FDA Executive Summary

prepared for the
December 11, 2008 meeting of the
Obstetrics and Gynecology Devices Advisory Panel

P080002
Female Health Company (FHC)
FC2 Female Condom
I. Introduction

Only one female condom is on the US market today: the Reality® female condom (FC1), manufactured by the Female Health Company (FHC). FDA approved this device in 1993 (P910064), and details of the FC1 approval are given later in this summary. In this current premarket approval (PMA) application (P080002), FHC presents its new version of the female condom (FC2), made from a different material and manufactured differently. FHC reports having made these changes to lower material and labor costs in hopes of increasing overall product distribution.

Regulatory Background

FDA regulates both male condoms and female condoms as medical devices because they are intended to prevent pregnancy and sexually transmitted diseases (STDs).

Male condoms. Based on a long history of safety and effectiveness, FDA classified male condoms into Class II (21 CFR 884.5300). Since that 1981 classification, hundreds of studies of the male condom have been reported in the peer-reviewed literature. These studies address the following:

1. physical performance characteristics as measured on the bench,
2. failure events reported during actual use (slippage & breakage), and
3. clinical outcomes of intended use, i.e., pregnancy and sexually transmitted infections (STIs).

The regulatory pathway for male condoms to reach market in the US is the 510(k) premarket notification.

Most male condoms are made from natural rubber latex (NRL), and the 510(k) for a male NRL condom typically contains information about the condom design, physical performance, and material safety per recognized standards and acceptable labeling.

For a male condom made from a synthetic material, the 510(k) would contain physical performance and material safety data, including that from a viral penetration assay. This 510(k) would also contain the results from a randomized cross-over human study comparing performance of the new condom to that of a control NRL condom based on self-reports of slippage and breakage during use.

To date, FDA has reviewed nearly a dozen such slip/break studies for synthetic male condoms, including three contraceptive studies that also nested slip/break evaluations within the overall study design.

FDA does not require manufacturers of synthetic male condoms to conduct new contraceptive or STI studies. It is sufficient for a manufacturer to show that the slippage and breakage event rates of its new condom are not inferior to an acceptable control male
condom made from NRL. In this case, FDA has concluded that there is a good evidence base and long history for supporting the two recognized failure modes as acceptable measures of performance of a male condom.

**Female condoms.** FDA is aware of only one female condom that was marketed prior to the 1976 Medical Device Amendments (the Gee Bee Ring, marketed in the 1930’s), and there is no available data on its safety and effectiveness. The female condom works differently from the male condom and has different failure modes. Therefore, in the absence of safety and effectiveness data, FDA classified female condoms into Class III (21 CFR 884.5330). The premarket pathway for female condoms is a PMA application, and – to date – FDA has approved only one female condom, the FC1 in 1993. This PMA approval was based on preclinical testing (including a viral penetration study), feasibility studies, and a single-arm contraceptive study conducted in the US and in Latin America.

A number of studies of the FC1 female condom, described later in this summary, were conducted after approval to show its effectiveness against STIs. More recently, clinical investigators have provided a more comprehensive set of definitions of female condom failure modes. There are four recognized failure modes for female condoms, and they are described later in this document. New designs and studies may identify yet other failure modes. There is no evidence yet on how different failure modes correspond to the clinical outcomes of interest (i.e., pregnancy and STIs).
II. Pivotal Clinical Trial of FC2: Failure Modes based on User Reports as Surrogate Endpoints for Pregnancy and STIs

*Can this study be used to infer STI Risk Reduction and Contraceptive Effectiveness?*

The key premise of this PMA is that a study comparing FC1 and FC2, using self-reports from study subjects to record known failure modes, is sufficient to demonstrate the safety and effectiveness of the new female condom (FC2). The sponsor asserts that if the failure mode event rates between FC1 and FC2 are sufficiently similar, then there is no need to conduct further studies to evaluate FC2’s barrier protection against the clinical outcomes of interest, i.e., pregnancy and STIs. FDA will be asking its advisory committee (the Ob/Gyn Devices Panel) to help in this decision-making process.

The one pivotal study submitted is a randomized cross-over trial of FC1 and FC2 conducted in South Africa by the Reproductive Health & HIV Research Unit (RHRU) of the University of Witwatersrand. (Henceforth in this summary, this study will be referred to as the RHRU Study.) The RHRU study was designed to record and compare four failure modes that can occur during use:

- breakage,
- slippage,
- invagination, and
- penile mis-direction.

Based on a comparison of the known failure modes as recorded by user self-reports, the sponsor intends to demonstrate that FC1 and FC2 are equivalent. Their premise is that if FC1 and FC2 are equivalent for failure modes, then they can be considered to be equivalent in terms of risk reduction with respect to pregnancy and STIs. The basis for this assumption is that FC1 effectiveness was already demonstrated in the FC1 PMA.

*Use of surrogate endpoints.* It is important to note that, with good evidence-based clinical judgment, FDA has allowed sponsors to use surrogate endpoints as a substitute for other clinical outcomes. For instance, for the past 20 years, clinical studies of PMAs for post-operative adhesion barriers have been allowed to compare the number, location, extent, and severity of adhesions formed after pelvic surgery, instead of the more difficult (and more easily confounded) clinical outcomes of pain, pregnancy, and small bowel obstruction. In another example, as described above, FDA has allowed manufacturers of male condoms made from new materials to use a comparative failure mode study instead of a contraceptive or STI prevention study. In any case, allowing a surrogate endpoint instead of the clinical outcome(s) of true interest should be based on good evidence.

Finally, in making the argument that one can infer contraceptive and STI protection based on an FC1-FC2 comparison of failure modes, it is important to appreciate the clinical evidence underlying the initial approval of FC1. Therefore, the PMA and this Executive Summary provide information to this effect. It is useful to remember that when FDA approved the PMA for FC1, FDA recognized the limited amount of information available
on effectiveness. However, in face of the AIDS epidemic of the 80’s and 90’s which persists today, and recognizing that FC1 represented the only “woman-controlled” device for barrier protection against STIs, FDA approved FC1 with mitigating labeling that positions it inferior to the male condom. Details of the labeling mitigation are later in this Summary. The sponsor is not proposing changes to this part of the labeling, so the same effectiveness benchmark should apply to FC2.

This PMA does not contain any studies of FC2 that address contraceptive effectiveness or STI risk reduction; indeed, the sponsor asserts that such studies are not necessary. This is an important review issue for the PMA and is reflected in the first panel discussion question.
III. Proposed Indications for Use

FC2 Female Condom, when used correctly and consistently, helps to prevent HIV/AIDS, other sexually transmitted infections (STIs) and unintended pregnancy. This is identical to that of FC1.

IV. Device Description

As shown in the image below, the FC2 female condom is comprised of a sheath, an outer ring, and an inner ring. Although not attached to the condom, the inner ring is inside the sheath and aids in insertion. Each component is described in detail below.

*FC2 Female Condom Image*

*Sheath and Outer Ring*

The sheath and outer ring of the FC2 female condom are made from “nitrile” rubber, a three component copolymer of acrylonitrile (26%), butadiene (68%) and methacrylic acid (6%), shown below.

![Butadiene](image_url)  ![Acrylonitrile](image_url)  ![Methacrylic Acid](image_url)
In addition to the material differences between FC1 and FC2 (nitrile instead of polyurethane), FHC manufactures the condoms differently. FC1 is manufactured by welding together sheets of extruded polyurethane. This welding procedure produces a seam (or joint weld) that runs along the axial direction of the device. In contrast, FC2 is manufactured via a dipping process, similar to that for medical examination gloves or natural rubber latex male condoms. During this process, glass formers are dipped into heated liquid nitrile latex, and the adherent material solidifies on the glass former. After a repeat dipping procedure, FHC rolls the open end of the FC2 sheath upon itself to fabricate the outer ring. Unlike FC1, the resulting FC2 product has no seam.

