Contraceptive Technology Update

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E2A

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TOPICS:

- Rationale for Family Planning
- Preventing Abortion
- Priorities in Contraceptive Technology
- Contraceptive Effectiveness
- Existing/Current Contraceptive Technology, including some newer methods:
  - Male Condoms
  - Female Condoms and New Woman’s Condom and SILCS/Caya Diaphragm
  - Implants
  - Injectables including Sayana Press
  - IUDs including the LNG-IUS and new products
  - Oral Contraception and Emergency Contraception
  - Fertility Awareness Methods
  - Permanent Methods
- New Contraceptive Vaginal Ring (NES/EE CVR)
- New Contraceptive Methods Needed
  - Biodegradable Implants
  - Multipurpose Prevention Technologies
- 110 Technologies Identified in the Global R&D Pipeline
Family Planning: Responds to a panoply of problems

- Enables couples to decide number/spacing of births
- Reduces child mortality
- Reduces maternal mortality/morbidity
- Reduces abortion
- Improves women’s opportunities
- Key intervention in HIV settings
- Essential component of health programs
- Mitigates adverse effects of population dynamics on:
  - natural resources
  - environment and climate change
  - economic growth
  - state stability
  - Infectious diseases (zoonotic)
Link Between FP and Preventing Abortion

...we are united in our determination to prevent unintended pregnancies, reduce the need for abortion, and support women and families in the choices they make.

-- Barack Obama January 22, 2009
Percent of Married Women Using Modern Contraception

Abortions per Woman

Georgia
Azerbaijan
Armenia
Romania
Belarus
Kyrgyzstan
Ukraine
Uzbekistan
Russia
Moldova
Hungary
Estonia
Turkmenistan
Westoff, 2003
Priorities in Contraceptive Technology

Concerning contraceptive technology, the priorities for preventing unintended pregnancies are:

- Expand access to, and availability of, a wide range of existing contraceptive methods in the public and private sectors, in facilities/clinics and in non-clinical and community-based programs.

- Tinker with existing methods to make them easier to use, easier to deliver, less expensive, and/or more acceptable, sometimes referred to as “adaptive technologies.”

- Develop totally new technology that is viewed by programs as filling a vital function that cannot be met by existing or adaptive technologies.
Effectiveness of contraceptive methods in typical use:

“Not all contraceptives are the same” [1]

<table>
<thead>
<tr>
<th>Method</th>
<th># of unintended pregnancies among 1,000 women in first year of typical use</th>
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<tbody>
<tr>
<td>Implant</td>
<td>0.5</td>
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<tr>
<td>Vasectomy</td>
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<tr>
<td>Female sterilization</td>
<td>5</td>
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<tr>
<td>IUD (Cu-T / LNG-IUS)</td>
<td>8 / 2</td>
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<tr>
<td>Injectable (Depo-Provera)</td>
<td>60</td>
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<tr>
<td>Pill</td>
<td>90</td>
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<tr>
<td>SDM</td>
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<td>Male condom</td>
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<tr>
<td>Female condom</td>
<td>210</td>
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<tr>
<td>Withdrawal</td>
<td>220</td>
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<tr>
<td>No method</td>
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</table>

Male Condom

**Brand Names:** Various (e.g. Prudence, Blue/Gold, Panther)

**Logistics:** Shelf life: 5 years

**Unit cost:** $0.03

**How it works:** A sheath usually made of latex that covers the erect penis and serves as a physical barrier to semen and disease organisms from entering the vagina during intercourse

**Effectiveness:** Effective (98%) when used correctly and consistently every time. Somewhat (85%) effective as typically used

**Benefits:** Prevents pregnancy and HIV/STIs; safe/no hormonal side effects; can be started & stopped anytime; can be used without guidance from health professional

**Considerations:** Allergies to latex or lubricant; requires constant supply; requires male cooperation; must be used consistently & correctly to be effective
YOU WANT ME TO PUT WHAT WHERE?!
Female Condoms

Brand Names: FC2

Logistics: Shelf life: 3 years; Unit cost: $0.55

How it works: A sheath or lining made of thin, transparent plastic film that fits loosely inside the vagina that forms a physical barrier to sperm and disease organisms from entering the vagina

Effectiveness: Effective (95%) when used correctly and consistently. Less effective (79%) as typically used

Benefits: Prevents pregnancy and HIV/STIs; safe/no hormonal side effects; can be started & stopped anytime; can be used without guidance from health professional; use initiated by woman

