MPT Product Development & Regulatory Issues 101
Live Webinar
MPT Product Development & Regulatory Issues 101

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Today’s Presenters

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Initiative for Multipurpose Prevention Technologies
Multipurpose Prevention: New Frontiers in Woman Centered Prevention

Joseph Romano, PhD
Senior Consultant to CAMI
Global Need... HIV & STIs

- Each year, 1.7 million people die from AIDS... and 2.5 million become infected.
- Every 60 seconds, a young woman is infected with HIV.
- 1 million people contract an STI every day.
- Women infected with an STI are 3-5 times more likely to contract HIV.

Map Source: UNAIDS
Global Need... *family planning*

- **222 million women** have an **unmet need for modern contraception**.
- **There are approximately 80 million unintended pregnancies** in the developing world.
  - Resulting in **40 million abortions**, **30 million unplanned births**, and **10 million miscarriages**.
- **Each day, close to 800 women in developing countries die** from complications related to pregnancy and childbirth.
- **An additional 15 to 20 million women suffer debilitating consequences of pregnancy.**

Map Source: WHO
What are Multipurpose Prevention Technologies (MPTs)?

A single product or strategy, configured for at least two SRH prevention indications:

- **Unintended pregnancy**
- **HIV**
- **Other STIs**

**WHY MPTs?**

- Greater *efficiency* in terms of cost, access and delivery of SRH prevention products
- Capitalize on the demand in populations using one product type to achieve uptake and use of a second “product”
Initiative for Multipurpose Prevention Technologies (IMPT)

Secretariat:

Steering Committee

Supporting Agency Coordination Committee

Technical Working Groups

Senior Technical and Regional Advisors

Communications & Advocacy

Scientific Agenda

Access, Demand & Uptake

Network of Expert Members

Research & Public Health Orgs.

SRH Policy & Advocacy Orgs.

Universities

Biotechnology Companies & Orgs.

National & Int’l Supporting Agencies

Multilateral Orgs.
Complexity of Developing MPTs

• Multiple product options, therefore prioritization is needed
• Objective development criteria consistent with regulatory approval and target market requirements necessary
## Priority MPT Drugs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Priority/Comments</th>
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<tbody>
<tr>
<td>HIV Prevention</td>
<td>Small organic molecule ARV: Potency &amp; Data</td>
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<td>- Approved drugs over earlier stage ARV</td>
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<td></td>
<td>- Long term use safety and resistance potential</td>
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<td></td>
<td>- Focus on alternatives to RTI (e.g., TNF) <strong>GAP</strong></td>
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<td></td>
<td>- rProtein/peptides: many options; high cost &amp; risk</td>
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<td></td>
<td>- HIV drug stigma?</td>
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<tr>
<td>Pregnancy</td>
<td>Hormone Based: Proven efficacy, wide use</td>
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<td>- LNG lead (?); Others to be studied</td>
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<td></td>
<td>- HC not prioritized for on demand use - Cycle Effects</td>
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<tr>
<td></td>
<td>- Potential risk of HIV with specific HC use <strong>GAP</strong></td>
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<tr>
<td></td>
<td>- non HC options very early stage <strong>GAP</strong></td>
</tr>
<tr>
<td>STI Prevention</td>
<td>Alternatives to broadly neutralizing API</td>
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<tr>
<td></td>
<td>- Minimal number of viable options <strong>GAP</strong></td>
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<td>- Rapid resistance selection with anti HSV drugs</td>
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Priority MPT Dosage Forms

1. Sustained Release: 
   - i.e., Vaginal Rings
2. Long Acting Injectable
3. On-Demand (pericoital)

GOAL: An MPT of each type for each of the prioritized combination indications
MPTs in the Pipeline

- Small Organic Molecules
- Broad Spectrum Natural Products
- Proteins/Peptides
- Non-Hormonal Contraceptives
Thank you!
Multipurpose Prevention Technologies: Pipeline Status and Future Prospects

Jim A. Turpin, PhD
DAIDS, NIAID, NIH
DHHS/NIH Required Disclaimer

The views expressed are those of the presenter and do not necessarily reflect the official policies of the Department of Health and Human Services (HHS), nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.
**Objective:** High level evaluation of current MPT candidates

- Advantages/Characteristics
- Risks

Evaluation will be from the perspective of drug and product development --- What is needed to move the proposed MPT products toward clinical testing and ultimately licensure?