It is unclear if the difference in outer ring material will affect female condom performance during actual use. The FC2 nitrile outer ring is softer and more flexible than the FC1 polyurethane outer ring, and the outer ring thickness of FC2 is increased to compensate for this.

**Inner Ring**

The FC2 inner ring is made of polyurethane and is identical to the FC1 inner ring.

**Lubricant**

Like FC1, the device is lubricated with a silicone-based lubricant.

**Dimensions**

Please see table below that compare the general characteristics of the FC2 and FC1 female condoms.

<table>
<thead>
<tr>
<th>Dimension</th>
<th>FC2</th>
<th>FC1</th>
</tr>
</thead>
<tbody>
<tr>
<td>length (mm)</td>
<td>164-184</td>
<td>160-180</td>
</tr>
<tr>
<td>width (mm)</td>
<td>76-83</td>
<td>76-82</td>
</tr>
<tr>
<td>sheath thickness (μm)</td>
<td>65-85</td>
<td>41-61</td>
</tr>
<tr>
<td>outer ring thickness (mm)</td>
<td>2.9-3.8</td>
<td>2.33-2.53</td>
</tr>
<tr>
<td>outer ring, minimum diameter (mm)</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>inner ring thickness (mm)</td>
<td>4.60-5.10</td>
<td>4.60-5.10</td>
</tr>
<tr>
<td>inner ring diameter (mm)</td>
<td>50.2-50.8</td>
<td>50.2-50.8</td>
</tr>
</tbody>
</table>

Relative to FC1, FC2 has a thicker sheath and outer ring but otherwise similar physical dimensions.
**FC2 Assembly and Lot Release Testing**

FHC receives the nitrile sheaths from a contract manufacturer and conducts initial lot testing. The inner ring is inserted, lubricant applied, and the device is packaged at this same location. Random samples of the finished lots are shipped to a FHC site in the United Kingdom, where the firm conducts final lot release testing.
V. Preclinical Testing

A. Materials Testing

Thermal Analysis

Determining the thermal behavior of polymeric materials used in medical devices is an important element of ensuring safety and efficacy. It is critical that the new nitrile material shows no unexpected thermal characteristics at relevant temperatures (i.e., those at which the device will likely encounter during storage or use). The thermal profiles of FC1 and FC2 were determined 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 moderate increases in temperature that the device may encounter during transportation, storage, and use.

Additional details are located in Nonclinical Studies – Part 3 of the Panel Pack.

Airburst Testing

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 project to measure of elasticity. In each case, higher numerical values are preferred over lower values because a higher pressure or larger quantity of air will be necessary to rupture a more robust material.

Airburst Specifications

The product specifications for FC1 and FC2 are given in the table below.

<table>
<thead>
<tr>
<th>Table 2. FC2 and FC1 airburst specifications.</th>
</tr>
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<tbody>
<tr>
<td>FC2</td>
</tr>
<tr>
<td>airburst pressure</td>
</tr>
<tr>
<td>airburst volume</td>
</tr>
</tbody>
</table>

As shown in the table above, the airburst pressure and volume specifications are 3.45 kPa and 5.0 L, respectively. To obtain these specifications, the sponsor:

1. Determined the average airburst volume and pressure of at least 2,000 condoms from the same lot as those used in the clinical study.
2. Set a provisional minimum airburst limit at 80% of the 1.5 percentile values of these airburst properties.

3. Determined the number of non-conforming condoms in the sample and noted whether they failed burst volume, pressure, or both. Based upon this information, FHC modified the airburst limits further.

This is an acceptable method for setting female condom specifications. The burst pressure specification for FC2 is lower than for FC1. The sponsor states that they increased the thickness of FC2 to more closely match the FC1 burst pressure specification. This is because the tensile strength of the nitrile film is lower than that of the polyurethane film.

Additional details are located in Nonclinical Studies – Part 4 of the Panel Pack.

**Airburst Data**

FHC tested 6,445 FC2s from 25 lots. The mean burst pressure was 5.4 kPa, and the mean burst volume was 11.3 L. The failure rate is below the 1.5% acceptable quality level for FC1 and for FC2.

Additional details are located in Nonclinical Studies – Part 3 of the Panel Pack.

**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 (mPa),
- force-at-break (N), and
- elongation (%).

The sponsor 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, temperature and conditioning with saline adversely impacted the mechanical properties.
Please see results below.

Table 3. FC1 and FC2 tensile data.

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

Results show that FC1 and FC2 are affected similarly depending on test condition. In general, the FC1 film has a greater intrinsic tensile strength and elasticity compared to that of FC2. Under conditions that represent clinical use, both the axial tensile strength and the force at break of the FC2 film are less than that of the FC1 film. It is unclear how the reduced tensile properties of FC2 (relative to FC1) may translate to clinical device performance.

Additional details are located in Nonclinical Studies – Part 3 of the Panel Pack.

_Tear Strength_

The sponsor also measured the force necessary to initiate and propagate a tear in both the FC1 and FC2 materials. In this test, a 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 sponsor tested 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. The table below contains the median tear test results:

### Table 4. FC1 and FC2 tear data.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Test Condition</th>
<th>Direction</th>
<th>Median Strength (N/mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC1 Polyurethane</td>
<td>Tested at 23°C</td>
<td>Length</td>
<td>75.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Circum.</td>
<td>73.1</td>
</tr>
<tr>
<td></td>
<td>Tested at 37°C</td>
<td>Length</td>
<td>72.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Circum.</td>
<td>62.8</td>
</tr>
<tr>
<td>1 hour in saline, tested at 37°C</td>
<td>Length</td>
<td>65.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Circum.</td>
<td>56.8</td>
</tr>
<tr>
<td>FC2 Nitrile</td>
<td>Tested at 23°C</td>
<td>Length</td>
<td>45.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Circum.</td>
<td>43.7</td>
</tr>
<tr>
<td></td>
<td>Tested at 37°C</td>
<td>Length</td>
<td>38.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Circum.</td>
<td>38.6</td>
</tr>
<tr>
<td>1 hour in saline, tested at 37°C</td>
<td>Length</td>
<td>31.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Circum.</td>
<td>35.4</td>
</tr>
</tbody>
</table>

Results show that the tear strength of the FC2 material is roughly 50% of that measured from the FC1 material under clinically relevant conditions. However, FC2 does not have a seam.

Additional details are located in Nonclinical Studies – Part 3 of the Panel Pack.

**Viral Penetration Testing**

An *in vitro* viral penetration test was performed to evaluate the viral barrier properties of the condom.

In this study, condoms were challenged by inoculating the inside of each condom with bacteriophage Φ174, a virus that is smaller than the Human Immunodeficiency Virus (HIV) and non-pathogenic to humans. The condoms were then sealed, immersed in sterile simulated serum, pressurized, and held for 30 minutes at 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. This test method was developed by FDA scientists for evaluating condoms and described in greater detail in the Panel Pack.

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 suggest that the FC2 failure rate is acceptable because it is comparable to that for male condoms and lower than that for FC1.

Additional details are located in Nonclinical Studies – Part 7 of the Panel Pack.

*Shelf Life Testing*

FHC proposed a three-year shelf life for the FC2. To support this claim, they conducted airburst testing on 20 samples aged at 50°C for 293 days and room temperature (RT) for 365 days. Although there is an initial decrease in airburst properties, the data indicate that the device is stable over time.

*Compatibility with Personal Lubricants*

It is important to know if the FC2 can be used safely with additional personal lubricants. The sponsor tested FC2 and found that it is compatible with a number of commonly used personal lubricants. FHC has not yet tested FC2 following exposure to a spermicidal lubricant.