Considerations: Requires constant supply; must be used consistently & correctly to be effective; requires some practice to use
Woman’s Condom

- Easy to handle/use, insert and remove
- Stable during use
- Comfortable for both partners
- Less expensive than current options
Product Features

- Manufactured by Dahua (China – not same company as for SI-II)

- U.S. clinical trials (2011-2012) will lead to FDA product registration – estimated for 2013

- CE Mark application planned for 2011
SILCS (Caya) Diaphragm: “One size fits most”

- Firm insertion edge w/ soft spring in rim for improved comfort
- Cervical cup membrane
- Silicone rather than latex
- Appropriate for OTC use
- No pelvic exam or fitting required

US CT completed in 2010
USFDA approval in 2012
Implants

**Brand Names:** Jadelle, *Implanon, Sinoplast*

**Logistics:** Shelf/Use life: 3-5 years; Unit cost: $8.50

**How it works:** Rods inserted under skin in upper arm release progestin (hormone) that prevents ovulation and thickens cervical mucus

**Effectiveness:** Jadelle and Implanon are the brands currently purchased by USAID; is highly effective (99%) for five years of use

**Benefits:** Long acting (3-5 yrs); low maintenance; immediate return to fertility upon removal; safe for breastfeeding mothers; no one can tell woman is using it; Implanon is effective for 5 years

**Considerations:** No protection against HIV/STIs; changes in bleeding patterns; minor side effects in some users; must be inserted/removed by trained provider; less effective if used with drugs affecting liver or for seizures
Zarin® (Sino-implant II)

- Subdermal Contraceptive Implant
## Comparison of Hormonal Implants

<table>
<thead>
<tr>
<th></th>
<th><strong>Jadelle</strong></th>
<th><strong>Implanon</strong></th>
<th><strong>Sino-implant (II)/Zarin</strong></th>
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<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Bayer Healthcare</td>
<td>Merck/MSD</td>
<td>Shanghai Dahua Pharmaceutical Ltd.</td>
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<tr>
<td><strong>Formulation</strong></td>
<td>150 mg levonorgestrel in 2 rods</td>
<td>68 mg etonogestrel in 1 rod</td>
<td>150 mg levonorgestrel in 2 rods</td>
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<tr>
<td><strong>Mean Insertion &amp; Removal time</strong></td>
<td>Insertion: 2 min Removal: 5 min</td>
<td>Insertion: 1 min Removal: 2-3 min</td>
<td>Insertion: 2 min Removal: 5 min</td>
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<tr>
<td><strong>Labeled duration</strong></td>
<td>5 years</td>
<td>3 years</td>
<td>4 years</td>
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<tr>
<td><strong>Trocars</strong></td>
<td>Autoclavable and Disposable</td>
<td>Pre-loaded disposable</td>
<td>Disposable</td>
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<tr>
<td><strong>Cost of implant (US$)</strong></td>
<td>$8.50</td>
<td>$8.50</td>
<td>$8.50</td>
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<tr>
<td><strong>Cost per Year (if used for duration)</strong></td>
<td>$1.70</td>
<td>$2.83</td>
<td>$2.13</td>
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<td><strong>WHO Prequal</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Application submitted</td>
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1 FOB price in country of origin.
**INJECTABLES**

**Brand Names:** Depo-Provera/ DMPA; Noristerat (NET-Enanthate) and Cyclofem (combined monthly injectable) not procured by USAID

**Logistics:** Shelf life: 5 years; Unit cost: $0.80

**How it works:** An intramuscular injection given every 3 months that releases a progestin (MPA) that prevents ovulation and thickens cervical mucus. Subcutaneous version available, and Sayana Press is being launched in LDCs

**Effectiveness:** 99.7% effective over three month period; re-injection should occur within two weeks before or four weeks after the three-month mark

**Benefits:** Long acting (3 months); low maintenance; safe for breastfeeding mothers; no one can tell woman is using it; beneficial non-contraceptive effects

**Considerations:** No protection against HIV/STIs; delay in returning to fertility (average 10 months from last injection); changes in bleeding patterns including amenorrhea; minor side effects; potential issues with bone loss; and concern about increase in HIV Acquisition yet WHO has not changed guidance on use
Will Sayana Press be a “Game-Changer?”

