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
Condoms: Regulatory Overview

male condoms: developments since classification

– preclinical characterization of condoms
– clinical studies (performance during actual use)
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
## Contraceptive trials of male condoms, 6-months reliance

Pregnancy rates given in percent

<table>
<thead>
<tr>
<th></th>
<th>perfect use</th>
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<th>typical use</th>
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<td>NRL</td>
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<td>Frezieres (1999)</td>
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<td>Steiner (2003)</td>
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<td>Walsh (2003)</td>
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<td>4.9</td>
<td>6.4</td>
<td>10.8</td>
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</table>
Condoms: Regulatory Overview

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
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

<table>
<thead>
<tr>
<th></th>
<th>‘perfect use’</th>
<th>‘typical use’</th>
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<tbody>
<tr>
<td>6-month</td>
<td>2.5%</td>
<td>12.4%</td>
</tr>
<tr>
<td>one-year (estimate)</td>
<td>5%</td>
<td>21%</td>
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</table>

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
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 x 5 x 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
  – \( \Delta \) of 2% for each failure mode
  – now moving towards \( \Delta \) of 2.5% for failure mode total
Female Condoms: Failure Mode Studies

what do human studies show?

- breakage
- slippage (slip-out)
- invagination (slip-in)
- mis-direction (mis-routing, penile mis-direction)
### Table of Condom Failure Mode Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Breakage</th>
<th>Slippage (slip-out)</th>
<th>Misdirection</th>
<th>Invagination (slip-in)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macaluso <em>et al</em> (2003)</td>
<td>0.7%</td>
<td>6%</td>
<td>2%</td>
<td>3%</td>
<td>11.7%</td>
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<td>Galvao <em>et al</em> (2005)</td>
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<td>6%</td>
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<tr>
<td>Valappil <em>et al</em> (2005)</td>
<td>0.11%</td>
<td>2.8%</td>
<td>---</td>
<td>2.8%</td>
<td>5.6%</td>
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<tr>
<td>Chen <em>et al</em> (2007) UAB (n=108) UNICAMP (n=400)</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>Valappil <em>et al</em> (2005)</td>
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<td>2%</td>
<td>5%</td>
<td>1%</td>
<td>8.3%</td>
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<tr>
<td>Macaluso <em>et al</em> (2007)</td>
<td>0.3%</td>
<td>10.6%</td>
<td>5.6%</td>
<td>3.0%</td>
<td>19.5%</td>
</tr>
</tbody>
</table>

*FC1 failure mode event rates, selected from earlier studies*
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 ($\Delta$ 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
PMA for FC2 female condom

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?
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!