*Comparison of Original FC1 and Current FC1 Data*

The initial contraceptive study of FC1 (Farr et al.) is described in more detail in the Clinical Testing section. This pivotal clinical study provided contraceptive effectiveness data to support approval of the PMA for FC1 in 1993. Since that time, FHC changed the way they manufacture FC1. Below is a comparison of the data from FC1s produced at about the same time as the Farr study, 1989-1990, using the same manufacturing process. The table below compares the early FC1 data to data from same lot of FC1 condoms used in the RHRU study, shown below.

<table>
<thead>
<tr>
<th></th>
<th>Burst pressure (kPa)</th>
<th>Seam Strength (MPa)</th>
<th>Tensile Strength (cross grain MPa)</th>
<th>Burst volume (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original FC1</td>
<td>5.5 (n=10)</td>
<td>9.88 (n=20)</td>
<td>42.37 (n=20)</td>
<td>Not known</td>
</tr>
<tr>
<td>Current FC1</td>
<td>5.33 (n=20)</td>
<td>20.25 (n=20)</td>
<td>50.55 (n=20)</td>
<td>10.8</td>
</tr>
</tbody>
</table>

In general, the data show that the FC1s used in the RHRU study had higher physical properties than ones like the FC1s used in the Farr *et al.* study. The sponsor states this is because the older FC1s were hand-made.
B. Biocompatibility Testing

Per the definitions in the International Organization for Standardization ISO 10993-1, Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing, the human contact potential posed by FC2 is characterized as short term, mucosal contact, with the potential for repeat use contact. Due to the new materials used for the construction of this device, FDA determined that biocompatibility testing should be conducted following the FDA draft guidance titled “Testing guidance for Male Condoms Made from New Material (Non-Latex),” dated June 29, 1995. It recommends that the following tests be conducted:

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

A brief summary of the biocompatibility testing performed on the FC2 Female Condom is provided in Appendix 1 of the Executive Summary.

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 toxic effects on muscle.

C. Microbiological Testing

Since the presence of certain microorganisms on non-sterile devices, such as the female condom, can potentially harm the user, it is the responsibility of the device manufacturer to ensure that bioburden levels on these devices after manufacture are acceptable.

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 Female Health Company conducted bioburden testing on 20 female condom samples from each of six lots.

FDA reviewed detailed protocols and results and found that the bioburden information was acceptable.

Additional details are located in Nonclinical Studies – Part 8 of the Panel Pack.
D. Preclinical Review Issues

1. As stated above, the FC2 outer ring is made of nitrile and is softer, more flexible, and thicker than the FC1 outer ring, made of polyurethane. It is unclear if these differences affect clinical performance. The panel should consider this issue when determining if the data from the FC1/FC2 failure modes study is adequate.

2. The data submitted by FHC have characterized the physical properties of the FC2 nitrile film. These data appear to be complete and scientifically sound. The nitrile copolymer-rubber has lower physical properties compared to a polyurethane derivative (FC1). However, it is difficult to predict in-use performance based solely on this information, which underscores the importance of an acceptable clinical study. The panel should consider this issue when determining if the information from the failure modes study is adequate.
VI. Clinical Testing

A. Background

In 1993, FDA approved a PMA (P910064) for the first female condom (FC1) to be marketed in the US. The pivotal clinical study supporting the FC1 PMA was a prospective, single-arm, open-label study conducted in the US and Latin America, and it provided a point-estimate of the six-month pregnancy rate when relying on the device for contraception. Even after excluding the data from Latin America, the overall contraceptive rate from this study was much higher than expected. Details of this study are contained in the initial SSED and a peer-review published paper (both contained in the FC2 PMA) with a brief summary below.

The FC1 PMA did not demonstrate whether FC1 protects against sexually transmitted infections. However, in the face of the growing AIDS epidemic in the United States, coupled with the general interest in a ‘woman-controlled’ barrier device, FDA approved the PMA subject to critical labeling mitigation. In particular, FDA requires that FC1 labeling carry the following key elements, prominently displayed on the retail package:

![Important Information]

When FDA approved the PMA for FC1, FDA also asked the National Institute of Child Health & Human Development (NICHD) to conduct postmarket studies of the Reality® female condom (FC1) to assess its efficacy at preventing STIs, especially HIV infection. The sponsor was not involved other than to supply FC1 female condoms. One such study of FC1 was conducted (unpublished) in a population of women visiting STD clinics in Alabama. The study authors submitted a Final Report on the study to NICHD, and it is included in this PMA application for FC2.
The primary human-use study supporting this PMA for FC2 is a randomized cross-over study of FC2 v. FC1, comparing the two condom versions with respect to *in-use* failure modes such as slippage, breakage, invagination, and mis-direction, based on user self-reports. The sponsor asserts that if this comparison is valid and acceptable, then one can infer comparable clinical effectiveness as demonstrated earlier for FC1, i.e., protection against pregnancy, with mitigated labeling as described above. Therefore, it is important to briefly review the clinical studies of FC1.
B. FC1 Clinical Outcome Studies

**FC1 Protection Against Pregnancy**

The pivotal clinical study supporting 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 are below, and additional details may be found in the FC1 PMA SSED and in the publication referenced below (Farr et al.).

<table>
<thead>
<tr>
<th>Table 6. Status of Subject Participation at End of Study.</th>
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<table>
<thead>
<tr>
<th>Completed 6-months</th>
<th>US</th>
<th>OUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of subjects</td>
<td>147/221</td>
<td>48/107</td>
</tr>
<tr>
<td>percent</td>
<td>66.5%</td>
<td>44.9%</td>
</tr>
<tr>
<td>Discontinued use</td>
<td>74/221</td>
<td>59/107</td>
</tr>
<tr>
<td>percent</td>
<td>33.5%</td>
<td>55.1%</td>
</tr>
<tr>
<td>Unplanned pregnancy</td>
<td>22/221</td>
<td>17/107</td>
</tr>
<tr>
<td>percent</td>
<td>10.0%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Returned for 6-month follow-up</td>
<td>153/221</td>
<td>54/107</td>
</tr>
<tr>
<td>percent</td>
<td>69.2%</td>
<td>50.5%</td>
</tr>
</tbody>
</table>

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.”

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.
FDA brought the FC1 PMA before its advisory committee for help in interpreting the study results. Although the pregnancy rate was much greater than expected and there was little evidence of STI protection, the panel recommended approval of the PMA. FDA agreed with the panel and approved the PMA for women whose partners could not or would not use a male latex condom for protection. However, they required that FC1 labeling contain the following four essential elements (also provided above):

1. Latex condoms for men are highly effective in preventing sexually transmitted diseases, including AIDS (HIV infection), if used properly.
2. If you are not going to use a male latex condom, you can use Reality (FC1) to help protect yourself and your partner.
3. Reality (FC1) only works when you use it. Use it every time you have sex.
4. Before you try Reality (FC1), be sure to read the directions in the box and learn how to use it properly.

In this new PMA, FHC asserts that the safety and effectiveness of the FC1 in preventing pregnancy and new STIs was demonstrated in the Farr et al. study. In addition, FHC concluded that the FC1-FC2 failure modes study, described later in this document, supports its conclusion that the FC2 will have the same clinical failure as FC1. FHC states that this study shows that FC2 is functionally equivalent to FC1 and, therefore, that FC2 will be just as effective in preventing HIV/AIDS and other STIs.

For this reason, FDA reviewed the literature for FC1 in terms of contraception effectiveness and STD protection. We present below a brief summary of study findings and limitations. The order of the studies coincides with the order in which the sponsor lists the studies in Section 2.1.1 of the PMA.


This is the peer-reviewed article of the study that supported approval of the FC1 PMA. It is described above and is located in Volume 3 of the Panel Pack.