Potential “home run”

Depo-subQ Provera 104:
◆ New formulation for subQ injection
◆ 30% lower dose (104 mg vs. 150 mg)
◆ Rapid onset of action
◆ Same effectiveness, same length of protection (>3 months)
◆ Approved by USFDA (2005) and EMA/UK

Uniject:
◆ Single dose, single package
◆ Prefilled, sterile, non-reusable
◆ Short needles for subQ injection (easier use by non-clinical personnel/CHWs)
◆ Compact; easy to use and store
◆ Potential for home- and self-injection
◆ Approval by EMA and LDC registration forthcoming
The LD Formulation of Depo-Provera Is Efficacious at Lower Peak Concentrations

Pharmacokinetic Profiles of the LD Formulation of Depo-Provera and Depo-Provera Contraceptive Injection

LD = lower dose.

Data on file.
INTRAUTERINE DEVICE (IUD)

Brand Names: Optima (Model TCu380A) ; numerous similar devices available

Logistics: Shelf life: 7 years; Use life: 10-14 years; Unit cost: $0.63

How it works: A small plastic T-shaped object containing copper is inserted in the uterus. The copper creates a hostile environment for sperm. There is also a progestin-releasing IUD (Mirena or LNG-IUS) not procured by USAID

Effectiveness: IUDs are more than 99% effective in preventing pregnancy

Benefits: One action leads to long-term protection (at least 10 years); low maintenance; no hormonal side effects; immediate return to fertility upon removal; safe for breastfeeding mothers; no one can tell woman using it; safe for use by HIV+ women and by nuliparous women and girls

Considerations: No protection against HIV/STIs; changes in bleeding patterns; must be inserted/removed by trained provider; may be associated with increased risk of Pelvic Inflammatory Disease (PID)
The Best of Both Worlds

Oral contraceptives

- Highly effective
- Reduction of menstrual loss
- Reduction of pelvic inflammatory disease

Intrauterine devices

- No daily motivation
- Long-acting
- Estrogen-free
- Rapidly reversible

Levonorgestrel intrauterine system
The levonorgestrel intrauterine system

- Rate-controlling membrane
- Hormone cylinder
- Uterine wall
- Section of system
- Levonorgestrel intrauterine system
- Detail
Change in hemoglobin during 5 years of use

- Levonorgestrel intrauterine system
- Cu IUD
Liletta - Newly Approved LNG-IUD
eloira
HORMONAL INTRAUTERINE CONTRACEPTIVE SYSTEM
**ORAL CONTRACEPTIVES (OCs)**

**Brand Names:** Microgynon, Combination 3, Micorlut (POP); numerous similar products and other products that are used for 3 months or for one year

**Logistics:** Shelf life: 5 years; Unit cost: $0.27 to $0.30/month

**How it works:** Daily pills. Either combined progestin and estrogen (COC), on progestin-only (POP). Release hormone(s) to prevent ovulation and thicken cervical mucus.

**Effectiveness:** OCs are 99% effective when used perfectly and 92% effective under typical use; POPs are slightly less effective for interval use and more appropriate for postpartum use.

**Benefits:** Safe; menstrual benefits; Immediate return to fertility; protection from ovarian & endometrial cancers; can be used for EC; decreased risk of PID

**Considerations:** No protection against HIV/STIs; requires daily administration; minor side effects; not suitable for women with liver or gall bladder problems; COC can reduce quantity & quality of breast milk; should not be used by women over 35 who smoke
EMERGENCY CONTRACEPTION (EC)
aka: “Morning After Pill”

How it works: Use of OCs (preferably a dedicated product of LNG 1.5g) within five days of unprotected sex to prevent pregnancy by preventing or delaying ovulation. Does not prevent implantation and cannot interfere with established pregnancy. Not intended to be used a primary method of contraception although it can be this purpose for women who have very infrequent sex.

Effectiveness: EC is 60 to more than 90% effective depending on when taken and the kind of EC.

Benefits: Safe; Easy to use; OCs are widely available; no clinic visit/physical exam required

Considerations: No protection against HIV/STIs; more effective when taken immediately after unprotected sex; minor short-term side effects esp. if COCs are used; should not be considered as a routine method.
Extent of Knowledge of EC

Legend – Purple (use) – Blue (some knowledge) – Red (not aware)
FERTILITY AWARENESS METHODS
(Standard Days Method, TwoDay Method, LAM)

Logistics: No cost for some methods; CycleBeads for SDM: $1.41

How it works: Enables woman to accurately determine the start and end of her fertility period. Also known as Natural Family Planning or Periodic Abstinence. Include both calendar-based (e.g. SDM) and symptoms-based methods (e.g. TwoDay, BBT, Billings, STM); calendar method/Rhythm is not program methods

Effectiveness: These methods are generally effective with perfect use (approx. 95%), but less effective with typical use (approx. 75-88%)

Benefits: These methods are generally effective with perfect use (approx. 95%), but less effective with typical use (approx. 75-88%)

Considerations: Very low cost/free; no material inputs; no side effects or invasive procedures; highly acceptable to some clients and providers; No protection against HIV/STIs; requires abstinence or barrier method (condoms) during fertile days; less forgiving of incorrect use; requires special counseling and the fertile period can be 10-12 days long.

