.

C. Additional Studies

Bioburden Testing

For a female condom, the bioburden level deemed acceptable for lot release is based the total aerobic microbial count (TAMC) and the total combined yeasts and molds count (TYMC) found on these samples. For the bioburden to be considered acceptable, the following results should be achieved, in accordance with Microbiological Attributes of Non-Sterile Pharmaceutical Products (USP <1111>) and Microbial Limits Test (USP <61>):

- TAMC - 10^2 cfu/g (or cfu/mL),
- TYMC - 10^1 cfu/g (or cfu/mL), and
- absence of the following microorganisms:
  - *Staphylococcus aureus,*
  - *Pseudomonas aeruginosa,*
  - *Candida albicans, and*
  - *Escherichia coli.*

The applicant conducted bioburden testing on 20 female condom samples from each of six lots (120 samples total). FDA reviewed detailed protocols and results and found that the bioburden information was acceptable.

Packaging

The applicant conducted testing on the FC2 packaging to show that the print is legible, that the package is of correct width (78-82mm), and that the sealed package does not leak. Of 1,000 samples, one sachet had illegible print, and three packages leaked. Three failures out of 1,000 samples is below the 2.5% AQL stated in ISO 4074 for male condoms. Because the female condom is similar in packaging and technology to the male condom, this AQL rate is acceptable.

Shelf Life Testing

The applicant subjected the FC2 samples to accelerated aging and real time testing to establish a three-year shelf life. For accelerated aging, they aged 20 samples from three lots each at 50°C for up to 293 days. For real time testing, they conduct airburst testing on 200 samples from three lots each. They will test yearly for five years.

In addition, they conducted initial water leak testing and plan to repeat testing at three and five years with 315 samples from three lots each. They also conducted interim airburst testing at six and 18 months using 32 samples from three lots each.

The data indicate that the airburst pressure decreases slightly with time, and the burst volume initially decreases. Based upon this information, a three year shelf life is justified.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Background

This PMA (P080002) is supported by a clinical study in South Africa (RHRU Study) that compared failure rates between the FC1 and the FC2 for the four female condom failure modes; it is described below.[1] Using the information from this study, as well as the bench tests described in Section IX, the FC1 contraceptive effectiveness and STI risk reduction studies are applicable to the FC2 Female Condom.

Study Design

The study was a prospective, multi-center, randomized, crossover clinical study. There was not a prespecified statistical hypothesis.

The control device was the FC1 Female Condom, a legally marketed alternative with the same indications for use.

The study was conducted at four investigational sites in South Africa between January and September 2004. The database for this PMA contained data collected from 276 subjects.

At the enrollment visit, each subject was randomly assigned to a condom use sequence, either 10 FC1 condoms followed by 10 FC2 condoms or the opposite. The applicant attempted to blind the subjects and investigators although some subjects and all investigators were familiar with the FC1.

Also at the enrollment visit, the investigators instructed subjects on how to complete the coital log. The coital log was intended to capture information on the number of acts of intercourse and the number of failures of the female condoms. It included the following types of failure:

- breakage, "rip during use/broke,"
- invagination, "pushed into vagina," and
- misdirection, "penis inserted outside condom."

The coital log did not have an entry for slippage. It was used as a "memory trigger" during the interviewer-administered questionnaire. This questionnaire was completed at each of the two follow up visits and served as the database for the study.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the RHRU study was limited to patients who met the following inclusion criteria:

- ≥ 18 years old;
- Not pregnant or nursing (pregnancy test done where necessary);
- Currently using a hormonal contraception method, IUD or sterilized (tubal ligation only);
- Currently sexually active (at least one sex act in the last month);
- In good general health and genital health as determined by medical history and a vulval/vaginal inspection (pelvic examination not conducted);
- Willing and able to follow procedural requirements of the study;
- Willing to give information on basic feel, fit, integrity during use, and ease of insertion and removal of the FCs;
- Willing and able to provide Informed Consent for study participation; and
- Willing to provide contact information where she could be reached during the study.

Patients were not permitted to enroll in the RHRU study if they met any of the following exclusion criteria:

- Syndromic diagnosis of STIs or reported symptoms as determined by client's history;
- Had allergies or known sensitivities to silicone products, latex products, or vaginal lubricants; or
- Within six weeks post-partum or post abortion.

