Symposium 6: Prevention of Multiple Reproductive Health Indications

High-impact products: Necessary attributes, development prospects, and challenges

Joe Romano
NWJ Group, LLC
March 6, 2012
Part 1: Necessary Attributes and Parameters
Type 1: Drug:Drug or Drug:Device
- API(s) for at least two SRH indications in a single dosage form
  - E.g., TFV gel for prevention of HIV and HSV
- API(s) in a device configuration for at least two SRH indications
  - E.g., Diaphragm releasing TFV

Type 2: Multi-Indication Vaccine
- Single product, multiple indication vaccine
  - E.g., Single vaccine preventing HSV and HPV
MPT Products: Wide Array of Possibilities

- Anti-Microbial
- Anti-Viral
- Anti-Fungal
- Pro-Biotic
- HC
- Non-HC
- Barrier

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

- Vaginal Tablets
- Oral Tablet
- Vaginal Ring
- Non-IVR Device
- Vaginal Gel
- Vaginal Film
- Injectable
- Implantable

Focus and Prioritization Required

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Necessary Attributes & Parameters: Target Product Profile

- May 5, 2011 Think Tank
  - USAID, CAMI, AVAC

- Think Tank Description of a TPP:
  - How a proposed candidate product addresses critical attributes

- Why a TPP?
  - To define attributes/parameters for MPT products with highest potential public health impact (i.e., prioritization)
  - To Guide donor investment and sponsor development strategies

- Two working groups formed
  - Drug-Drug/Drug-Device
  - Vaccines
Necessary Attributes: Target Product Profile WG Results

- **Indications:**
  - HIV & Pregnancy
  - HIV & STI
  - HSV, HPV, BV
  - STI & Pregnancy

- **Dosage Forms:**
  - Sustained release
  - Topical over oral
  - Peri-coital over daily

- **Product Related:**
  - 40°C storage
  - 36 month shelf life
  - Concealable presentation

<table>
<thead>
<tr>
<th>Critical Attribute</th>
<th>Critical Attribute</th>
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<tbody>
<tr>
<td>Indications</td>
<td>Adherence</td>
</tr>
<tr>
<td>Target Population</td>
<td>Time to Market</td>
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<tr>
<td>Administration Route</td>
<td>R&amp;D Costs</td>
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<tr>
<td>Product Presentation</td>
<td>Reversibility</td>
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<tr>
<td>Dosage Form &amp; Schedule</td>
<td>Side Effects</td>
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<tr>
<td>Efficacy</td>
<td>IP Status</td>
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<tr>
<td>Storage Conditions</td>
<td>Access Potential</td>
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<tr>
<td>Shelf Life</td>
<td>Other Health Benefits</td>
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<tr>
<td>Cost</td>
<td>Contra-indications, warnings, precautions, use by preg/lact women</td>
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<tr>
<td>Packaging</td>
<td></td>
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<tr>
<td>Disposal/Waste</td>
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Part 2: Development Prospects
• Contraceptive products exist in multiple configurations
• Drugs for treatment of HIV and STI are available
• Infectious disease prophylaxis established
• Prevention of HIV:
  – PMTCT
  – Caprisa 004
  – iPrEx
  – Partners PrEP
• Individual and multi-purpose vaccines: MMR, DPT
Early to Later Stage MPT Product Candidates: HIV and Pregnancy