LAM: 98% effective when all three criteria are met
PERMANENT METHODS
(Tubal Ligation and Vasectomy)

How it works: Female sterilization/tubal ligations (via, e.g., minilaparotomy or laparoscopy) blocks or severs the fallopian tubes preventing fertilization. Male sterilization/vasectomy closes off vas deferens, keeping sperm out of semen

Effectiveness: Provides life-long protection and are highly effective (>99%) although over 10 years TL is 98.2%

Benefits: Permanent; no side effects; reduce risk of PID

Considerations: No protection against HIV/STIs; Requires physical examination and surgery; possible complications of surgery; should be provided as not reversible
Nestorone® / Ethinyl Estradiol 1-Year Ring (CVR)

*Delivers NES/EE 150/15µg /day, 13 cycles 3 weeks on followed by 1 week off

*Developed by the Population Council
*Sponsored by USAID, NICHD, WHO

NES Core

8.4 mm (3/8”) in cross section

NES / EE Core

58 mm (2 1/4”) in diameter
The CVR is an effective, convenient, easily-used new contraceptive method

**Strengths**
- **Monthly ring-good for one year**
  - Daily action not required
  - Not coitus dependent
  - Eliminates need for repeated visits to doctor & pharmacy
- **Effective**
- **Lack of androgen effect**
  - Weight /lipids favorable
- **High level of user satisfaction**
- **Under a woman’s control**
  - She decides when to stop & start
  - No need for a trained health provider
  - Rapid return to fertility if desired

**Challenges**
- Medical risks & side effects similar to currently available hormonal contraceptives
- Additional safety requirements regarding effect of NCE on cardiac rhythm a new “requirement”- studies still to be done for NDA
- **NDA expected in 2016**
- Manufacturing process improvements underway but the product will still be too expensive to use in the public sector
- Totally new process needed to meet the requirement – it must be low cost ($5.00)!
Most trial participants were satisfied, found the CVR easy to use, would pay for it if available, recommend it to friends, and preferred it to other methods they have used (Results: N=861)
New Contraceptive Methods Needed

While tremendous success can be achieved by expanding access to existing methods, some additional methods would likely have immediate application if they were of low cost:

1. Non-hormonal, non-steroidal or non-estrogen or novel progestin-only oral contraceptives
2. Biodegradable progestin-only implants
3. Non-surgical methods of male and female sterilization
4. Novel multi-purpose/dual protection methods
5. Post-testicular methods for men
Biodegradable Contraceptive Implant – New Method Under Development

Picture shows actual size of Anterion Therapeutic’s injector and medicinal pellets. The area on the arm indicated by a circle and arrow illustrates the lack of scarring post implantation.
Aim: develop multipurpose prevention options that...

- Prevent unintended pregnancy
- Protect against HIV, other STIs & RTIs
- Provide additional health benefits

Our Ultimate Goal:
An expanded range of
- Effective
- Acceptable
- Accessible

prevention options that address the sexual and reproductive health concerns of women as they change over time.
TFV/Levonorgestrel (LNG) IVR: Segmented Reservoir Design

- Builds on the TFV-only reservoir IVR design
- Segmented approach allows for independent optimization of each drug’s delivery needs
- LNG release rate is controlled by:
  1. Rate-controlling membrane (thickness and diffusivity)
  2. Length of the LNG segment
TFV/LNG IVR: Product Design Objectives

- **Release Rates:**
  - TFV: 10 mg/d
  - LNG: 10 or 20 µg/d

- **Duration:** 90 days

- **Dimensions/Mechanical properties:**
  - Same as TFV IVR, similar to NuvaRing®
SILCS/Contraceptive TFV Gel

- Work funded by USAID #APS-OAA-10-000003: Fast-track Late-stage Development of MPTs

- Objectives:
  1. Develop the combination of SILCS diaphragm with TFV gel as a MPT with the potential to address multiple indications:
     1. Contraception
     2. HIV prevention
     3. HSV prevention
  2. Reformulate the TFV gel to enhance contraceptive efficacy
# 110 technologies identified in global R&D pipeline

