

FC₂ PMA –
FDA Advisory Panel Meeting
December 11, 2008

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Introduction / History

FC₂

- Access/Need
- Design, Characteristics and Use same as FC₁
- Material to lower Manufacturing Costs

FC1 SEAM



FC1

POLYURETHANE

FC2

NITRILE

Introduction

□ Strategy

- Same design; same instructions for use
- Same failure modes as FC1; same rates
- FC1 PMA approved with failure mode studies and contraception study
- Demonstrate FC2 has same failure modes/rates of failure
- FC1 safe and effective therefore FC2 effective barrier
- Least burdensome: contraception study not needed – additional information doesn't justify delay

□ Development Plan- FC1 PMA-S

- Viral permeability study
- Tox and biocompatibility studies
- Comparative study vs. FC1
 - Reproductive Health and HIV Research Unit S.A. (RHRU)
 - Experts in FC studies: WHO, USAID, FHI

Introduction

- WHO review of FC2
 - World experts to review data
 - Recommended distribution
 - 20+ million FC2 distributed in 77 countries – no new issues identified

- FDA
 - Full PMA required
 - FDA Points for consideration
 - No contraception study
 - FC2 robustness
 - Adequacy of RHRU protocol

Points Raised by FDA

- Reliance on One-on-One Interviews – Not Coital Log
- Recall – time between failure and interview
- Slippage – not included on the log
- Multiple Sex Acts/Given Day – one slot/day on log
- No Coital Log
- Inclusion of Commercial Sex Workers (CSWs)
- Blinded ?

Analysis of Results Showed

No meaningful differences in findings between

- Women with logs or women without logs
- Data with or without CSWs included
- Performance of FC1 and FC2 comparable for each clinical failure outcome

Summary

- FC2 developed using standard principles – least burdensome approach
 - Ensured material was effective barrier
 - Ensured it was safe and biocompatible
 - Ensured we can make it consistently
 - Performed a comparative study to FC1

- Research showed
 - FC2 is safe and biocompatible
 - FC2 failure rates equivalent to FC1
 - FC1 in RHRU study performed similar to FC1 in PMA failure mode studies supporting its approval

Michael Pope, B.Sc.
Vice President Global Operations
The Female Health Company

FC2 Development Objectives

- Simplify the manufacturing process
- Increase capacity
- To make more available at a lower price
- Match performance/characteristics of FC2 to FC1
- Same sheath dimensions
- Same inner ring
- Same insertion method.. same lubrication
- Outer ring less rigid – thickness increased to compensate

Manufacturing Options Review

- Dipping process as used for male condoms and medical gloves selected
 - Well established manufacturing process
 - Capable of very high volumes
 - Potential for low cost

- Well established process for medical devices

FC1 Manufacturing

FC1 Manufacturing



Fc2 Manufacturing



Dipping Material

- Nitrile latex
 - ▣ Similar elongation, modulus and feel to polyurethane
 - ▣ Widely used for medical glove manufacture
 - ▣ Good to excellent chemical/solvent resistance
 - ▣ Good biocompatibility

Nitrile/FC2 compared with Polyurethane/FC1

- Tensile properties of nitrile polymer are not as high as polyurethane. When measured under physiologic conditions nitrile approximately 40% of strength of polyurethane
- Tensile properties addressed by
 - ▣ Increasing the thickness
 - ▣ Eliminating the seam
- Under physiological conditions (exposed to saline for 1 hour at 37°C) **force at break of FC2 is 4.8 N** compared to **FC1 is 4.4 N** when measured across the seam of FC1.

Lubricant Compatibility

- FC2 evaluated with a wide range of personal lubricants
 - ▣ Compatible with water based personal lubricants
 - ▣ Compatible with vegetable oils tested
 - ▣ Compatible with Petroleum Jelly and Mineral (Baby) oil.

- FC2 results are comparable to FC1

Viral Barrier Properties

- FC2 tested for viral barrier properties using Φ X174 bacteriophage test
- Results show that FC2 is a good barrier, as good as male condoms and FC1. All three show excellent barrier properties.