Will artificially for discussion purposes divide the field into 4 categories

1. HIV/Contraceptive MPT
2. STI/Contraceptive MPT
3. On Demand
4. Emerging
Global Challenges for Hormone Contraceptive-Anti-HIV/STI MPT

**Nonclinical:**
Appropriate nonclinical studies—
1. Release of products from vehicle in manner appropriate to prevent fertilization and HIV/STI infection—FDA requiring dissolution studies for proposed usage interval
2. Demonstration of mechanism of action, in vitro and in animal models: contraceptive vs. antiviral
3. Unexpected interactions –Extractables/Leachables, nonclinical safety
4. Impact of ring removal and reinsertion on integrity, safety and efficacy of the product

**Manufacturing:**
- Current IVR technology takes advantage of polymer extrusion technologies---Many of the proposed products require additional manufacturing steps
- Use of new polymers—Qualify and obtain high quality supplies
- Availability of large quantities of high quality APIs
- Stability and cold chain requirements
Clinical:
What clinical trials are needed?
- Prevention of pregnancy and HIV/STI infection are very different clinical trials—is it sufficient to show individual components retain efficacy in the co-formulated vehicle?
- “Bridging” may be a lot more complex than expected

Behavioral:
Is coupling contraception with anti-HIV/STI a slam dunk?
- Public Perception
  - Extensive issues with HC side effects (Yaz law suit)
  - NuvaRing --- lawsuits and Vanity Fair
  - Same medicines AIDS patients use---Aren’t ARVs toxic?
- Impact of ring removal on efficacy
Global Challenges for Hormone Contraceptive/Antiviral MPT

**Regulatory:**

- No licensed anti-HIV products are currently being developed as MPTs.
- What nonclinical and clinical studies will be required for licensure of what is effectively a combination product? Must show all components are active and efficacious.
- Most ARVs have some level of reproductive toxicity in nonclinical studies—what will need to be repeated with combined with a reproductive health indication?
- Qualification of new polymers.
- What will be required for “Bridging”—equivalency principal.
Intravaginal Rings

- Offer sustained/continuous release compatible with estrous cycle management

Continuous IVR
- Matrix
- Reservoir

Segmented Rings

Pod Rings

BioRing™
MPT Products: CONRAD IVR

**Product**
- 90 day IVR with Tenofovir (TFV) and Levonogestrel (LNG)
- Currently in clinical product GMP manufacturing and IND submission
- Phase 1: Late 2014 30 day exposure

**Advantages**
- Most nonclinical and clinical advanced product—will potentially be first MPT to phase 1 testing
- Developed by highly experienced group and license holders for TFV
- Clinical evidence for efficacy in humans for both components

**Risks**
- Manufacturing ---Segmented IVR---3 polymers/4 welds
- Qualification of new polymers
- Cost of goods?
- Product developed as a 90 day IVR --first product in field a “bridge too far”? 
MPT Products: IPM

Product
• Up to 90 day IVR with dapivirine (NNRTI) + LNG
• Preclinical and analytic assay development, early GMP

Advantages
• ASPIRE and Ring trial for dapivirine silicone IVR—can establish dapivirine and silicone IVR safety and efficacy
• Addressing drug–drug interactions
• Completed and ongoing behavioral/marketing studies for IVR delivery format
• Matrix IVR

Risks
• Prototype development hurdles
• Cost of goods
MPT Products: Population Council

Product
- MIV-150 (NNRTI), Zinc acetate, Carrageenan, Griffithsin and LNG in IVR or On-Demand formulations
- Preclinical development—multiple API IVR formats

Advantages
- Efficacy demonstrated in animal models for HIV, HSV, HPV, and prevention of contraception for the various components and some combinations
- STI indications paired with HIV indications, could have broader acceptance by diverse populations with different anti HIV/STI needs.

Risks
- Product supply and cost of goods
- Outstanding preclinical toxicology issues to be resolved
- Multiple combinations proposed—What product will be advanced?
- As proposed a very complicated regulatory pathway, pursuit of multiple products simultaneously will potentially be time and resource consuming
MPT Products: BioRings™

Product
- Contraceptive anti-HIV IVR from Hydrophilic polymeric hydrogel
  - Contraception
    - Ferrous Gluconate – Sperm mobility
    - Acrobid Acid - Increases barrier function of mucus
    - Polyamino-Polycarboxlic acid - Buffer to pH 4.0
  - Anti-HIV: Boc-Lysinated Betulonic Acid Anti-HIV or TFV
- Early Preclinical ---Prototype IVR stage

Advantages
- Non-hormonal contraceptive
- Hydrophilic polymeric hydrogel FDA approved for human use and similar hydrophilic polymeric hydrogel (OvaPrene) contraceptive ring in Phase II
- Anti-HIV not currently used for treatment

Risks
- Very complex 4 novel product IVR---What will be the Regulatory landscape for this product?
- Potential acceptability issues: color of IVR
- Betulonic acids are very early in preclinical anti-HIV development---significant development will be needed.
MPT Products: Pod Rings