In this review, the author comments on the limitations of the Farr study and reviews the literature to provide an estimate of FC1 efficacy compared to other barrier methods. The Farr study established the contraceptive efficacy of the female condom—a six-month life-table probability of failure of 15%
(12% in the United States vs. 22% in Latin America)-- but it did not include randomization with another method of contraception. Thus, it is not possible to conclude comparative efficacy. This author found that comparisons using other female barrier methods as historical controls, however, provide evidence that, among women in the United States, the contraceptive efficacy of the female condom during typical use is not significantly different from that of the diaphragm, the sponge or the cervical cap. The six-month probability of failure during perfect use of the female condom is 2.6% among U.S. women, similar to rates for the diaphragm and the cervical cap but significantly lower than that for the sponge. The author notes that meaningful comparisons with the male condom are not possible because of the lack of data from carefully controlled prospective clinical trials. Extrapolations from the results on contraceptive efficacy suggest that perfect use of the female condom may reduce the annual risk of acquiring the human immunodeficiency virus by more than 90% among women who have intercourse twice weekly with an infected male.


A clinical trial was conducted in 10 centers throughout Japan to assess the contraceptive efficacy and acceptability of the Reality® female condom. All 195 subjects contributed data on acceptability and 190 contributed data on efficacy (five subjects, none of whom became pregnant, were excluded from the efficacy analysis: two because of low coital frequency, one for not providing coital diaries or usage feeling questionnaires, and two for use of other methods of contraception). The 6-month life table probability of becoming pregnant was 3.2% during typical use and 0.8% during correct and consistent use of the female condom. The author notes that the lower coital frequency in the Japanese cohort compared to the aforementioned Farr trial may account for the lower risk of pregnancy.
FC1 Protection Against STI

Since approval of FC1 in 1993, there have been several published studies that evaluated FC1 for protection against sexually transmitted infections. The following is a brief summary of each study. A full report of each is in the Panel Pack. FHC had no input on the protocol or execution of the studies.


The purpose of this study was to determine whether the female condom is as effective as the male condom in preventing sexually transmitted infection. Women attending public STD clinics participated in a behavioral intervention promoting the female condom. They returned to the clinic for six months to report on their sexual behavior and condom use, and to be examined for STD. The authors found that consistent and correct use of either condom was associated with a 70% reduction in STD rates as compared to inconsistent use (relative rate=0.3, 95% confidence interval: 0.1-0.6). STD incidence was lower among consistent users who mixed condom types than among exclusive male condom users. The authors concluded that consistent condom use reduces STD risk, but incorrect use and condom failure may greatly reduce effectiveness. They also concluded that the female condom appears to be at least as effective as the male condom as a barrier to STD.

There are, however, several limitations to this study. In our opinion, the most significant limitation was that one group received a supply of male condoms and the other group received female condoms with male condoms as a backup. This type of design fails to separate the effect of the female condom from the male condom, and therefore cannot provide any evidence of equivalence between the two. If women in the female condom arm are using male condoms, and none of the male condom arm women are using female condoms; then the benefit of the female condom may be overestimated. It actually may be attributable to male condom use.


This article address failure modes, not STI protection, and the results are located in Table 7 of the section entitled FC1 Failure Modes Studies Since PMA Approval.

This study looked at the suitability of the female condom for the prevention of STDs or HIV over extended periods of time. As part of a six-month prospective follow-up study of 1,159 STD clinic patients, clients were interviewed during their initial visit, exposed to a behavioral intervention promoting condoms, given a physical examination and provided with instructions on completing a sexual diary.

Among 895 women who reported having engaged in vaginal intercourse during the study period, one-half had sex with only one partner, while one-quarter each had two partners or three or more partners. A total of 731 women reported using the female condom at least once during the follow-up period—85% during the first month of follow-up. The authors found that women at risk of STDs find the female condom acceptable and will try it, and some use it consistently. This study did not look at the effectiveness of the female condom against STD transmission. It does not provide any data on the effectiveness of the FC1 female condom.


In this study, 1442 women attending a sexually transmitted disease clinic were randomly assigned to receive either female or male condoms. The groups were then followed-up to assess their rates of acquiring gonorrhea, chlamydia, early syphilis, or trichomoniasis. It is not explained why HIV was excluded from this group. The authors found that the incidence rates for the first new post-intervention STD per 100 women-months of observation were 6.8 in the female condom group and 8.5 in the male condom group (rate ratio = 0.79, CI: 0.59-1.06). The authors conclude that women counseled on, and provided with, female condoms fared no worse and experienced a non-significant reduction in STDs compared to the male condom group.

A limitation found in the previous study holds true here as well. Women were counseled on female condom use. The results of this study may not be reflective of STD rates following use by the general population. However, this is a much more serious limitation of this study. A subgroup analysis by the authors found that women in the male condom arm had little access to female condoms and rarely used the female condoms. However, women in the female condom arm had continued access to male condoms from sources.
outside of the clinic, and findings from the substudy revealed that male condoms accounted for 1/3 of condom protected sex acts in this study arm.

The authors suggest that women in the female condom arm may have improved negotiating power to use any type of condom when the female condom is given as an option. Even if this is true, it fails to separate the effect of the female condom from the male condom, and therefore cannot provide any evidence of equivalence between the two. If 1/3 of the women in the female condom arm are using male condoms, however almost none of the male condom arm women are using female condoms, the benefit of the female condom may be overestimated while actually be attributable to male condom use.


The purpose of this study was to determine if appropriate use of the female condom decreased the rate of recurrent vaginal trichomoniasis in previously diagnosed and treated women. One hundred and four sexually active women with vaginal trichomoniasis were treated with metronidazole and assigned to a group using the female condom or a control group during a 45-day period of continued sexual activity. Fifty women served as controls, and 54 women were assigned to use the female condom. Only 20 women used the female condom each time they had sexual intercourse. Reinfection with trichomonas occurred in 7/50 (14%) controls, in 5/34 (14.7%) noncompliant users, and in 0/20 compliant users of the female condom. The authors concluded that compliant use of the female condom is effective in preventing recurrent vaginal trichomoniasis. The authors did not analyze the results based on an intent-to-treat analysis but preferred to evaluate the outcome based upon the compliant use of the device. This has the potential of selecting out a significant portion of the study subjects in the analysis.


The authors followed 1000 sex workers in Madagascar for 18 months to assess whether adding female condoms to male condom distribution led to increased protection levels and decreased STDs. For months 1-6, participants had access to male condoms only; in the final 12 months, they had access to male and female condoms. The researchers interviewed participants about condom use every two months and tested for chlamydia, gonorrhea and trichomoniasis every six months. Following six months of male condom
distribution, participants used protection in 78% of sex acts with clients. Following female condom introduction, protection at months 12 and 18 rose to 83% and 88%, respectively. Aggregate STD prevalence declined from 52% at baseline to 50% at month six. With the female condom added, STD prevalence dropped to 41% and 40% at months 12 and 18, respectively. The authors concluded female condom introduction is associated with increased use of protection to levels that reduce STD risk. The longitudinal design makes it difficult to assess whether increased knowledge and awareness after the male condom phase may have influenced the female condom phase results. In addition, as in the French study described above, it is unclear from the self-reports whether women could also have been using male condoms in the second phase.


This study estimated the additional protection against STDs offered to sex workers by giving them the option of using the female condom when clients refused to use a male condom. Sex establishments in four cities in Thailand were randomized into two study groups: one in which sex workers were instructed to use male condoms consistently (male condom group); and one in which sex workers had the option of using the female condom if clients refused or were not able to use male condoms (male/female condom group). Randomization was done by sex establishments, and not by individuals, to minimize sharing of female condoms across study groups. The proportion of unprotected sexual acts (defined as sexual acts in which condoms were not used, torn, or slipped in or out) and incidence rate of STDs (gonorrhea, chlamydial infection, trichomoniasis and genital ulcer disease) were measured over a 24-week period and compared between the two study groups.