Air Burst Properties/1

- All condom standards (ISO and ASTM) specify airburst requirements (not tensile or tear)
- FDA has questioned the robustness of FC2 based on **minimum release specification** rather than actual values
- Airburst specification for FC1 and FC2 set using different procedures. Not relevant to compare minimum values of FC1 and FC2

Airburst properties/2

Actual Values

□ Measured values of burst properties show:

□ Average FC1 **burst pressure** is 50 to 60 mBar
FC2 65 to 75 mBar

□ Average FC1 **burst volume** is 9 to 10 litres
FC2 9 to 11 litres

SUMMARY:

FC2 airburst strength **comparable** to FC1

FC2 Physical Property Summary

- Burst Properties of FC2 are comparable to FC1
- Softer outer ring does not impact the failure modes including invagination: results comparable to FC1
- Break strength of FC2 device comparable to a welded FC1 device
- Lubricant compatibility as good as FC1
- Excellent barrier properties (like latex and FC1)

Mags Beksinska, B.Sc., M.Sc., Ph.D. pending
Clinical Investigator

Reproductive Health & HIV Research

Unit University of Witwatersrand, Durban, South Africa

AIMS OF THE STUDY

- To evaluate the functional performance and short term acceptability of the Reality FC (FC1) and the synthetic latex FC (FC2).
- To compare the rates of clinical, nonclinical and total clinical failure: breakage, invagination, misdirection and slippage

Methodology

- Study conducted in 3 SA sites:- Commercial City family planning clinic in Durban, (urban FP, STI and student clients), Umbumbulu clinic (rural FP clients) and commercial sex workers based in a hotel in Durban.
- Randomized, double-blind, crossover trial where participants were randomly assigned to one of two condom use sequences (use of Reality-FC1 followed by synthetic latex-FC2 or the opposite order).

Methodology

- ❑ Women were required to be using an effective method of contraception at recruitment and were screened for STIs
- ❑ Women asked to use 10 condoms of each type, record each use on coital log and return as soon as they had used all 10 condoms
- ❑ At each visit, a pelvic examination was performed to exclude infections and any adverse reaction resulting from condom use.
- ❑ One-on-one interviews conducted at each visit, asking formal questions on a questionnaire, using the coital log as reference, and probing responses for clarification.

Statistical Design

- Sample size was estimated using WHO guidelines which recommend use of at least 1000 condoms of each type and at least 200 participants using 5 condoms each
- RHRU study sample exceeded this by increasing to 10 condoms per woman to increase sample size
- Sample of women increased to cover for loss-to-follow-up

Data collection

- All data from coital log confirmed on interview or information provided during interview was entered as part of questionnaire data base
- Questionnaire/interviews formed the data set
- Data double entered in EPI-INFO statistical package (Centers for Disease Control (CDC), Atlanta Georgia)

Staff FC training experience

- All 4 nurse researchers were master trainers of barrier methods (including Female Condoms). Master trainers are qualified to “train trainers”. Two of the four were experienced at international level.
- Had extensive experience in training providers and clients in FC use since introduction of FC in South Africa in 1998
- Involved in development of training manuals and materials around FC for SA Dept of health and international agencies

Participant instruction how to use Female condoms

- Nurses instructed women how to use condom in their home language (English or Zulu)
- Pelvic models used to demonstrate fitting, removal, how problems occur and how to avoid problems
- Leaflets provided in Zulu and/or English to take with them

Demonstration



Participant Instruction How to Use Coital log

- Nurses explained how to use log:-
 - ▣ How to record no problem/ defined problem
 - ▣ Nurses discussed start day with women on log and crossed out days of week prior to start day as a guide.
 - ▣ Told women they could write any comments or notes at back of log

- Appointment made for estimated time to complete 10 uses

Coital Log Design

- Coital log collected information on number of condoms used, number of sex acts, tears/breaks during use, invagination and misdirection
- Coital log did not include 'slippage'
- Coital log design similar to WHO design

