Advances in Barrier Methods & the Future of Multipurpose Prevention Technologies (MPTs)

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Universities of California, San Francisco & Berkeley Initiative for MPTs (IMPT)

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## Disclosures

<table>
<thead>
<tr>
<th>Anke Hemmerling, MD, PhD, MPH</th>
<th>Commercial Interest</th>
<th>Role</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Nothing to disclose</td>
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</table>
Objectives

By the end of this session participants will be able to:

- Define Multipurpose Prevention Technologies (MPTs).
- Identify an important attribute of a diverse product development pipeline for women’s reproductive health needs that encompass contraception as well as STI protection.
- Analyze at least one complexity in developing new products that combine multiple indications and active pharmaceutical ingredients into singular products.
Sexual & Reproductive Health Risks are Interlinked

- Unintended Pregnancy
- HIV
- Other Sexually Transmitted Infections (STIs)

Women need better protection
HIV, HSV-2, HPV, & Unmet Need for Modern Contraception among Women

Source: Schelar, et al. [Link](http://www.contraceptionjournal.org/article/S0010-7824%2815%2900577-6/)

*Principal component 1: HSV-2, HIV, and HPV by country and region.
**Principal component 2: Unmet need for modern contraception by country. See manuscript for full description of principal components analysis and methods.
Multipurpose Prevention Technologies (MPTs)

MPTs combine protection against:
- Unintended pregnancy
- HIV
- Other STIs
A Suite of Products is Needed

Contraception + HIV & STI Prevention

Contraception + HIV Prevention

Contraception + STI Prevention

HIV + STI Prevention
Initiative for MPTs (IMPT)
Expansion of Focus

Science & Technical Aspects of MPT Development
- Scientific Feasibility
- Product Prioritization & Gap Analysis
- Dosage Form Specific TPPs
- MPT Pipeline Database

Social-behavioral & Market Access
- Market Access Framework
- Market Research
- Impact Modeling
- Communications and Advocacy among key stakeholder groups

Delivery & Distribution
Barrier Methods

Male and female condoms are the only currently available methods for prevention of multiple SRH risks

- Diaphragms
- Cervical Caps
- Other Cervical Barriers
- Female Condoms
- Male Condoms
## Your Mother’s Diaphragm

### PROS
- Effective if consistently correctly used
- Perfect-use pregnancy rate 6%
- Limited STI reduction potential
- Reusable

### CONS
- Requires Anticipatory motivation
- Correct use during coitus
  - 6 hrs before & 6 hrs after
  - + spermicide
- Typical-use pregnancy rate 12%
- Requires MD to fit
- Before 2014: 2 U.S. diaphragms
  - Milex Wide-Seal Arcing Style
  - Omniflex Diaphragm
SILCS Diaphragm - Caya®

- Developed by PATH
  - with support of CONRAD + USAID
- Marketed in Europe as Caya® (sole source) by Kessel, Germany
- FDA approved September 2014

- Single size reusable, covers cervix
- Flexible rim with room for drug load
- Silicone membrane, 2 cups
  - Larger cup fits loosely over cervix
  - Smaller cup aids as hooking rim for removal
- No provider or fit training
SILCS (Caya®) (sole source) as MPT

- Flexible rim with room for drug load can serve as reusable delivery system for an ARV microbicide gel
Overview Additional Barriers

**Protectaid®**  
*Pirri Pharma*, Canada (sole source)  
Polyurethane foam sponge impregnated with F-5 Gel (N9, BKC, NACOL)  
Canada & Europe

**Semina Diaphragm**  
*Semia Industries, Commerce Ltd.*, Brazil (sole source)  
Silicone diaphragm, coil spring, 60-85mm (5mm increments)

**Duet™** (sole source)  
Single size  
3 layers of protection  
Vaginal-side gel, barrier film, cervical-side gel

**Shanghai Lily**  
*SL Life Rubber Product Co., Ltd*, China (sole source)  
Latex  
4 sizes: 54, 58, 62, 66mm

**FemCap**  
*FemCap, Inc.* (sole source)  
Silicone cap, removal strap, brim holds spermicide/trap sperm  
3 sizes: 22, 26, 30mm  
In U.S. & Europe
## Overview of Female Condoms