Condom use was found to be very high in both groups (97.9 and 97.3 % of all sexual acts, respectively, P > 0.05). Male condom use was lower in the male/female condom group when compared with the male condom group (88.2 and 97.5%, respectively, P < 0.001). However, the authors felt this reduction in male condom use was counterbalanced by the use of female condoms in 12.0% of all sexual acts in the male/female condom group, contributing to a 17% reduction in the proportion of unprotected sexual acts in this group when compared to the male condom group (5.9 versus 7.1%, respectively, P = 0.16). Female condom use was sustained over the entire study period. There was also a 24% reduction in the weighted geometric mean incidence rate of STDs in the sex establishments of the male/female condom group compared to the male condom group (2.81 versus 3.69 per 100
person-weeks, \( P = 0.18 \). Thailand has a 100% condom use policy that is strictly enforced and therefore the results may not be generalizable to other countries where there is no such policy.


The objective of this study was to measure the impact on STD prevalence of a female condom introduction and risk-reduction program at Kenyan agricultural sites. The investigators conducted a cluster-randomized trial to determine whether a replicable, community-level intervention would reduce STD prevalence. Six matched pairs of plantations were identified. The six intervention sites received an information/motivation program with free distribution of female and male condoms, and six control sites received only male condoms and related information. Participants were tested for cervical gonorrhea and chlamydia by ligase chain reaction on urine specimens, and vaginal trichomoniasis by culture, at baseline, six and 12 months.

The authors found that consistent male condom use was more than 20% at 12 months in both arms. Consistent female condom use was reported by 11 and 7% of intervention site women at six and 12 months. Unadjusted STD prevalence was 16.5 and 17.4% at six months, and 18.3 and 18.5% at 12 months, at the intervention and control sites, respectively. Logistic regression models confirmed the null effect of the female condom intervention.

The sponsor in there review of this study in the PMA states that “the investigators reported a 25% decline in STIs in both groups, demonstrating that use of a condom, either male or female, led to a decline in STI rate in this population.” The conclusions presented by the sponsor are inconsistent with the study findings. In the published article, neither group achieved a 25% decline in STDs. Furthermore, the investigators concluded that the female condom introduction did not enhance STD prevention at these sites.


The objective of this study was to measure long-term use of the female condom among couples at high risk of HIV infection and to evaluate the effect of female condom use on unprotected coital acts. Ninety-nine Zambian couples with symptomatic STD received female condoms, male condoms, and spermicides and were counseled to use either condom plus spermicide for
each coital act. Couples were followed up at three-, six-, and 12-month visits. Barrier contraceptive use was measured prospectively by coital log.

The authors found that female condoms were reportedly used in 24%, 27%, and 23% of coital acts and by 86%, 79%, and 67% of the returning couples during each time interval. Higher-level female condom users used male condoms less often but had fewer unprotected coital acts (5% vs. 14%; p < 0.05) than lower-level female condom users. The authors concluded that a majority of couples at high risk of HIV infection used the female condom in conjunction with other barrier methods over a one-year period. Like the Macaluso study (F), this study did not look at the effectiveness of the female condom against STD transmission and it is therefore unclear why the sponsor included this paper in this section. It does not provide any data on the effectiveness of the FC1 female condom.


The investigators conducted a systematic review of 137 articles and abstracts related to various aspects of the female condom as well as a closer analysis of five randomized controlled trials on effectiveness. The authors found that these five studies indicated strongly the benefits of female-condom use in increasing protected sex acts, and two studies found promising decreases in STD incidence with the introduction of the female condom. Ten studies provided detailed information on patterns of long-term use, many suggesting that the female condom reaches women less likely to use other dual protection methods. The authors conclude that there exists limited but convincing evidence that the female condom is effective in increasing protected sex and decreasing STD incidence among women. In addition, the authors state that future research on the female condom must move away from assessing acceptability and focus on assessing effectiveness and improving impact in diverse settings. Though there is no new data in this study, the authors’ conclusions of positive but limited evidence of female condom effectiveness and the future need for more effectiveness studies are apt.


This report is a review of a workshop on the female condom held in Baltimore, MD in September 2005. The workshop was sponsored by the Program for Appropriate Technology in Health (PATH), the United States Agency for International Development (USAID) and the United Nations Population Fund (UNFPA). The report advocates the need for female condoms as well as provides a summary of the literature, which is covered in
this memo. This report does not offer any additional data on FC1 effectiveness.
**FDA Comments**

Of the studies reviewed, the most favorable for FC1 are Farr *et al.* (for pregnancy protection) and French *et al.* and Fontanet *et al.* (for STI protection). However, all of the STI studies are hindered by significant methodologic limitations related to comparison groups, detecting the true effect of FC1, and self-reporting bias. Regardless of the sponsor’s assertion in the PMA, Feldblum found that the female condom did not enhance STD prevention.

Vijayakumar *et al.* summarizes the literature best by saying “there exists limited but convincing evidence that the female condom is effective in increasing protected sex and decreasing STD incidence among women. Future research on the female condom must move away from assessing acceptability and focus on assessing effectiveness and improving impact in diverse settings.”

The sponsor provides a few examples (Macaluso 2000, Musaba 1998) of studies that do not look at FC1 effectiveness but more on acceptability.
C. FC1 Failure Modes Studies

1. Slip/Break Studies, General

For many years, manufacturers and others have conducted *in-use* slip/break studies of male condoms to establish a measure of performance with respect to its two known failure modes. Event rates for male condom slippage and breakage during use typically range between 0.5–2%. Contraceptive studies of male condoms with nested slip/break studies have validated such studies.

Because the condom failure modes studies are based on user self-reports, study design must carefully address all aspects that could undermine data reliability. This is especially true with factors that challenge memory recall of each condom use and the various failure modes the study subject is asked to assess. In particular, this means properly designed easy-to-use coital logs, prompt log entry after use of a given condom, minimal study duration for an individual subject, minimal timeframes for condom use, masking procedures, etc. Condom slip/break studies are typically two-arm studies (new condom type v. control condom type), and the study design should include measures to ensure that the subject’s use of one condom type is spaced separately from use of the other type.

FC1 is the only marketed female condom, and there are a limited number of such failure mode studies. More recently, study observations and risk analyses have identified four failure modes for FC1:

- breakage,
- slippage,
- invagination, and
- penile mis-direction.

These are clinical female condom failures, that is, those that occur during the sex act or are noticed upon withdrawal. They do not include non-clinical failure modes such as non-clinical breakage. Non-clinical breakage is when the condom tears as the user is removing it from the package.

These failure modes are defined and described in more detail in Beksinska *et al.* (2007). Research continues on the use of biomarkers for semen exposure, but these studies are not sufficiently validated to infer the actual degree of risk (of pregnancy or STI) for any specific failure mode.

FC1 is the only female condom marketed, and only a limited number of such studies have been conducted. Moreover, it is difficult to compare event rates, or differences in event rates, from one study to another because study designs differ and earlier studies did not fully account for all possible failure modes.
2. FC1 Failure Modes Studies Since PMA Approval

Other studies that evaluated FC1 failure modes report event rates that, by and large, are much higher than those reported in the FC1-FC2 study conducted in South Africa (Beksinska et al, 2006). These differences are probably attributable to methodologic considerations, including differences in failure definitions, counseling of study subjects, design and use of coital logs, promptness between sex and log entry, etc. Published papers on each of these studies can be found in the panel pack.