WHO contraceptive efficacy coital log

 WORLD HEALTH ORGANIZATION	Study A15230 Contraceptive Effectiveness of Female and Male Condoms Detailed Diary	DIA Page 1 Rev. 11-12.04.02									
A15230DIA01											
(a) Center number <input style="width: 20px; height: 20px;" type="text"/> <input style="width: 20px; height: 20px;" type="text"/> <input style="width: 20px; height: 20px;" type="text"/>		(b) Subject <input style="width: 20px; height: 20px;" type="text"/> <input style="width: 20px; height: 20px;" type="text"/> <input style="width: 20px; height: 20px;" type="text"/>									
(c) Diary sequence number <input style="width: 20px; height: 20px;" type="text"/> <input style="width: 20px; height: 20px;" type="text"/>		(d) First day of diary <table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; text-align: center;">day</td> <td style="width: 20px; text-align: center;">month</td> <td style="width: 20px; text-align: center;">year</td> </tr> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table>	day	month	year						
day	month	year									
Day of week	Week 1	Week 2	Week 3	Week 4	Week 5						
	M T W T F S S	M T W T F S S	M T W T F S S	M T W T F S S	M T W T F S S						
1. Menstrual bleeding 0 = none B = bleeding	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>						
2. Number of acts of intercourse (0, 1, 2, 3 etc)	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>						
3. Male condoms	M T W T F S S	M T W T F S S	M T W T F S S	M T W T F S S	M T W T F S S						
(a) Number used	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>						
(b) no problem	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>						
(c) slipped off	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>						
(d) broke	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>						
4. Female condom	M T W T F S S	M T W T F S S	M T W T F S S	M T W T F S S	M T W T F S S						
(a) Number used	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>						
(b) no problem	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>						
(c) slipped off	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>						
(d) broke	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>						
(e) pushed into vagina	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>						
(f) penis inserted outside condom	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>	<input style="width: 20px; height: 20px;" type="checkbox"/>						
Last day of diary					<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; text-align: center;">day</td> <td style="width: 20px; text-align: center;">month</td> <td style="width: 20px; text-align: center;">year</td> </tr> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table>	day	month	year			
day	month	year									

Why adapted WHO coital log was used in FC1/FC2 trial

- One page format log was simple to use and easy to understand, some women only had primary education
- Used in multi-centred international trials including the WHO 4-centre pregnancy efficacy trial & RHRU staff had gained experience in using this log
- Women returned at similar intervals to WHO trial to complete interviews/questionnaires for the data base

Differences in logs

- We removed the term “slipped off” from the log as it was misunderstood in the WHO efficacy study.
- “Slipped off” is a male condom definition
- “Slipped off” was noted in the WHO study when FC was inserted like a male condom on the penis, which is not a clinical failure.

Slippage definition for FCs

- Slippage definitions for FC have changed over time and at the time this study was conducted(2003): no clear published definition of clinical failure

- FC slippage definitions at that time included :
 - Moving in and out e.g. riding the penis like a male condom

 - FC comes out and penis comes out of FC

 - FC comes out still covering the male penis

Slippage definition for FCs

Partial Slippage

WHO technical review established that as long as FC continues to cover the penis, it is not technically a clinical slippage failure.

Complete Slippage

Slippage is defined as a clinical failure when FC slips completely out of the vagina during intercourse.

(World Health Organization: Female Condom Technical review committee, 2007

who.int/reproductive-health/publications/fc2/fc2report.pdf)

Questionnaire Statement

- Q307 : Did the female condom stay in place every time during intercourse?
1= Yes, every time
2= No
3= Not sure
- If answer is 1 go to 309 If no, what happened?

Women who said they felt the condom moved were asked to detail “what specifically happened”. This is where ALL the movement problems were probed. Additional information on not only slippage but invagination and misdirection was gained. This was in addition to the specific questions on invagination, misdirection and breakage detailed later in the interview.