<table>
<thead>
<tr>
<th>Female Condom</th>
<th>Material:</th>
<th>Available in:</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cupid Female Condom (sole source)</td>
<td>natural latex, poly-urethane foam internal retainer</td>
<td>India, Brazil, Indonesia, South Africa, Mozambique</td>
<td>Cupid Limited India</td>
</tr>
<tr>
<td>Female Condom FC2 (sole source)</td>
<td>nitrile polymer, inner ring for easier insertion and positioning, softer outer ring</td>
<td>U.S. and 100 countries</td>
<td>Female Health Company</td>
</tr>
<tr>
<td>Phoe Nurse (sole source)</td>
<td>polyurethane, plus insertion tool, water-based lubricant</td>
<td>China, Brazil</td>
<td>Tianjin Kangdunbao Co. China</td>
</tr>
</tbody>
</table>

## Overview of Female Condoms

<table>
<thead>
<tr>
<th>Product</th>
<th>Material</th>
<th>Available in</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panty Condom (sole source)</td>
<td>polyethylene w lube, re-usable panty holds condom in place</td>
<td>Colombia</td>
<td>Innova Quality S.A.S., Colombia</td>
</tr>
<tr>
<td>Origami Internal Condom (sole source)</td>
<td>nitrile polymer molded with anatomy-specific design, inserted before intercourse</td>
<td>late 2016 in US, EU</td>
<td>Origami Healthcare Products Inc., Strata Various Product Design</td>
</tr>
<tr>
<td>Woman's Condom (sole source)</td>
<td>polyurethane, dissolving capsule for insertion, foam for stability, water based lubricant</td>
<td>China (as O'Lavie)</td>
<td>PATH, Shanghai Dahua Medical Apparatus Company Ltd., China</td>
</tr>
</tbody>
</table>

Upcoming Trends in Condoms

**S.T.EYE Condom (sole source)**
glows green, detects bacteria/STIs

- green=chlamydia, yellow=herpes, purple=HPV, blue=syphilis
- by TeenTech awards students at Isaac Newton Academy in Ilford


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**Skyn Condom (sole source)**
thin polyisoprene, self lubricating, skin-to-skin sensation, biodegradable


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**Hydrogel Condom (sole source)**
ultra-strong, skin-like prosthetics tissue makers

- Australia's University of Wollongong, Project Geldom improved naturalistic feel, building in automatically released internal lube or Viagra


Courtesy of Michelle Forcier
MPTs: Many Possibilities

Indications
- Pregnancy
- HSV
- HPV
- HIV
- BV
- Chlamydia
- Gonorrhea
- Syphilis
- Candida
- Trichomonas

Delivery Methods
- Topical daily
- Topical pericoital
- Systemic sustained
- Topical sustained
- Oral daily
- Oral pericoital

Product Types
- Vaginal film
- Vaginal tablet
- Oral tablet
- Vaginal ring
- Non-IVR device
- Vaginal gel
- Injectable
- Implantable

Active Pharmaceutical Ingredients
- HC, Non-HC
- Barrier
- Probiotic
- Antimicrobial
- Antifungal
- Antiviral

MPT Product Possibilities
Discovery
Candidate Identification
Preclinical Virology
Preclinical Studies (Critical Path)

Pre-IND
IND
NDA

Preformulation Formulation Vehicle optimization (delivery)

In vitro & Ex vivo Testing
Animal Safety Toxicology & Pharmacology
Acute Chronic Reproductive Carcinogenesis

Preformulation → Formulation → Vehicle optimization (delivery)

Chemistry, Manufacturing & Control (CMC) → Scale-up → Commercial Supply

Behavioral & Social Sciences
Perceptibility: Individual preferences for Physical & Rheological Properties: target population
Initial Acceptability Expanded Acceptability Marketing Research
Confirmation Perceptibility Identification of population specific issues Creating population specific approaches
Development of use instructions

Phase I Initial Safety
Phase II Expanded Safety
Phase III Safety & Efficacy
Phase IV Additional Monitoring
Post Licensure Marketing

Additional Monitoring
MPTs: a promising response to current challenges around hormonal contraceptive methods and HIV.

2016 International Conference on Family Planning – 27 January 2016 – Nusa Dua, Indonesia

Critical Elements for inclusion in pipeline

Bench Science Pipeline Inputs

Contraceptives (HC & non-HC)
ARVs & non-ARVs
Delivery Platforms Etc.

