



Obstetrics & Gynecology Devices Panel

FDA advisory committee meeting
December 11, 2008



Today's Agenda: PMA for a Female Condom

- Regulatory Overview of Condoms
- Condom Failure Modes Studies
- Today's PMA – Introduction



Device Classification

- Class I (General Controls)
- Class II (Special Controls)
- Class III (Premarket Approval)

pre-Amendments (May 28, 1976)



Condoms: Regulatory Overview

- **Class I: common, low risk devices**
General controls (most exempt from premarket submission)
- **Class II: more complex, higher risk**
General Controls, including premarket notification [510(k)]
Special Controls (guidances, standards, clinical studies, etc.)
- **Class III: most complex, highest risk**
Premarket Application [PMA]
supported by data: wide range, incl. clinical studies



Male Condoms

- pre-Amendments status
 - many male condoms on market before 1976
 - Panel recommendation:
 - safe and effective with Class II controls

1981 FDA classifies male condoms into Class II



510(k) Premarket Notification

substantial equivalence (“me too”)

- ⇒ in terms of safety & effectiveness
- ⇒ predicate device for comparison
- ⇒ with respect to intended use and design



male condoms: *developments since classification*

- preclinical characterization of condoms
- clinical studies (performance during actual use)



Condoms: Regulatory Overview

male condoms – preclinical studies

- physical properties: test methods and benchmarks
 - tensile properties
 - airburst properties
 - water leak testing (for QA release)
- barrier properties: viral penetration assay
- expiration date: shelf-life test protocol

⇒ performance standards, an evolving process



male condoms – human studies

- STI protection
- contraception
- failure mode studies: slippage & breakage during use



human studies: STI protection

- Hundreds of studies of the male condom
 - different trial designs
 - different STIs
 - varying quality
- Conclusion:
 - male condoms work very well
 - degrees of protection, depending on the specific STI



human studies: contraceptive protection

- pre-Amendments

clinical experience: long history of safe & effective usage

- since classification

CDC surveys (NSFG)

three contraceptive efficacy studies



Condoms: Regulatory Overview

contraceptive trials of male condoms, 6-months reliance
pregnancy rates given in percent

	<i>perfect use</i>		<i>typical use</i>	
	NRL	syn	NRL	syn
Frezieres (1999)	1.1	2.4	6.3	4.8
Steiner (2003)	--	--	5.4	9.0
Walsh (2003)	1.0	4.9	6.4	10.8



male condom, contraceptive effectiveness†
one-year of reliance

- 'perfect' use 2%
- 'typical' use 15%

†from *Contraceptive Technology* (2007)



Male condom – current status

- Class II (Special Controls)
- 510(k) pathway to market
- made from natural rubber latex - standards
- made from synthetic material - clinicals



Female Condoms



Female Condoms

pre-Amendments status

- ID'd one pre-1976 female condom
 - no data available on safety and effectiveness*
- 1988 panel recommendation: Class III
- FDA classified female condoms into Class III



Class III (Premarket Approval)

- ✓ submit PMA application to FDA
- ✓ show safety & effectiveness, “reasonable assurance”
- ✓ valid scientific evidence
- ✓ with respect to:
 - target population
 - prescribed conditions of use (labeling)
 - benefit vs. risk



Female Condoms

1991 1st PMA for female condom (FC1)

– preclinical studies

– human studies

small feasibility studies

6-month contraceptive study

1993 FDA approved PMA for FC1



Female Condoms

1993 FDA approval of FC1

6-month single-arm contraceptive study, US data

	<i>'perfect use'</i>	<i>'typical use'</i>
6-month	2.5%	12.4%
one-year (estimate)	5%	21%

Panel: reasonable assurance S&E, mitigating labeling



1993 approval of female condom, mitigating labeling

- Latex condoms for men are highly effective.
- If not using a male condom, use a female condom for protection.
- Use every time you have sex.
- Before you try it, read instructions.



female condom – current status

- Class III (Premarket Approval)
- PMA pathway to market
- only one approved PMA



Condom Failure Mode Studies

What is a failure mode?