Typical Slippage Responses

“Slipped out twice from the vagina during sex”

“The condom was pulled out during sex and we inserted a new one”

Questionnaire

- After 10 uses of each type of condom women returned to the site to complete a questionnaire relating to:
 - Problems/failure modes on using device
 - Details regarding whether the device stayed in place during use (slippage, invagination, misdirection)
 - Specific features relating to the ease of insertion and removal, fit, and comfort
 - Overall preference for either condom type
 - Partners experience with the condom types

Study Results

- 289 women screened, 276 enrolled;
 - 233 used only one type of condom
 - 201 completed the study (used both condoms)

- 3791 female condoms used:
 - 1910 FC1; 1881 FC2

- Total of 194 failures(5% of total used) recorded; 88% recorded < 30 days of use

Data Collection

- Coital log and Questionnaire complementary – standard practice
- Questionnaire completed in one-on- one interviews, referencing coital log
- Events clarified:-
 - ▣ Invagination probed for complete (clinical failure) or partial.
 - ▣ Tears - site and reason for tears –all documented
 - ▣ Asked “did condom stay in place”; if the answer was no, interviewer probed what exactly happened.

Results: FC1 and FC2 Female Condoms

Criteria	FC1			FC2			Difference in P per condom use (%)	95 % CI	
	Condom			Condom				Lower (%)	Upper (%)
	No.	Total ¹	P (%)	No.	Total ¹	P (%)			
Breakage									
Total breakage	14	1915	0.73	16	1889	0.85	0.12	-0.64	0.87
Clinical breakage	9	1910	0.47	8	1881	0.43	-0.05	-0.62	0.53
Non-clinical breakage	5	1915	0.26	8	1889	0.42	0.16	-0.21	0.53
Misdirection	24	1910	1.26	12	1881	0.64	-0.62	-1.33	0.09
Invagination									
Total outer ring displacement	60	1910	3.14	56	1881	2.98	-0.16	-1.24	0.91
Completely displaced	10	1910	0.52	17	1881	0.90	0.38	-0.25	1.01
Partially displaced	50	1910	2.62	39	1881	2.07	-0.54	-1.50	0.41
Slippage									
Complete slippage	4	1910	0.21	2	1881	0.11	-0.10	-0.39	0.19
Partial slippage	3	1910	0.16	3	1881	0.16	0.00	-0.25	0.26
Total clinical failure ²	47	1910	2.46	39	1881	2.07	-0.39	-1.67	0.89

P = Proportion with event

¹ The total number of uses for clinical breaks, slippage, incorrect penetration and displacement outcomes excludes uses for which non-clinical breaks were reported.

² Total clinical failure is defined as having any of the following outcomes: clinical breakage, incorrect penetration, outer ring completely displaced or complete slippage.

Study Conclusion

Based on the results of our study
FC1 and FC2 are
functionally equivalent.

Literature Review

Breakage rates in RHRU and other studies

- Clinical break/tear RHRU study
 - **0.47%** FC1, **0.43%** FC2.

- Valappil et al **0.11%** (7985 condoms)
- Macaluso et al **0.7%** (2232 condoms)
- Jivasak- Apimas et al **0.6%** (2285 condoms)
- Sinpisut et al **1.3%** (1068 condoms)

NB Comparison made with studies using at least 1,000 condoms

Invagination rates in RHRU and other studies

- RHRU sub-divided invagination into full and partial* - (3791 condoms).

FC1 complete 0.52%, partial 2.62% total **3.14%**

FC2 complete 0.9%, partial 2.07% total **2.97%**

- Valappil et al **2.8%** (7985 condoms)
- Macaluso et al **3.0%** (2232 condoms)
- Jivasak-Apimas included invagination and slippage as one figure **5.3%** (2285 condoms)

NB Comparison made with studies using at least 1,000 condoms

* Other studies have not differentiated between complete and partial invagination

Slippage rates in RHRU & other studies

- Definition of slippages varies from study to study
- RHRU rates :
 - FC1 Complete 0.21%, partial 0.16% **total 0.37%**
 - FC2 Complete 0.11%, partial 0.64% **total 0.64%**
- Valappil et al **2.8%** (7985 condoms)
- Macaluso et al **6.0%** complete, **7.0%** partial (2232 condoms)
- Jivasak-Apimas included invagination and slippage as one figure **5.3%** (2285 condoms)
- FC1 PMA: included invagination and slippage as one figure in 2 separate studies: **2.05%** and **2.7%**