Stages of Development Pipeline

Discovery Preclinical Clinical

End users
Healthcare Service Delivery
Policy/Advocacy

MPT
Options for MPTs

Co-formulated:
Multiple API formulated into a single dose

Co-administered:
Two separate products used together

Co-packaged:
Two different doses packaged together into single product for simultaneous co-use

MPT Concept:
Oral Truvada® (sole source) + Oral Contraceptives
MPTs in the Development Pipeline

- Long acting vaginal rings
- Fast dissolving films and tablets
- Innovative gels
- Injectables
- Nanofiber delivery systems
- Biotherapeutics
Priorities for 1st Generation MPTs

**On demand**
- Used at time of intercourse
- For intermittent sex
- Oral or topical

**Sustained release**
- Vaginal ring or long-acting injectable
- No daily administration required
- Potential for increases in adherence and effectiveness
### Sustained Release Devices: MPT IVRs

<table>
<thead>
<tr>
<th>90-day Dapivirine (sole source) + LNG (IPM)</th>
<th>90-day TFV + LNG (CONRAD) (sole source)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Silicone matrix ring" /></td>
<td><img src="image2.png" alt="Segmented PU ring" /></td>
</tr>
<tr>
<td>• Silicone matrix ring</td>
<td>• Segmented PU ring</td>
</tr>
<tr>
<td>• Advanced pre-clinical stages</td>
<td>• Phase I clinical study</td>
</tr>
<tr>
<td>• Pregnancy, HIV</td>
<td>• Pregnancy, HIV, HSV-2</td>
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<td></td>
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</table>
## MPTs in development: **Gels and Films**

<table>
<thead>
<tr>
<th>HIV + Other STIs</th>
<th>Phase</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0% Tenofovir Vaginal Gel</td>
<td>Phase III</td>
<td>HIV, HSV</td>
</tr>
<tr>
<td>mapp66 (mAb) Vaginal Film</td>
<td>Phase I</td>
<td>HIV, HSV</td>
</tr>
<tr>
<td>MIV-150 + Zinc acetate + Carrageenan Vaginal Gel</td>
<td>Phase I</td>
<td>HIV, HSV, HPV</td>
</tr>
<tr>
<td>Tenofovir Vaginal Film, Tablet</td>
<td>Phase I</td>
<td>HIV, HSV</td>
</tr>
<tr>
<td>TFV/FTC Vaginal Tablet</td>
<td>Phase I</td>
<td>HIV, HSV</td>
</tr>
<tr>
<td>VivaGel</td>
<td>Phase I</td>
<td>HIV, HSV, BV</td>
</tr>
<tr>
<td>SILCS Diaphragm + MIV-150 + Zinc acetate + Carrageenan Vag Gel</td>
<td>Advanced Pre-clinical</td>
<td>HIV, HSV, HPV, Pregnancy</td>
</tr>
<tr>
<td>Griffithsin vaginal insert/gel</td>
<td>Early Pre-clinical</td>
<td>HIV, HSV, HPV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy, HIV &amp; Other STIs</th>
<th>Phase</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphora gel</td>
<td>Phase I</td>
<td>BV, Gon, Pregnancy</td>
</tr>
<tr>
<td>PPMC SAMMA gel</td>
<td>Pre-clinical</td>
<td>HIV, HSV, HPV, Chl, Gon, Pregnancy</td>
</tr>
</tbody>
</table>
### MPTs in development: Intravaginal Rings

<table>
<thead>
<tr>
<th>HIV + Pregnancy &amp; Other STIs</th>
<th>Phase</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir + Levonorgestrel IVR</td>
<td>I</td>
<td>HIV, HSV, Pregnancy</td>
</tr>
<tr>
<td>Dapivirine + Levonorgestrel IVR</td>
<td>AP</td>
<td>HIV, Pregnancy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV &amp; Other STIs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir + Acyclovir IVR</td>
<td>I</td>
<td>HIV, HSV</td>
</tr>
<tr>
<td>Tenofovir Disoproxil Fumerate (TDF) IVR</td>
<td>I</td>
<td>HIV, HSV</td>
</tr>
<tr>
<td>Tenofovir + IQP-0528 IVR</td>
<td>AP</td>
<td>HIV, HSV</td>
</tr>
<tr>
<td>Griffithsin IVR</td>
<td>EP</td>
<td>HIV, HSV, HPV</td>
</tr>
</tbody>
</table>
Uniting researchers and developers in contraception & HIV prevention