2. Follow-up Schedule

All subjects were scheduled to return for follow-up examinations after 10 uses of each condom, respectively. The staff obtained data regarding condom use from the coital logs and the questionnaire.

Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

With regards to safety, there were no prespecified endpoints.

With regards to effectiveness, performance was evaluated based on four major failure modes experienced during intercourse:

- condom breakage;
- slippage (condom came out of vagina);
- misdirection (penis entered to the side of the condom); and
- invagination (outer ring of condom was pushed into vagina).

These failure modes were identified as being of key importance by Macaluso *et al.* [iii]

With regard to success/failure criteria, "the expected outcomes of the study from the reference condom (FC1) was a breakage rate of less than 5%.... If the breakage rate for the FC2 exceeds this standard, the new condom will not be considered for further development and testing."

A. Accountability of PMA Cohort

Of 276 subjects enrolled in PMA study, 84% (233) subjects returned for the first follow up visit, and 73% (201) subjects returned for the second follow up visit. Please see the *per subject* accountability tree below.

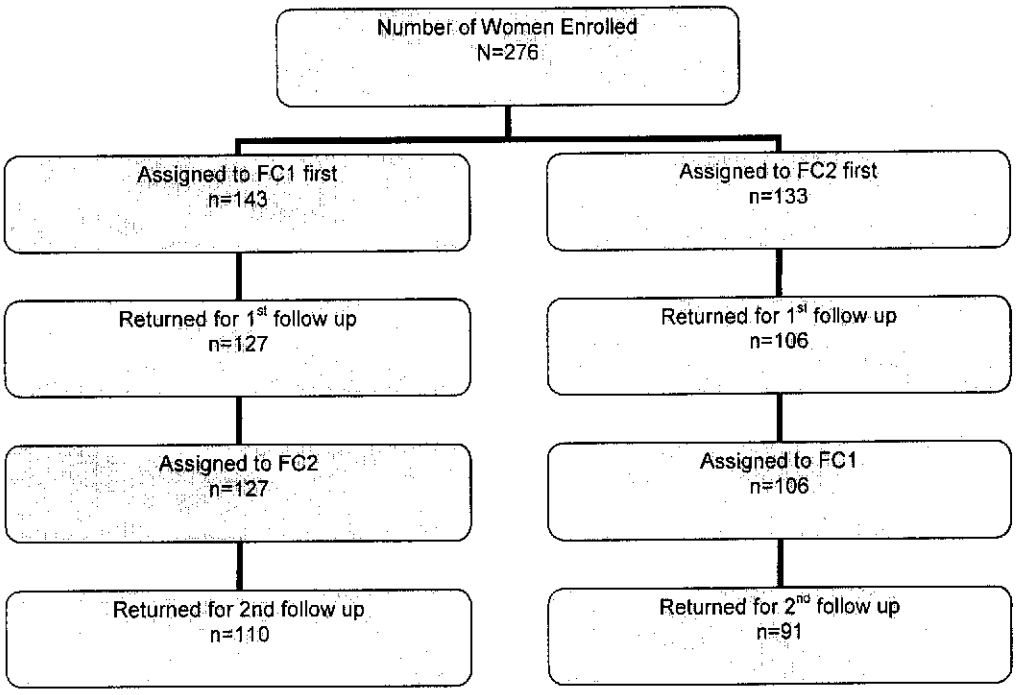

Figure 2. Per subject accountability tree for the RHRU Study.

B. Study Population Demographics

The demographics of the study population are atypical for a failure modes study performed in the US. This is because commercial sex workers (CSW) participated in the study. This study was conducted in South Africa where AIDS is pandemic, and female-controlled STI protection is urgently needed. Therefore, the study included CSWs, an at risk population. The subgroup analyses did not indicate that inclusion of CSWs in the study biased results for or against the FC2. Please see Section 3C below for additional information.

Table 6. RHRU Study population.

	Students n=65	Urban Family Planning n=64	Rural Family Planning n=67	STI Clients n=21	CSW n=59	Total n=276
Mean Age (yrs)	23	34	28	35	27	28
Regular Partner (%)	85	55	64	48	25	57
Mean Education (Grade level)	11.2	10.6	10.0	11.4	9.7	10.5
Employment	5%	41%	0%	62%	3%	16%

C. Safety and Effectiveness Results

1. Safety Results

Reports of adverse events were collected from the coital logs and exit interviews for the FC1 and the FC2 cohorts of 218 and 216 subjects, respectively. Results are presented in the table below. Please note that no adjustment has been made for multiplicity. Thus, for example, the smallest p-value (0.030) would not remain significant after a Bonferroni-type adjustment.