Misdirection rates in RHRU and other studies

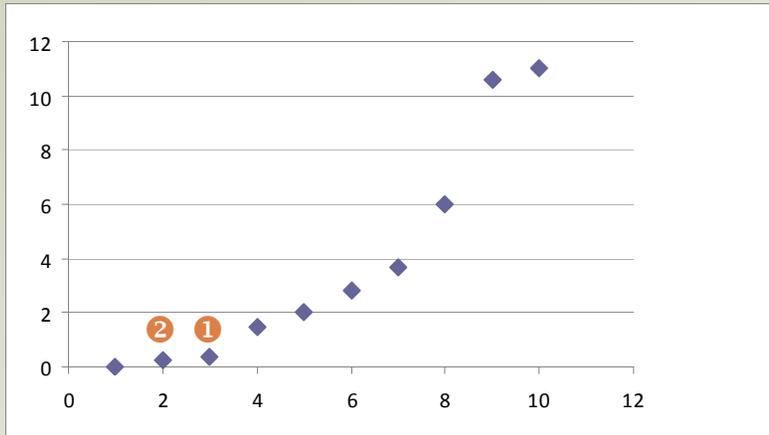
- Misdirection as a failure mode has not been reported consistently in the literature.
- RHRU rates :- FC1 **1.6%**, FC2 **0.64%**
 - Valappil et al **not reported** (7985 condoms)
 - Macaluso et al **2.0%** (2232 condoms)
 - Jivasak-Apimas **not reported** (2285 condoms)
- NB Comparison made with studies using at least 1,000 condoms

Total clinical failure in RHRU & other studies

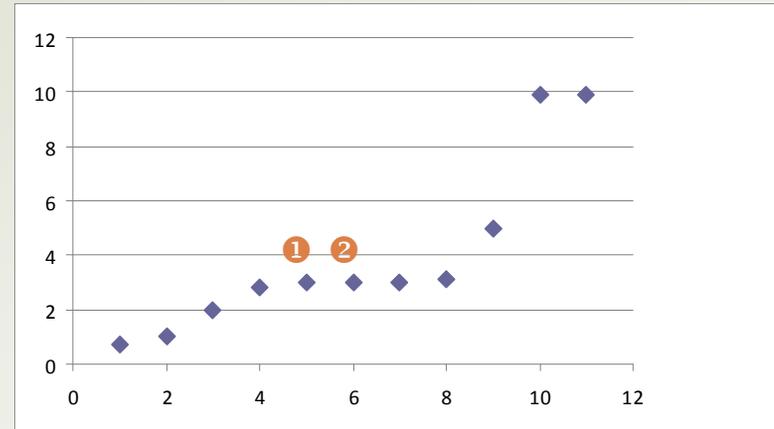
- RHRU rates :-
 - FC1= 2.46%, (5.08% with partial invag)
 - FC2 = 2.24%, (**4.31%** with partial invag)

- Valappil et al **5.7%** (7985 condoms)
- Macaluso et al **7.0%** (2232 condoms)
- Jivasak-Apimas not determined (2285 condoms)