- **Unite experts** in contraception and MPT development to discuss MPT research
- Review **gaps and challenges**, identify research priorities for including HC into MPTs
- **Expert recommendations** for developers and funders
Uniting researchers and developers in contraception & HIV prevention

- **Technical Meeting** on Hormonal Contraceptives in MPTs (09/2014)
- **Priority Survey** for the Field (02/2015)
- **Stakeholder Round Table** on Hormonal Contraceptives in MPTs (05/2015)

**Participants:** United States Agency for International Development (USAID), Bill & Melinda Gates Foundation, Contraceptive Clinical Trials Network (CCTN), National Institutes of Health (NICHD, NIAID, NIH OAR), CONRAD, International Partnership for Microbicides, Population Council, FHI 360, Guttmacher Institute, California Family Health Council, Planned Parenthood, Gilead, Merck
The Contraception Side of MPTs
Barriers to Conception –
Mechanisms of Action for Contraception

Topical effects:
Creating unfavorable conditions for implantation and sperm capacitation (despite ovulation).

Systemic effects:
Suppressing ovulation.

Exposure

Ovulation

Cervical mucus

Endometrial effects

Others ??

Conception
What we know about hormonal contraception

- Foundational HC research in 1960-1990s
  - Limited measures of PK and PD
  - Limited surrogate markers for effectiveness
  - High HC plasma levels that prevent ovulation have best contraceptive efficacy
  - Complete ovulation suppression not needed (e.g. IUDs)
Contraceptive Pharmacokinetics: threshold for contraceptive efficacy

Achilles, SL. 2014
Drug-drug interactions can impact metabolism

CYP3A4 inducers: Efavirenz, Nevirapine

Progestin + CYP3A4 (Cytochrome P450) = Progestin

Potential Sequelae from Sub-Therapeutic Dose: Pregnancy
HC candidates for MPTs

- Levonorgestrel
  - to date progestin with most available data
  - oral contraceptives, levonorgestrel containing transdermal implant not available in the U.S; levonorgestrel-containing OCs; 2 levonorgestrel-containing IUDs, WHO IVR
  - Possible drug-drug-interaction with selected NNRTIs

Newer progestins or combinations of LNG with estrogen may have advantages such as better bleeding profiles:

- Etonogestrel
  - the transdermal implant and vaginal contraceptive ring containing etonogestrel currently available in the U.S. (with ethinyl estradiol)
  - Possible drug-drug-interaction with selected NNRTIs

- Desogestrel
  - Prodrug to etonogestrel, in oral contraceptives
What we **DO NOT** know about hormonal contraception: Research Priorities #1

1. **Systemic effects of HC**
   - Exact plasma levels needed for preventing ovulation and reaching contraceptive efficacy for each HC

2. **Topical effects of HC**
   - Systematic investigation of MoA other than ovulation

3. **Impact of drug-drug-interactions of HC with other APIs** impact HC concentrations and efficacy
What we **DO NOT** know about hormonal contraception: Research Priorities #2

4. Which **HCs** are suitable for MPTs?

5. Which HCs best used for **on-demand MPTs**?

6. Understanding **relationship between bleeding patterns and acceptability** of HC options in different cultural settings

7. **Contraceptive efficacy** of standard HC dosing in women with **high BMI**
Conclusions

- Researchers, developers and supporting agencies should partner
  - to systematically identify and fill critical research gaps
  - develop streamlined “Go/No Go” criteria

- Collaborative process
  - avoids duplication of efforts
  - ensures most pressing questions are prioritized
  - most effective use of limited resources

- MPT field needs to follow developments in the larger fields of HIV and family planning
Keeping up to date with MPT R&D

http://mpts101.org/mpt-database
Resources

- [www.theIMPT.org](http://www.theIMPT.org)
- [http://www.cervicalbarriers.org/products/faq.cfm](http://www.cervicalbarriers.org/products/faq.cfm)
Thank you!