<table>
<thead>
<tr>
<th>Discovery (Target ID, Screening, proof-of-principle)</th>
<th>Early Development (Pre-clin, Ph1, Ph2)</th>
<th>Late Development (Ph3)</th>
<th>Developing world registration/Launch</th>
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<tbody>
<tr>
<td><strong>Hormonal</strong></td>
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<tr>
<td>Female</td>
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<tr>
<td>- GnRH II receptor antagonists</td>
<td>DPV+LNG ring</td>
<td>Nestorone/E2 Vaginal Ring</td>
<td>Depo-subQ + Uniject</td>
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<td>- PC6-inhibitor</td>
<td>MIV-150+LNG ring</td>
<td>Nestorone/E2 transdermal gel</td>
<td>Gestrone and EE Patch</td>
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<td>- LIF and IL-11</td>
<td>TFV+LNG ring</td>
<td>Nestorone transdermal spray</td>
<td>BufferGel</td>
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<td>- SGK1/AKT</td>
<td>Estrol+ Progestin OC</td>
<td>LNG butanoate Biodegradable NET Pellets</td>
<td>Generic LNG IUS</td>
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<td>- Phosphodiesterase 3/5/9 inhb.</td>
<td>Single-rod gestodone implant</td>
<td>Ulipristal Vaginal Ring</td>
<td>Nestorone/EE vaginal ring</td>
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<td><strong>Non-hormonal</strong></td>
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<td>- Meloxicam</td>
<td>RISUG polymer</td>
<td>SILCS Diaphragm</td>
<td>Sino-implant (II)</td>
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<td>Quinacrine pellets</td>
<td>Ortho Evra</td>
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<td>- Cornell Vaginal Ring</td>
<td>WEE2</td>
<td>C31G (spermicide)</td>
<td>EllaOne</td>
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<td>- Nanocomposite copper IUD</td>
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<td>PATH woman’s condom</td>
<td>Cyclofem</td>
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<td>- Meloxicam Vaginal Ring</td>
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<td>Femilis IUS</td>
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<td>- Polidocanol for NSS</td>
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<td><strong>Dual Protection</strong></td>
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<td>- Faslodex</td>
<td>TU + NET-EN</td>
<td>GTx C-6 (SARM) Oral testosterone 11β/19/17β (SARM) DMAU</td>
<td>DMPA + TU Desogestrel + Testosterone</td>
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<td>- CDK2</td>
<td>MENT</td>
<td>H2-Gamendazole Testicular heat</td>
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<td>- α4-Na, K-ATPase</td>
<td>LNG + generic androgen</td>
<td>Triptyrygium wilfordii deriv. Inc. triptolide Artificial cryptoorchidism Testicular ultrasound Inhibition of vas deferens propulsive contractility</td>
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<td>- LDH C</td>
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<td>- BDADs</td>
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<td>- Adjudin</td>
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<tr>
<td>- FS/β-Melphalan Conjugates</td>
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<td>- Carica papaya extract</td>
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<td>- Vasaligal vas deferens polymer filter</td>
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<td>- Non-invasive laser vascetomy</td>
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<td><strong>Male</strong></td>
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<td>- H2-Gamendazole</td>
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<td>- Triptyrygium wilfordii deriv. Inc. triptolide</td>
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<td>- Artificial cryptoorchidism</td>
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<td>- Testicular ultrasound</td>
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<tr>
<td>- Inhibition of vas deferens propulsive contractility</td>
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</tbody>
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1. Plus polidocanol for non-surgical sterilization (NSS) to make 19 GCE technologies
2. FC2 has completed WHO reg. process and is ready for procurement

Note: LNG (levonorgestrel); TU (testosterone undecanoate); NET-EN (norethisterone enanthate); RISUG (reversible inhibition of sperm under guidance); EE (ethinyl estradiol); MENT (7 alpha-methyl-nortestosterone); PC (proprotein convertases); GAPDHS (Glyceraldehyde-3-phosphate dehydrogenase, testis-specific); HIFU (High intensity focused ultrasound); SARM (selective androgen receptor modulator); DMAU (Dimethandroline 17β-Undecanoate); E2 (estrogen estradiol); BDAD (bis-dichloroacetyl-diamines); LDH-C (Lactate Dehydrogenase C); DMPA (Deltamethrin 17β-Undecanoate)