Table 7. Adverse effects reported in the RHRU Study.

	FC1 % subjects (n) n= 218	FC2 % subjects (n) n=216	p-value
Discomfort during insertion	13.7% (30)	13.4% (28)	0.89
Discomfort after insertion before sex	3.2% (7)	1.8% (4)	0.54
Pain after insertion before sex	1.3% (3)	2.3% (5)	0.50
Pressure/urge to urinate	0.9% (2)	0% (0)	0.50
Discomfort during sex	1.3% (3)	<1% (1)	0.62
Uncomfortable to use	5.1 % (11)	2.3% (5)	0.20
Burning/rash/itching	0% (0)	2.3% (5)	0.030
Bleeding	<1% (1)	<1% (1)	1.0
Confirmed STI	<1% (1)	0% (0)	1.0

In summary, none of the adverse effects were serious, and there was no significant difference between the FC1 and the FC2 groups.

2. Effectiveness Results

The analysis of failure rates was based on the 218 subjects who used 1910 FC1s and the 216 subjects who used 1881 FC2s. Outcomes are presented in the tables below.

Table 8. Failure rates per condom.

Failure Mode	FC1		FC2		Difference (FC2 – FC1) % (95% CI)
	Number of events per total condoms used[1]	%	Number of events per total condoms used	%	
clinical breakage	9/1910	0.47	8/1881	0.43	- 0.04 (-0.62 to 0.53)
penis misdirection[1]	24/1910	1.26	12/1881	0.64	-0.62 (-1.33 to 0.09)
total invagination[2] (partial+complete)	60/1910	3.14	56/1881	2.98	-0.16 (-1.24 to 0.91)
complete slippage[3]	4/1910	0.21	2/1881	0.11	-0.10 (-0.39 to 0.19)

[1] Penis misdirection is actually recorded as "Incorrect Penetration."
[2] Condom invagination is actually recorded as "Outer Ring Displacement."
[3] Data on slippage was collected indirectly during the interview.

Failure rates per condom use are estimated using the GEE approach to account for within-couple correlation.[IV] The upper boundary of a 95% confidence interval for such a difference with respect to some failure rate is really a 97.5% upper confidence bound for the same difference, and can be used as a test statistic in testing superiority and/or non-inferiority hypotheses with a one-sided alpha of 0.025. Specifically, the upper boundary being less than 0 (or delta) provides evidence for the superiority (or non-inferiority) of the FC2 to the FC1. In the above table, the largest upper confidence bound is 1.01%, which implies that with a standard delta of 2%, the FC2 will be found statistically non-inferior to FC1 with respect to all failure rates considered. On the other hand, all upper confidence bounds are positive, and therefore superiority of the FC2 to the FC1 cannot be established at the same significance level for any failure rate.

Table 9. Failure rates per subject.

	FC1		FC2	
	Number of events per subject using the FC1	%	Number of events per subject using the FC2	%
clinical breakage	5/218	2.3	7/216	3.2
slippage	3/218	1.4	2/216	0.93
total invagination (partial+complete)	50/218	23	40/216	18.5
misdirection	19/218	8.7	11/216	5.1

Invagination occurred at a considerably higher rate relative to the other failure modes. Based upon this information, the applicant proposed labeling to instruct the user to hold the outer ring during insertion and to be aware of the outer ring during intercourse.

3. Subgroup Analyses

The following characteristics were evaluated for potential association with outcomes:

Inclusion of Commercial Sex Workers

CSW experience with condoms might lead to better results than might be expected in the general population. Additionally, none of the 59 CSWs filled out the coital log. Of 168 missing coital logs, 105 (63%) were supposed to have been completed by commercial sex workers (CSWs).

FDA requested that the applicant compare overall failure rates with and without CSW data. The applicant provided this analysis and differences are very small as seen in the following table of failure rates without CSW:

Table 10. FC1 and FC2 failure rates, subgroup analysis without CSWs.