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Development</th>
<th>Developing world registration / Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dual protection</strong></td>
<td>Praneem tablet (P2)</td>
<td>DPV+LNG ring (PC)</td>
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<tr>
<td>Bioengineered Lactobacillus</td>
<td>Duet+TFV gel (P1)</td>
<td>DPV+(P+E) ring (PC)</td>
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<tr>
<td>PC6-inhibitor</td>
<td>SILCS+TFV gel (PC)</td>
<td>MIV-150+LNG ring (PC)</td>
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<tr>
<td>Dendrimer gels</td>
<td>TFV+LNG ring (PC)</td>
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<tr>
<td>Rehydrating foam</td>
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<tr>
<td><strong>HIV prevention</strong></td>
<td>DPV ring (P3)</td>
<td>TMC278 LA (P1)</td>
</tr>
<tr>
<td>Bioengineered Lactobacillus</td>
<td>TDF and TDF/FTC oral (P2)</td>
<td>Maraviroc+DPV gel (PC)</td>
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<tr>
<td>Glycerol monolaurate</td>
<td>VivaGel (P2)</td>
<td>TFV ring (PC)</td>
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<tr>
<td>CCR5/GP 120/inhibs</td>
<td></td>
<td>MIV-150 ring (PC)</td>
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<tr>
<td>GP 41 inhibs</td>
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<tr>
<td><strong>Contraception</strong></td>
<td>P-only oral (pericoital) (P3)</td>
<td>Ulipristal vaginal ring (P2)</td>
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<tr>
<td>Bioengineered Lactobacillus</td>
<td>C31G gel (P3)</td>
<td>LNG butanoate (P1)</td>
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<tr>
<td>LIF and IL-11</td>
<td>BufferGel (P3)</td>
<td>LNG gel (P1)</td>
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<td>SGK-1/AKT</td>
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PC = Pre-clinical; P2 = Phase II; R = Regulatory; P1 = Phase I; P3 = Phase III; L = Launched

Note: DPV = Dapivirine, TFV = Tenofovir, TDF = Tenofovir disoproxil fumarate, FTC = Emtricitabine, LNG = Levonorgestrel, P-only = progestin-only, P+E = progestin + estrogen
Source: USAID-sponsored CAMI MPT Product Mapping; expert interviews; BCG research

Courtesy M. Kerrigan BMGF
Dual Protection Concepts Closest to Potential Launch: HIV & Pregnancy

<table>
<thead>
<tr>
<th>First generation new DP (launch by ~2020)</th>
<th>Next generations of new DP (launch likely beyond ~2020)</th>
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<tbody>
<tr>
<td><strong>Continuous use</strong></td>
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<tr>
<td>Systemic HIV Px</td>
<td>Implant that releases ARV and HC</td>
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<tr>
<td>Oral: ARV + HC</td>
<td>IUD that releases ARV</td>
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<tr>
<td>Vaginal ring: ARV + HC</td>
<td>Injectable passive immunization + HC</td>
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<tr>
<td>**Topical HIV Px</td>
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<tr>
<td>Vaginal ring: ARV + HC</td>
<td>ARV gel + HC gel</td>
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<td></td>
<td>Lactobacillus (HIV Px + contraception)</td>
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<tr>
<td><strong>Pericoital use</strong></td>
<td></td>
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<tr>
<td>Systemic HIV Px</td>
<td></td>
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<tr>
<td>Oral ARV + oral HC</td>
<td></td>
</tr>
<tr>
<td>**Topical HIV Px</td>
<td></td>
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<tr>
<td>Cervical barrier + ARV gel</td>
<td>ARV tablet/film + HC tablet/film</td>
</tr>
<tr>
<td>Gel: ARV gel + HC gel</td>
<td>Non-ARV-based dual protection gel/foam</td>
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<tr>
<td>Female condom + ARV gel</td>
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Courtesy M. Kerrigan BMGF
MPT Candidate: TNF-LNG IVR for Pregnancy, HIV, and HSV

• **90 Day TNF/LNG IVR:**
  - Segmented configuration
  - Different PU and architecture for controlled delivery of 2 API
  - Manufacturing via component fabrication and assembly
  - TFV release in sheep
  - LNG release in rabbits

TFV IVR in Sheep

1.0% TNF Gel
- - - Distal Tissue
- - - Proximal Tissue

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Courtesy D. Friend, CONRAD
MPT Candidate: MIV-150, Zn-Acetate, Carrageenan Gel

- **Indications:**
  - HIV, HSV, HPV(?) prevention

- **MIV-150/ZA/CG**
  - 50 μM MIV-150 (NNRTI), 14 mM Zn-acetate in carrageenan
  - Safe in initial preclinical studies
  - Stable: 9 mos, 30°C, 65% RH; 6 mos, 40°C, 75% RH