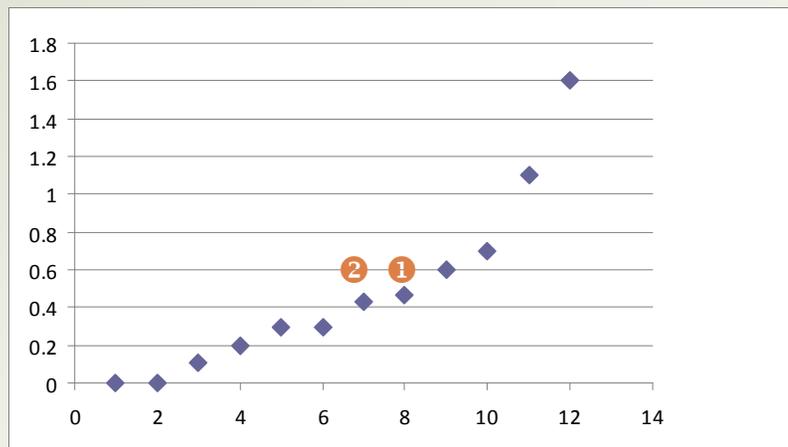
Total Slippage



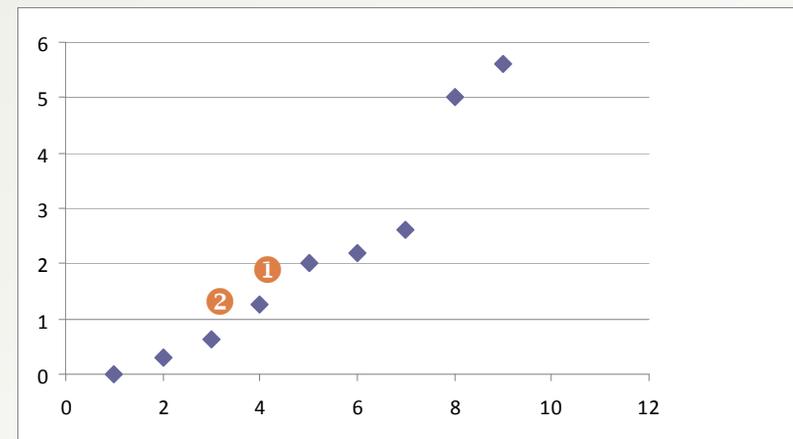
Invagination



Breakage



Misdirection



Literature Review: Conclusions

- Breakage and total clinical failure rates are consistent across studies irrespective of investigator or study population.
- Variance in slippage rates between studies may be indicative of which definition of slippage was used.
- Misdirection has not been reported consistently.
- As with male condoms FC failure is catastrophic and memorable.

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FDA Points Raised

- Contraception Study ?
 - Value added/information gained does not justify the delay (~ 5 years)

- Robustness of FC2 device
 - RHRU study showed FC2 comparable to FC1
 - FC1 performed/same results as it did in the failure mode studies supporting its PMA approval in 1993

- Protocol Adequate?

Points Raised:

- Coital log vs. one-on-one interviews – complementary
- Recall:
 - **4 weeks standard return**; RHRU ave. **<30 days**
 - **194** failures in >3800 uses;
 - **84 of 194** were additional failures identified thru one-on-one interviews
 - **34 of the 84** were from participants **using** coital logs, e.g. not noted on coital logs
 - Recall at >30 days similar % of problems compared with and without logs

Points Raised cont'd

Slippage:

- Noticed and remembered
- Unusual occurrence
- 12 reports of slippage (6 complete; 6 partial):
 - 3 no logs; 9 with logs
 - 4 reports (partial slippage/non-clinical) - reported between 31 – 40 days post use

Slippage is remembered

Points Raised

- Multiple Sex Acts/Given Day – one slot/day
 - 1500 days sex reported on log
 - multiple sex in ~50% (~750)
 - 75 multiple sex days reported problems
 - Number of problems noted on log
 - 47 one act/day
 - 86 >one act/day -- 65% of total
- Problems are noted and remembered

NB: if more than one event occurred/condom, all recorded; normal practice is to only note one.

Points cont'd

- No coital logs
 - Users remember failure and interviews resulted in more information gained
 - Rates of failure the same, with or with coital logs

Points Raised cont'd

□ Inclusion of CSWs

- CSWs do and will use FC so should be included in the study: representative group
- 88% of CSWs were new users
- 93% of all participants were new users
- No meaningful rate differences with or without CSWs
- MC use very different from FC use

Points Raised

- Blinded

- Users and nurses not told which device was used
- FC1 has a seam; FC2 does not: can't fully mask
- Prior users might remember; if seam mentioned in interview then nurse would know
 - 19 of 276 women had used FC at least 1x
 - 9 of them reported a problem:
 - 3 CSWs, 1 student, 3 City clinic, 2 STI

Points -- Summary

- We do not believe that a contraception study would give meaningful information to justify delaying approval given the time required to complete and gain FDA approval (5 or more years)
- FC2 is robust as demonstrated in the RHRU study – failure modes results showed FC2 comparable to FC1
- The RHRU study is adequate to demonstrate functional comparability. The total clinical failure rates for FC1 in the RHRU study were similar to the total clinical failure rates for FC1 studies reported in the literature as well as the FC1 failure mode studies in the FC1 PMA approved in 1993.