Failure Mode	Failure Rate (%)		Difference	
	FC1	FC2	FC2 – FC1	95% CI
clinical breakage	0.54	0.54	0.00	(-0.73, 0.73)
misdirection	1.63	0.68	-0.95	(-1.84, -0.06)
complete invagination	0.48	0.88	0.41	(-0.27, 1.09)
complete slippage	0.27	0.07	-0.20	(-0.55, 0.15)
total clinical failure	2.92	2.18	-0.74	(-2.29, 0.81)

With the exception of misdirection, the differences are not statistically significant. In the case of misdirection of the penis, when CSW data are excluded, there is a statistically significant difference between the FC2 and the FC1 that favors the FC2.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

There are no clinical studies of the FC2 Female Condom evaluating contraceptive effectiveness or STI risk reduction. However, information from such studies is available for the FC1 Female Condom. Given the physical similarities between the two female condoms and the results of the RHRU Study, information from the FC1 Studies can be applied to the FC2 Female Condom. Therefore, these studies are described below.

FC1 Clinical Outcome Studies

FC1 Protection Against Pregnancy

The original female condom, the FC1, was approved in 1993. The pivotal clinical study supporting the FC1 approval was a prospective, single-arm, multi-center, international clinical trial. Three hundred seventy-seven subjects were enrolled, 262 at six sites in the US, and 115 at three sites in Mexico and in the Dominican Republic. Summary results for this clinical study are below, and additional details may be found in the SSED from the FC1 PMA (P910064) and in the publication arising from this study.[ii]

Table 11. Status of subject participation at end of study.

	US		OUS	
	number of subjects	percent	number of subjects	percent
completed 6-months	147/221	66.5%	48/107	44.9%
discontinued use	74/221	33.5%	59/107	55.1%
unplanned pregnancy	22/221	10.0%	17/107	15.9%
returned for 6-month follow-up	153/221	69.2%	54/107	50.5%

Farr *et al.* state that "the 6-month gross cumulative pregnancy rates were 12.4 and 22.2 for the US and [OUS] groups, respectively. The 6-month gross cumulative life-table perfect-use pregnancy rate was 2.6 for the US subgroup and 9.5 for the [OUS] subgroup."[ii]

Of the 39 pregnancies in both populations combined, 12 were attributed to method failure and 24 were attributed to user failure by study subjects. Three were classified as "other." All 39 unintended pregnancies were *counted* as method failures, however.

The following studies report FC1 contraceptive effectiveness: Farr *et al.*, described above, and Trussell *et al.*[ii v vi]

In the latter study, the contraceptive effectiveness of the FC1 was evaluated in a single arm, multi-center study in Japan. The 6-month typical use pregnancy rate in that study was 3.2%. This outcome has been attributed to lower frequency of intercourse in this study population compared to the two study populations in the pivotal clinical trial of the FC1.

Nevertheless, the above studies provide reasonable assurance of the FC1 contraceptive effectiveness.

FC1 Protection Against STI

Since approval of the FC1 in 1993, there have been several published studies that evaluated the FC1 for protection against sexually transmitted infections.[vii-xvi]

This literature shows a trend towards STI risk reduction associated with use of the female condom. From an epidemiologic perspective, the effectiveness literature on the FC1 has methodologic limitations. However, it is important to note that these studies are difficult to design to account for potential confounders.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on December 11, 2008, the Obstetrics and Gynecology Devices Panel recommended that the Female Health Company's PMA for the FC2 Female Condom be approved with the condition to revise the labeling.

In reaching its conclusion, the Panel considered the following:

- use of an acute performance outcomes study, *i.e.,* a female condom failure modes study based on user reports, to provide reasonable assurance of the FC2 safety and effectiveness;

  The Panel found that the failure modes study, combined with *in vitro* data on the barrier properties of the FC2, is acceptable to provide reasonable assurance of FC2 safety and effectiveness.

- the impact of the study design concerns on the data reliability;

  The Panel stated that the study design limitations do not impact the overall reliability of the RHRU study data. However, the panel expressed concerns about data reliability in terms of the *quantitative* findings on rates of condom failures.

- whether the data, as provided, constitute valid scientific evidence to provide reasonable assurance of safety and effectiveness of the device;

  The Panel had previously voted to accept the concept of an acute performance outcomes study, *i.e.,* a female condom failure modes study based on user reports and to consider these study outcomes potentially reliable despite the many potential sources of bias. Nevertheless, the Panel did not reach a consensus on this question, other than to agree that the data support a finding of non-inferiority of the FC2 compared to the FC1 for the four failure modes as originally defined.