- **Activity:**
  - Protects in NHP/SHIV-RT model 24 hr post dose
  - Prevents vaginal and rectal HSV-2 infection in mice (high dose challenge)

- Phase 1 clinical studies planned for Q3-Q4 2012

Courtesy M. Robbiani, Population Council
Pre-Clinical MPT Candidate Products: Funded by USAID

• 60 Day Dapivirine + HC IVR (IPM)
  • HIV and Pregnancy Prevention
• MZL Peri-coital Gel (Population Council)
  – HIV, STI, Pregnancy prevention
• 30 Day MZL IVR (Population Council)
  • HIV/STI/Pregnancy prevention

Courtesy J. Manning, USAID
MPT Candidate Drug Device Combination: Drug + Barrier

- SILCS Diaphragm + 1.0% TFV Gel (PATH, CONRAD, NICHD)
  - Barrier contraception via SILCS
  - HIV/HSV prevention via TFV gel

- Female condom + Microbicide film (PATH, CONRAD, NICHD)
  - EU CE Mark received 12/10
  - WHO prequalification underway
  - U.S. contraceptive ongoing
  - Fast dissolving film delivers ARV to upper vagina and cervix

Courtesy of J. Manning, USAID
MPT Vaccine Concepts

• Work by K. Whaley, Chair of MPT Vaccine Working Group
  – Solicited MPT Vaccine Concepts
  – 11 responses

• Some Examples:
  – A. Wu; Center for Public Health Research, Nanjing University
    • HIV-1, HSV-2, HPV: Targeted induction of neutralizing Ab via synthesized peptides and ADVAX adjuvant
  – L. Stanberry, Columbia University
    • HIV-1, HSV-2, HPV: Maintain protective [cervicovaginal antibodies] and/or detectable pathogen specific T-cells; Tampon vaginal delivery of nanoemulsions of protein antigens
Part 3: Development Challenges
MPT Development & Timelines

**Pre-clinical**
- Pre-form/Co-Formulation; Phase 1 Manufacture
- API Development/Characterization
- Pre-clinical virology, pharmacology, safety
- Combination Preclin Studies
- Biocompatibility (Device)

**IND Submission**
- Pre-Clinical
  - Q1 → Q2 → Q3 → Q4 → Q5 → Q6 → Q7 → Q8

**Clinical**
- Phase 1 PK/PD, Safety
- Phase 2 Expanded Safety (Intl.)
- Phase 3 Plan Submission
- Phase 3 Start

**DDI**

**Combination with only approved API:**

**At least one experimental API:**

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MPT Development Challenges

- Hormonal Contraception and HIV Risk
  - Relevance to HIV + Pregnancy MPT product design and development

- Regulatory
  - May 10, 2012 FDA Scientific Advisory Meeting: Oral truvada for HIV prevention

- Resources
  - Money, trial capacity, participants, development partnerships

- **Regional MPT Needs**
  - Specific MPT priorities for different countries/regions
  - Multiple, alternative TPPs
Cost Benefit Model for MPT: HIV and Pregnancy Prevention

**Scenario A:** Preventing 10,000 infections in women using HIV PrEP only-

Assumptions:
- 3% Incidence, **50% adherence**, 95% efficacy, PPY
- cost of PrEP = $150

Cost to avert 10,000 infections: **$105M**

**Scenario B:** Preventing 10,000 infections in women using dual protection HIV PrEP/contraception MPT

Assumptions:
- 3% incidence, **60% adherence**, 95% efficacy, PPY
- cost for PrEP+Contraception = $160 (+$10)

Cost to avert 10,000 infections: **$94M** (↓11% vs PrEP only)

Courtesy BCG/BMGF

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Summary:

- General MPT product attributes/priorities defined
  - Regional differences
- Some MPT product development consistent with TPP is underway
  - Is it sufficient? Gap analysis needed ("Roadmap" Exercise)
- MPT product development has typical and unique challenges
  - Resolution of MPT challenges to be determined
Thank You and Questions

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M. Brady, Population Council
B. Young-Holt, CAMI/PHI
P. Harrison, CAMI/AVAC

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