1. acute mechanical failures
2. noted by user at time of sex
 - slippage during use
 - breakage during use



Standardized Protocols for Condom Breakage and Slippage Studies: A Proposal

*M Steiner, J Trussell, L Glover, C Joanis, A Spruyt, and L Dorflinger
Am J Public Health. 1994; 84:1997-2000*

- Steiner *et al* noted the wide variation in trial design, execution, and analysis; results from such studies cannot be readily compared.
- concluded that trial design needs to be standardized
- identified several areas where standardization would be useful



Selection of Study Subjects

- Use of back-up contraception, low STI risk: these subjects may not use condoms with the same care as typical user
- Condoms break more often during anal sex: need to distinguish anal sex from vaginal sex
- Commercial sex workers break condoms *less* frequently: need to distinguish CSWs from general population
- No condom experience, tend to break condoms *more* frequently: need to distinguish experienced from inexperienced



Definitions, Questionnaires

- Standardized definitions for slippage and breakage; differentiate “clinical” from “nonclinical” events
- Precise wording of questions to minimize bias leading to under-reporting events
- Caution against relying on retrospective data, even if recall is confined to last year or even last month



Other

- Use of lubricants
- Penis size/condom size
- “clustering”: condoms failures tend to occur more often for a smaller subgroup
- Condom quality: document date of manufacture; test sample of condoms to be used in study



Failure Mode Studies Today

- two failures modes ID'd during sex, male condoms

slippage

breakage

- prospective, cross-over, randomization
- user reports (coital diary), prompt data entry
- study size, based on non-inferiority test and expected event rates (1-2%)
.....typically $200 \times 5 \times 2 = 1000$ uses of each condom type



Condom Failure Mode Studies

- male condom: at least 12 high quality studies
 - prospective, randomized, properly powered, well-designed
- mostly randomized: NRL vs. synthetic
- good stability in event rates, esp. for NRL
 - slippage: ranges from 0.4 to 1.3%
 - breakage: ranges from 0.5 to 2.0 %

male condoms, failure mode studies

What have we learned?

- selection of study subjects
 - literacy, motivation, condom experience, multiple acts/day
- instruction of subjects re: protocol/compliance
- design of coital log
- promptness of data entry

male condoms, failure mode studies

Where is it going now?

- industry & regulatory bodies moving toward international standard, in draft
- follows non-inferiority model
 - Δ of 2% for each failure mode
 - now moving towards Δ of 2.5% for failure mode total



Female Condoms: Failure Mode Studies

what do human studies show?

four failure modes, during use

- **breakage**
- **slippage** (slip-out)
- **invagination** (slip-in)
- **mis-direction** (mis-routing, penile mis-direction)



Condom Failure Mode Studies

FC1 failure mode event rates, selected from earlier studies

		breakage	slippage (slip-out)	misdirection	invagination (slip-in)	total
1	Macaluso <i>et al</i> (2003) n = 175♀	0.7%	6%	2%	3%	11.7%
2	Galvao <i>et al</i> (2005) n=400♀	---	---	---	---	6%
3	Valappil <i>et al</i> (2005) n = 869♀	0.11%	2.8%	---	2.8%	5.6%
4	Chen <i>et al</i> (2007) UAB (n=108♀) UNICAMP (n=400♀)	0.2%	11%	0.3%	5%	16.5%
		0.3%	2%	5%	1%	8.3%
5	Macaluso <i>et al</i> (2007) n = 108♀	0.3%	10.6%	5.6%	3.0%	19.5%



female condoms, failure mode studies

What have we learned?

- more complex picture
- breakage stable across studies
- more variability for other failure modes
- importance of careful study design to ensure reliable user reporting



female condoms, failure mode studies

Where is it going now?

- industry & reg bodies moving toward international standard (in draft)
- follows non-inferiority model (Δ of 3%)
- use of biomarkers
(promising, but not sufficiently validated)



Today's Challenge

PMA for new version of female condom



possible reasons to bring PMA to panel

- new device, new review issue(s)
- controversial
- need for special expertise

Special Expertise Needed

- Clinical Trials Design & Execution - Condoms
 - Contraception
 - STI risk reduction
 - acute failure modes
- Practical problems with Clinical Trials
 - Patient-reported outcomes (uniform training, timely completion of CRFs)
 - Subject Compliance with Protocols
 - Drop out, lost-to-follow-up
 - Use of male condoms
 - Problems interpreting contraceptive studies (non-compliance, use of EC)
- International perspective
 - non-US studies
 - public health impact, worldwide



FDA review policy for female condoms

current approach, unchanged since 1993 FC1 approval

- ◆ single-arm, 6-month contraceptive study
- ◆ no STI study, but mitigating labeling

⇒ today's PMA does not fit FDA's current paradigm



today's PMA

- ◆ focus on acute mechanical failure, comparison to FC1
- ◆ contraceptive & STI protection inferred from original FC1
- ◆ sponsor: reasonable assurance of safety & effectiveness
- ◆ will keep mitigating labeling



FDA looking for panel's help:

What data is sufficient to show
reasonable assurance of safety &
effectiveness?

The international perspective

Female condoms are a small part of the condom market, but ...

- offer an additional option for barrier protection as part of the overall condom distribution offerings around the world, esp. in high HIV prevalence areas
- 3rd party donors of condom products around the world are keenly interested in whether FDA has approved a product for market in the US.



Thank you!