Doug Taylor, PhD
Director of Biostatistics
Family Health International

Background

- Interest lies in assessing true differences in complete slippage, clinical breakage, invagination, and misdirection rates between FC2 and FC1
- Statisticians compute confidence intervals for true differences; plausible range of values based on data observed in the trial
- For female condom, no established standard for acceptable range of values exists
- Epidemiological, regulatory and procurement decisions guided by observed confidence intervals

All Study Data

	Observed Rates			95% CI
	FC2	FC1	Diff.	
Slippage	0.11%	0.21%	-0.10%	(-0.39%, 0.19%)
Breakage	0.43%	0.47%	-0.05%	(-0.62%, 0.53%)
Invagination	0.90%	0.52%	0.38%	(-0.25%, 1.01%)
Misdirection	0.64%	1.26%	-0.62%	(-1.33%, 0.09%)
Total failure	2.07%	2.46%	-0.39%	(-1.67%, 0.89%)

Inclusion of Sex Workers

- Extensive experience with condoms could lead to perfect use and few or no condom failures
- If no failures observed then no information to compare condom performance, FC2 versus FC1
- If failures observed among novice users but not experienced users then might conclude a learning effect, with performance improving over time
- Enrolling a heterogeneous population (e.g., CSWs) is an advantage, so long as failures are observed

Excluding Sex Workers

	Observed Rates			95% CI
	FC2	FC1	Diff.	
Slippage	0.07%	0.27%	-0.20%	(-0.55%, 0.15%)
Breakage	0.54%	0.54%	0.00%	(-0.73%, 0.73%)
Invagination	0.88%	0.48%	0.41%	(-0.27%, 1.09%)
Misdirection	0.68%	1.63%	-0.95%	(-1.84%, -0.06%)
Total failure	2.18%	2.92%	-0.74%	(-2.29%, 0.81%)

Accuracy of Condom Failure Data

- FDA has expressed concern that relying on in-depth interviews rather than coital logs could have led to misreporting of failure rates
- Given complexity of failure modes, questionnaire based on in-depth interviews was essential to a successful trial
- Even if misreporting did occur, misreports of ever having experienced a failure unlikely

Per-Woman Analysis

	Women with events	
	FC2	FC1
Slippage	2 (0.9%)	3 (1.4%)
Breakage	7 (3.2%)	5 (2.3%)
Invagination	11 (5.1%)	8 (3.7%)
Misdirection	11 (5.1%)	19 (8.7%)
Any clinical failure	25 (11.6%)	33 (15.1%)

Note on Effectiveness Studies

- Functionality studies evaluate rates of condom failure during actual use
- Effectiveness studies evaluate pregnancy rates over many months/cycles of typical use

Observed pregnancies rates impacted more by condom non-use than condom failure during use

Use of other methods (e.g., emergency contraception) further shrinks apparent differences in pregnancy rates

Cannot expect true differences in condom failure will translate into detectable differences in pregnancy rates

Statistical Summary

- Strong statistical evidence that FC2 and FC1 are comparable in clinical performance
- Multiple subgroup analyses (e.g., excluding CSWs, first use period vs. second) lead to consistent findings
- Proportion of women ever reporting clinical failure also comparable between FC2 and FC1
- Effectiveness study unlikely to identify meaningful differences in condom function between FC2 and FC1

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Summary

- FC2 developed using standard principles – least burdensome approach
 - ▣ Ensured material was effective barrier
 - ▣ Ensured it was safe and biocompatible
 - ▣ Ensured we can make it consistently
 - ▣ Performed a comparative study to FC1

- Research showed
 - ▣ FC2 is safe
 - ▣ FC2 failure rates equivalent to FC1 failure rates
 - ▣ FC1 in RHRU study performed similar to FC1 in PMA failure mode studies supporting its approval

Summary cont'd

- We believe that the studies already completed are appropriate and adequate to establish FC2 is safe and effective.
- FC2 is an important method for STI protection and contraception outside the United States.
- FDA approval of FC2 will expand its use by additional women who need and want it in the U.S. and developing countries.
- An effectiveness study is unlikely to add to our understanding of the performance of FC2.