- the labeling, and if information on female condom failure modes should be included; and

  The Panel made the following labeling changes for FDA to consider:

  - enhance discussion of invagination compared to that in the FC1 label;
  - don't advise user to "discontinue using" if they encounter a problem (unless there is an alternative that is available);
  - do not include quantitative outcomes data on failure modes based on RHRU study; and
  - include a brief discussion of the RHRU study in labeling of the FC2.

- the applicant's postmarket plan.

  The Panel did not recommend a post-approval study. However, they recommended that FDA encourage the National Institues of Health and others to provide funding for additional studies of female condom effectiveness in the interest of public health. A panel member recommended that adolescents and other non-traditional groups be represented in such studies.

Link to transcripts: http://www.fda.gov/ohrms/dockets/ac/cdrh08.html#obstetrics

B. FDA's Post-Panel Action

FDA concurred with the Panel's recommendations, and the applicant addressed all remaining labeling concerns.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

Preclinical testing of the FC2 Female Condom indicates that it is an effective barrier to viral particles, is compatible with aqueous and silicone based lubricants (petroleum based lubricant data is equivocal), and is biocompatible.

The adverse effects of the device are assessed based on data collected in a clinical study conducted to support PMA approval as described above.

Data from the RHRU Study showed that adverse events from FC2 use are not serious and occur at about the same rate as that for the FC1. The panel found that this information was acceptable to provide reasonable assurance of safety for the FC2, and FDA agrees with the panel recommendation.

B. Effectiveness Conclusions

The objective of the RHRU Study was to compare rates of condom breakage, outer ring displacement (invagination), penile misdirection and condom slippage out of the vagina between the FC2 and the FC1. The original research question was whether the breakage rate of the FC2 exceeded 5% (presuming a breakage rate of <5% for the FC1). (By way of comparison, failure modes studies of new male condoms made of synthetic material typically test for non-inferiority with respect to two outcomes: slippage and breakage, *i.e.,* the new condom type is not worse than the control condom by more than a specified delta which has usually been set at 2%.)

The RHRU study succeeded with respect to the study "objective" in that the breakage rate was less than 5% for the FC2. The observed rates for the four failure modes were less than 1.5% for all except for "partial invagination" for which the higher observed rate was 2.62% (for the FC1). There were no statistically significant differences in rates of any failure mode between the FC2 and the FC1. Therefore, from the standpoint of the non-inferiority test applied retrospectively, the study succeeded because the FC2 was not worse than the FC1 by more than the delta of 2% typically applied in failure mode studies of male condoms.

C. Overall Conclusions

FDA has concluded that the preclinical and clinical data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

FDA's conclusion is based primarily on two bodies of evidence. First, FDA's conclusion is based on outcomes data from the RHRU Study which demonstrated that the FC2 is equivalent to the FC1 with respect to the risk of the following four types of condom failures:

- breakage,
- invagination,
- misdirection (of the penis), and
- slippage (out of the vagina).

Second, FDA has concluded that the clinical performance (contraceptive and STI risk reduction) of the FC2 can be inferred from the contraceptive outcomes study conducted on the FC1 that was the basis for approval of the PMA for the FC1 in 1994. Taking these two lines of reasoning, FDA concludes that the scientific data supporting this PMA are adequate to support a conclusion that the FC2 is safe and effective for helping to prevent HIV/AIDS, other sexually transmitted infections, and unintended pregnancy.

FC2 labeling will continue to contain the four key elements of "*Important Information*" already required on FC1 labeling:

- Natural rubber latex condoms for men are highly effective at preventing sexually transmitted infections, including HIV/AIDS, if used correctly.
- If you are not going to use a male natural rubber latex condom, you can use the FC2 Female Condom to help protect yourself and your partner.
- The FC2 Female Condom only works when you use it. Use it correctly every time you have sex.
- Before you try the FC2 Female Condom, be sure to read the directions and learn how to use it correctly

The FDA Advisory Panel on Obstetrics and Gynecology Devices unanimously recommended approval during an open public meeting on December 11, 2008. Specifically, the Panel found that the slippage breakage clinical study comparing the FC2 against the FC1 condom (the RHRU Study), together with contraceptive effectiveness data from the pivotal clinical trial of the FC1 Female Condom (P910064) and slip/break studies of the FC1, together meet the FDA standard for valid scientific evidence to show safety or effectiveness.

XIV. CDRH DECISION

CDRH issued an approval order on March 10, 2009.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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