Table 7. Selected FC1 failure mode event rates from earlier studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Breakage</th>
<th>Slippage (slip-out)</th>
<th>Mis-direction</th>
<th>Invagination (slip-in)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macaluso et al. (2003)(^1) n = 175♀</td>
<td>0.7%</td>
<td>6%</td>
<td>2%</td>
<td>3%</td>
<td>11.7%</td>
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<tr>
<td>Galvao et al. (2005)(^2) n = 400♀</td>
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<td>---</td>
<td>---</td>
<td>6%</td>
</tr>
<tr>
<td>Valappil et al. (2005)(^3) n = 869♀</td>
<td>0.11%</td>
<td>2.8%</td>
<td>---</td>
<td>2.8%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Chen et al. (2007) UAB (n = 108♀)</td>
<td>0.2%</td>
<td>11%</td>
<td>0.3%</td>
<td>5%</td>
<td>16.5%</td>
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<tr>
<td>Chen et al. (2007) UNICAMP (n = 400♀)</td>
<td>0.3%</td>
<td>2%</td>
<td>5%</td>
<td>1%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Macaluso et al. (2007)(^4) n = 108♀</td>
<td>0.3%</td>
<td>10.6%</td>
<td>5.6%</td>
<td>3.0%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Beksinska et al. (2006) (FC1-FC2 in South Africa) n = 201♀</td>
<td>0.47%</td>
<td>0.21%</td>
<td>1.26%</td>
<td>0.52%</td>
<td>2.46%</td>
</tr>
</tbody>
</table>

\(^1\) The authors also provided a summary total for all mechanical problems of 17% that included (1) semen leaked onto woman’s body, (2) condom rode on penis, and (3) inner ring problem.

\(^2\) The authors only provided a summary value for “mechanical problems” that included (1) broke during intercourse, (2) condom came out of the vagina, (3) penis entered to the side of the condom, (4) outer ring pushed inside the vagina, (5) semen leaked onto woman’s body, (6) condom clung to penis, moving with it during intercourse, and (7) problem with inner ring during intercourse.

\(^3\) The authors note that rates significantly decreased with use and increased with number of previous failures. The authors also note that intensive behavioral counselling could contribute to lower observed failure rates than might be expected for women who purchase OTC. In addition, the subjects were not randomized to either male or female condoms, and there is no discussion as to how selection bias may have been minimized when selecting participants.
This raises the question whether women who showed more of an interest in using the female condom had been selected for that group. This selection bias may decrease the likelihood of device failure in the female condom group.

4 The authors also provided a summary total for all mechanical problems” of 34% that included (1) semen leaked onto woman’s body, (2) condom rode on penis, and (3) inner ring problem.
3. **FC1 Slip/Break Studies that include a Biomarker of Semen Exposure (PSA)**

The literature has suggested use of prostate-specific antigen (PSA) assays of an intravaginal swab after condom use as a marker for semen exposure. A PSA assay might be used in a conventional condom failure modes study as an adjunct to track subject compliance with the protocol. In the future, if properly validated, PSA might be used in condom studies as a surrogate biomarker for risk of pregnancy or sexually transmitted infections. However, the relationship between the amount of semen exposure and risk of pregnancy or STDs has not yet been established.

The only FDA-approved PSA assays are for serum PSA as a marker for prostate disease.

Listed below are published articles in the peer-reviewed literature that describe failure modes studies of the FC1 female condom and also use PSA assay of intravaginal swabs.


D. FC1/FC2 Comparison Study (RHRU Study)

Performance and Acceptability of the Reality Polyurethane Female Condom (FC1) and a Synthetic Latex Prototype (FC2): A Randomized Cross-Over Trial among South African Women

The sponsor of this PMA did not design or conduct this study. It was conducted by the Reproductive Health & HIV Research Unit of the University of Witwatersrand, South Africa.

The RHRU Study was a prospective, randomized, multi-center, crossover trial conducted between January 2004 and September 2004. The study was designed to be double blinded. Each condom was provided in an identical plain white plastic package. Neither subjects nor staff was informed of condom identity until the completion of the last follow-up. However, subjects who had experience with FC1 could not be blinded and it was possible for staff to identify which condom was being described based on descriptions of problems reported by subjects during interviews.

Study Objectives

The study objectives were to:

- compare FC1 and FC2 with respect to:
  - breakage (clinical and non-clinical),
  - invagination,
  - penile mis-direction, and
  - slippage;
- compare other adverse events between FC1 and FC2; and
- compare acceptability of FC1 to FC2.

Below are definitions of the four female condom failure modes used by the investigators.

**Breakage**, also referred to as clinical breakage, is defined as the number of female condoms reported to have ripped/torn/broken during intercourse and is calculated by dividing the number of female condoms reported ripped/torn/broken during intercourse by the number of female condoms used during intercourse.

**Invagination**, also referred to as outer ring displacement, is defined as an outer ring that is pushed into the vagina (partially or fully) during intercourse and is calculated by dividing the number of incidents of reported outer ring displacement by the number of female condoms used during intercourse.

**Penile Mis-direction**, also referred to as mis-routing or incorrect penetration, is defined as vaginal penetration whereby the penis is inserted between the female
condom and the vaginal wall and is calculated by dividing the number of reported incidents of incorrect penetration by the number of female condoms used during intercourse.

Slippage, also referred to as complete slippage in this case, is defined as a female condom that slips completely out of the vagina during intercourse and is calculated by dividing the number of female condoms that slipped out completely during intercourse by the number of female condoms used for intercourse.

The sponsor also obtained data on non-clinical breakage, partial invagination, and partial slippage. FDA’s review does not focus on these outcome measures as they are unlikely to be associated with true clinical risk.

**Statistical Hypothesis**

The RHRU study did not have a formal prospective research hypothesis with a statistical basis.

On page 4-1505, the submission states “The expected outcomes of the study from the reference condom (FC1) were a breakage rate of less than 5%.”

While a quantitative research hypothesis was not pre-specified, it seems natural in the present study to test for non-inferiority of FC2 as compared to FC1. Here non-inferiority means that FC2 is not worse than FC1 by a specified amount "delta", which represents the smallest clinically meaningful difference between two groups. There does not appear to be a standard value of delta for comparing female condoms, which is not surprising since FC2 is by far the first female condom to be compared with another female condom. In studies comparing male condoms, a 2% delta has been frequently adopted and widely accepted. If such a non-inferiority test is applied to the RHRU study using a 2% delta, it is apparent that FC2 easily passes the test for each of the four previously defined failure modes. While FDA has not attempted to determine the appropriate delta for a non-inferiority test of female condoms, there is no reason to believe a smaller delta should be used for female condoms than for male condoms.

Therefore, the focus of the FDA review of the RHRU study is on the study methodology and data reliability of user reports.

Study subject inclusion and exclusion criteria are listed below.

**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.

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; and
- Within six weeks post-partum or post abortion.

Execution of RHUL Clinical Trial

The investigators planned to recruit at least 275 women with a target of at least 50 subjects for each of the following populations:

- Students from Durban Institute of Technology (Students);
- Family planning clients from the Durban Commercial City Family Planning Clinic (Urban FP);
- Rural family planning clients from Umbumbulu Clinic, KwaZulu-Natal (Rural FP);
- STI clients completed treatment and free of STIs from Durban Commercial City Family Planning Clinic (STI); and
- Commercial sex worker “network” in Durban (CSW).

A total of 276 females were enrolled. Subjects were asked to use ten FC1 and ten FC2 condoms. This was a cross-over trial in which subjects were randomized to the order in which they were to use the series of ten condoms.

Blinding of both subjects and staff to condom was attempted. Each condom was provided in an identical plain white plastic package labeled either “F” or “G”. Subjects and staff were not informed which condom was FC1 and which was FC2 until completion of the last follow-up visit. Study subjects who had experience with FC1 could not be blinded, however. Also, it sometimes was possible for staff to identify which condom was used based on descriptions of problems subjects reported.
There were three formal study visits, i.e. one baseline visit, and two follow-up visits. The follow-up visits were intended to be scheduled after a subject completed 10 uses of each condom, respectively. Two to three months was allotted for completing use of 10 condoms during each phase of the cross-over study.

Study subjects were instructed to complete an entry on a Coital Log each day to record whether problems occurred or not. A single form with columns for each day was used for this purpose. The actual study database was a set of questionnaires completed by study personnel during follow-up interviews. During the follow-up interviews, subjects were allowed to refer to the Coital Logs to trigger their memories regarding condom failure modes. Although two to three months was allowed to complete use of each set of 10 condoms, 80% of subjects with coital logs and 73% of subjects without coital logs follow up interviews occurred within 30 days or less after the subject received the condoms.
Below is a figure indicating study participation and number of condoms used.

**Fig. 1. Flow chart of study participation and condoms used**

![Flow chart of study participation and condoms used](image)

- Total condom packets opened = Total number of packets opened (includes condoms not used for sex).
- Total condoms used = Total number of condoms used for vaginal intercourse.

\(^c\) Loss to follow-up = 75 (43 did not return for 1\(^{st}\) visit; 32 did not return for 2\(^{nd}\) visit).
**RHRU Study Demographics**

Below are demographics for the RHRU Study regarding age, partner and female condom experience.

Table 8. Population demographics in RHRU study: age, partner and experience with female condoms.

<table>
<thead>
<tr>
<th></th>
<th>Students (N=65)</th>
<th>Urban FP (N=64)</th>
<th>Rural FP (N=67)</th>
<th>STI (N=21)</th>
<th>CSW (N=59)</th>
<th>Total (N=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>23.2</td>
<td>33.7</td>
<td>27.7</td>
<td>35.0</td>
<td>27.2</td>
<td>28.5</td>
</tr>
<tr>
<td>Regular partner</td>
<td>85%</td>
<td>55%</td>
<td>64%</td>
<td>48%</td>
<td>25%</td>
<td>57%</td>
</tr>
<tr>
<td>Casual partner</td>
<td>2%</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
<td>58%</td>
<td>14%</td>
</tr>
<tr>
<td>Currently Uses FC</td>
<td>3%</td>
<td>11%</td>
<td>0%</td>
<td>10%</td>
<td>8%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Two hundred and one (72.8%) subjects completed both follow-up visits. Of these 201 subjects, a majority of subjects had used at least eight condoms prior to each follow-up visit.

Performance was reported in the PMA based on four major categories of problems experienced during intercourse as listed above:

- breakage,
- slippage,
- invagitation, and
- penile mis-direction.
FC1 and FC2 failure mode event rates are below.

Table 9. FC1 and FC2 failure mode event rates.

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>FC1</th>
<th>FC2</th>
<th>difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>breakage</td>
<td>9/1910</td>
<td>8/1881</td>
<td>-0.04 (-0.62 to 0.53)</td>
</tr>
<tr>
<td>mis-direction</td>
<td>24/1910</td>
<td>12/1881</td>
<td>-0.62 (-1.33 to 0.09)</td>
</tr>
<tr>
<td>invagination</td>
<td>10/1910</td>
<td>17/1881</td>
<td>0.38 (-0.25 to 1.01)</td>
</tr>
<tr>
<td>slippage</td>
<td>4/1910</td>
<td>2/1881</td>
<td>-0.10 (-0.39 to 0.19)</td>
</tr>
<tr>
<td>total failures</td>
<td>47/1910</td>
<td>39/1881</td>
<td>-0.39 (-1.67 to 0.89)</td>
</tr>
</tbody>
</table>

1 Mis-direction is actually recorded as “Incorrect Penetration” in the PMA (page 4-1519).
2 Invagination is actually recorded as “Outer Ring Displacement” in the PMA (page 4-1519).
3 FDA NOTE: Data on Slippage per se was collected neither on the subject’s Coital Log, nor on the staff questionnaire.

The sponsor also obtained data on non-clinical breakage, partial invagination, and partial slippage. As stated before, these events are not included as clinical failures. However, they are included in Volume 2 of the Panel Pack.

The above table, adapted from Table 6 in the PMA, gives the estimated rates of the four female condom failure modes, by condom and by subject, as well as estimates and 95% confidence intervals for the differences between condom types with respect to these failure rates.

Failure rates per condom use are estimated using the Generalized Estimating Equations (GEE) approach to account for within-couple correlation (Taylor and Dominik, 1999, *Journal of Biopharmaceutical Statistics*, 9(2), 365-377). The differences in Table 6 are taken as FC2-FC1. 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 FC2 to FC1. In Table 6, the largest upper confidence bound is 1.01%, which implies that with a standard delta of 2%, FC2 will be found statistically non-inferior to FC1, i.e., not worse than FC1 by more than 2%, with respect to all failure rates considered. On the other hand, all upper confidence bounds in Table 1 are positive, and therefore...
superiority of FC2 to FC1 cannot be established at the same significance level for any failure rate.

Finally, in evaluating clinical data from studies conducted outside of the US, FDA considers whether the study population (in the RHRU study, 20% commercial sex workers) is applicable to the US population. FDA regulations (21 CFR 814.15(d)) state the following requiring research conducted outside of the United States:

“A PMA based solely on foreign clinical data and otherwise meeting the criteria for approval under this part may be approved if:

(1) The foreign data are applicable to the US population and US medical practice;
(2) The studies have been performed by clinical investigators of recognized competence; and
(3) The data may be considered valid without the need for an on-site inspection by FDA, or, if FDA considers such an inspection to be necessary, FDA can validate the data through an on-site inspection or other appropriate means.”

At least one study suggests that male condom failures are very low in a CSW population, probably because of experience and motivation. This may be true for female condoms as well. Moreover, because CSWs may have multiple sex events per day and compliance with self-report requirements can be very difficult, user report data from this population may not be reliable. In addition, because Nevada is the only state in the US where prostitution is legal, it would seem that the CSW cohort of the RHRU study population may not be applicable to the general US population. However, FDA believes that the remaining population is applicable to the US population.
FDA Clinical Review Issues

1. No Entry for slippage on coital log

Page 4-1509 of the submission states “Information on number of acts of intercourse, slippages, breakages, and other problems encountered during use was recorded in the coital log.” A review of the coital log on page 4-1543 reveals, however, that there was no entry for “slippage.” The following types of failure are included on the Coital Log:

- Rip during use/broke
- Pushed into vagina
- Penis inserted outside condom

The Coital Log also had an entry for “no problem.”

As noted above, female condom slippage from the vagina is considered one of the four primary failure modes. Therefore, FDA was concerned by the failure to capture slippage on the coital log and asked the sponsor to explain this. As stated earlier, the sponsor neither designed nor conducted the RHRU study. The sponsor has explained to FDA that the principal investigator did not include slippage on the coital log because this term had been a source of confusion in a previous female condom study sponsored by the World Health Organization. Based on her experience with female condom studies, the principal investigator judged slippage to be rare, and therefore, a memory that could be elicited during the follow up interview. The questionnaire used to interview subjects during the follow-up interview did not include explicit entries for “slippage” or “partial slippage.” However, it did include the following questions:

- [Question 307] Did the female condom stay in place every time during intercourse?
- [Question 308] If no, what happened?

The sponsor states that Entries 307 and 308 on the investigator’s questionnaire provide an acceptable (albeit indirect) method for collecting reports of slippage. It is important to note that multiple female condom use and substantial time may have elapsed between condom event and the interview. As stated before, the responses to the questionnaire were the source for the failure modes data.

2. Coital log not designed for more than one female condom use per day

Another problem with the Coital Log noted by FDA is that it was not designed to collect data on the number of times each failure mode occurred on a given day. It was designed to allow a subject to place a check mark or “x” next to each of three
different failure modes per day. This means that if more than one coital act occurred on a particular day, the Coital Log only allows the subject to record that at least one event of each type of failure occurred.

To better understand the extent to which failure rates could be affected by multiple failures in a day, FDA asked the sponsor to clarify the following:

- number of times in the study when more than one coital act occurred on a given day,
- whether, for those days, the subject reported only "no problem," and
- date of multiple condom uses and the date of the follow up visit.

On the basis of information provided by the sponsor, we provide separate analyses below. Please note this data is only for those subjects who were interviewed with coital logs.

It appears that there were 63 days when a problem occurred with FC1 and 55 days when a problem occurred with FC2. Of these, there were 42/63 days when more than one condom use occurred with FC1 and 33/55 days when more than one condom use occurred with FC2. The following is a breakdown of failures on the days when more than one condom was used for FC1 and FC2, respectively:

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>FC1</th>
<th>FC2</th>
</tr>
</thead>
<tbody>
<tr>
<td>multiple condoms used (days)</td>
<td>42</td>
<td>33</td>
</tr>
<tr>
<td>subjects reporting</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>min # breaks</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>min # invagination</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>min # mis-direction</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>min # combination failures</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

The above numbers may not correspond 1:1 with outcomes data reported in the PMA. The database for study outcomes is the study questionnaire completed by study personnel, not the coital log.

The above data suggest that FC1 is more likely to invaginate and that male partners are more likely to misdirect the penis when FC1 is used compared to FC2. It is more concerning that it appears FC2 was more likely to break compared to FC1. This is plausible given that the biomaterials review of FC2 states that it has lower physical properties compared to FC1. In the original PMA (Table 6, page 4-1519), however, it appeared that the poorer results for rip/break for FC2 were skewed by "non-clinical breakage."

The following is a presentation of the FC1/FC2 failure outcomes after excluding data when more than one sex act occurred in a given day.
Table 11. FC1 and FC2 failures after exclusions when > 1 sex act in any given day

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>FC1 (21 failures, n=20 condoms)</th>
<th>FC2 (22 failures, n=16 condoms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>break</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>invagination</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>mis-direction</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>combination</td>
<td>1 (invag + misdir)</td>
<td>3 (two invag + misdir; one break + invag)</td>
</tr>
</tbody>
</table>

1 The above numbers may not correspond 1:1 with outcomes data reported in the PMA. The database for study outcomes is the study questionnaire completed by study personnel, not the coital log.

This table qualitatively shows no substantial difference between the two condoms.

3. Inclusion of commercial sex workers in RHRU Study

Another clinical review issue for the PMA is that 168 (38%) of the 436 available questionnaires were completed without coital logs. The main reason, according to the sponsor, is that commercial sex workers were instructed by their employers not to complete the coital logs, which accounts for 105 (63%) of the missing coital logs.

As stated above, at least one study suggests that male condom failures are very low in a CSW population, probably because of experience and motivation. This may be true for female condoms as well. Moreover, because CSWs may have multiple sex events per day and compliance with self-report requirements can be very difficult, user report data from this population may not be reliable.

FDA requested and the sponsor provided an analysis of results when CSWs are excluded. The sponsor provided this analysis on pages 37 and 38 of the July 3, 2008 amendment. The subgroup analysis without CSWs (Table 12) does not appear to impact the overall study findings.
Table 12. FC1 and FC2 Failure Modes Rates excluding data from CSWs.

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>FC1</th>
<th>FC2</th>
<th>difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>events/total used</td>
<td>%</td>
<td>events/total used</td>
</tr>
<tr>
<td>breakage</td>
<td>8/1473</td>
<td>0.54</td>
<td>8/1469</td>
</tr>
<tr>
<td>mis-direction¹</td>
<td>24/1473</td>
<td>1.63</td>
<td>10/1469</td>
</tr>
<tr>
<td>invagination²</td>
<td>7/1473</td>
<td>0.48</td>
<td>13/1469</td>
</tr>
<tr>
<td>slippage³</td>
<td>4/1473</td>
<td>0.27</td>
<td>1/1469</td>
</tr>
<tr>
<td><strong>total failures</strong></td>
<td>43/1473</td>
<td>2.92</td>
<td>32/1469</td>
</tr>
</tbody>
</table>

¹ Mis-direction is actually recorded as “Incorrect Penetration” in the PMA (page 4-1519).
² Invagination is actually recorded as “Outer Ring Displacement” in the PMA (page 4-1519).
³ FDA NOTE: Data on Slippage per se was collected neither on the subject’s Coital Log, nor on the staff questionnaire.

4. Other methodological concerns

One of FDA’s clinical review issues is overall study methodology. Unlike most condom slip/break studies in which a single detailed Case Report Form (CRF) is promptly completed after each act of intercourse, the CRF in this study was a coital log consisting of a single form with multiple entry fields that was reused each time a subject had intercourse. This form greatly limited the amount of data that could be collected for a particular day. Also, unlike most condom slip/break studies, in the RHRU study the database for study outcomes is not based on the coital logs; rather, it was based on an interview and a questionnaire completed by study personnel during a follow up interview.

There was a substantial time delay between day of use and filling out the questionnaire during the actual interview, which raises the question of accuracy of reporting events on the questionnaires and whether the investigator conducting the interview could inadvertently influence subject responses (“expectation bias”). According to the sponsor, the role of the coital log was to trigger the memory of subjects so that during the interview they would recall specific events/device failures. The sponsor does not believe the time lag between use of a condom and the interview resulted in inaccurate reporting. The sponsor believes that the interview process made reporting failures more accurate by clarifying whether an event met the definition of a clinical failure and whether the correct type of event was reported. The sponsor has also argued that failures were sufficiently rare that subjects recalled them for their uniqueness and were extremely unlikely to forget these unusual events.
Commercial sex workers did not fill out coital logs, so the user report data is based solely on the interviews. Many of the interviews, as stated above, occurred well after condom use.
VII. Post-market Plan

The sponsor has provided the following information on the post-approval evaluation of this device; it is just that which the regulations require of approved PMAs.

All procedures as stated in the Quality Systems performance standard references will be followed for release of product, recording all customer complaints, following MDR and product recall requirements. Specific procedures related to these programs are presented in the Manufacturing /Quality control sections of the PMA. The procedures include:

- Quality Release
- Medical Device Reporting (MDR)
- Product Recall
- Traceability
- Corrections and Removals

A report to include the following information will be filed annually:

1. any changes described in 814.39(a) and changes required to be reported to FDA under 814.39(b) and comment on whether or not the changes that FHC considers to have fallen under 814.39(b) qualify, i.e., did not require the submission of a supplement.

2. summary and bibliography of:
   a. unpublished reports of data from any clinical investigations or non clinical laboratory studies involving the device or related devices and known to the applicant
   b. reports in scientific literature concerning the device.

The sponsor has not proposed a post-approval study. Please note that post-approval studies are used to evaluate long-term, real world uses of devices. Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness. Information from a post-approval study can be used to add items to labeling that are not needed prior to approval.

The plan to conduct a post-approval study, if decided upon, does not decrease the threshold of evidence required to find the device approvable. The premarket data submitted to the Agency and presented in this Panel Pack must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.
Appendix 1 -- Biocompatibility Tests Conducted

Cytotoxicity - ISO Elution Method: The sponsor 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 sponsor 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 sponsor 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 sponsor was asked to justify the use of these extraction conditions on a device that had the potential for repeat use. The sponsor adequately justified the use of the extraction 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 WP2uvrA).

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. The company was asked to address issues regarding dilution of test extracts prior to testing. The sponsor adequately justified the dilution of the RPMI culture medium and 95% ethanol extracts.
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.