**Product:**
- Customizable ARVs and HC
- Early Preclinical ---Prototype IVR stage for MPT

**Advantages**
- Up to 6 pods each with different drug
- Use pods to control dose (# and release pore)
- Pod design facilitates combining biophysically/chemically incompatible products
- In vivo release demonstrated for acyclovir

**Risks**
- Complex manufacturing ---construction of Pods
- Proof of concept for release of ARV sufficient for prevention
- Propose to use EVA or silicon rings as support for Pods---additional manufacturing process for IVRs with no drugs and holes for Pods?
- Access to licenses for drugs and polymer
MPT Products: MERCK

**Product**
- Contraceptive, anti-HIV EVA IVR
  - Viviviroc (CCR5 inhibitor) + MK2048 (integrase Inhibitor) + HC (Progestin)
- Preclinical
  - 2 ARV IVR prototyped and first in human planned q4 2014 – q2 2015
  - HC + 2 ARV prototype in development

**Advantages**
- Major Pharmaceutical company involvement
- Manufacturing takes advantage of NuvaRing expertise and infrastructure
  - 30,000,000 million units a year
  - Continuous extrusion, one weld
- INDs and clinical experience for all components: HC licensed as IVR (NuvaRing)
- NuvaRing: Real world use acceptability safety and efficacy

**Risks**
- Still early in development—prototyping HC + ARV
- What will be the contraceptive/ARV regulatory path—new entity or bridging for contraception possible
- User perceptions changes---NuvaRing lawsuits
STI/Contraceptive MPTs
MPT Products:
Pod IVR for STI Prevention

Product
• Pod IVR for STIs (Acyclovir, + HC)
• Human PK study completed

Advantages
• Uses licensed anti-HSV drug
• Phase 1 PK trial showed release from IVR
• Has all the advantages of Pod format

Risks
• Issues noted for ARV IVR POD
MPT-Product: Tenofovir for STI Prevention

Product
1% Vaginal Tenofovir gel
CAPRISA 004 trial ~50% efficacy for HSV

Advantages
• CAPRISA 004 Clinical trial data
• Single product dual indication
• Pharmaceutical company involvement (Gilead)
• Gilead has expressed an interest in pursuing a license for this indication

Risks
• No additional clinical evidence that 1% Vaginal Tenofovir gel can prevent HSV infection
• Gel has adherence issues (VOICE)
• Vaginal gel cannot be used rectally
MPT-Product: mAb for STI Prevention

Product
- Plant produced anti-HIV and HSV antibody in a film or Pod IVR
  - Anderson, Whaley and Moench: Integrated Preclinical Clinical Program for HIV Topical Microbicides award
- Planned Pre-Phase 1 Clinical trial in 2014-2015 for mab film

Characteristics
- GMP plant produced antibodies—Production and purification of kg of API possible
- Film and IVR development completed
- Awaiting regulatory input (FDA pre-IND) to further define the pathway for mAB product development
MPT Products
for Multiple STI Prevention

Product
• PPCM (formerly SAMA) polyanion that interferes with glycoprotein mediated fusion of pathogens to target cells
• Developed by Yaso Biotechnologies

Advantages
• Contraceptive in Rabbit model
• Broadly active
  • Anti-HSV and HIV in murine model
  • Has anti-CT, NG and bovine papilloma virus activity
• NIH funding for IND- enabling efforts
• Not being developed as a HIV antiviral

Risks
• Potency?
• Gel formulation –adherence?
• Complex sulfonated polyanion—potential large scale manufacturing issues?
• Early stage development risks
On-Demand MPT

Unknown territory

Major questions from development perspective:

• Will addition of the contraceptive overcome adherence issues seen with coital or pericoital prevention products?

• What duration of action will the on-demand products have to have to achieve >95% prevention of contraception and significant prevention (>50%) of HIV/STI infection?

• How different will the on-demand MPT regulatory pathway be from the sustained release MPT development pathway?
On-Demand MPT

CONRAD/PATH

Product
SILCS diaphragm with microbicide gel

Advantages
• Entering Phase 1 evaluation with TFV 1% gel in 2014
• Developing a contraceptive TFV 1% gel in parallel

Risks
• Will require user to consistently apply the microbicide gel to the diaphragm
• Post use diaphragm cleaning
• Any unexpected interactions of the gel and diaphragm—Leaching, product stability, chemical interactions
On Demand MPT

Product
• Water-soluble polymers designed to dissolve in the vagina and release its active ingredient
• Currently theoretical

Advantages
• Precise and reproducible dosage form
• Minimal leakage
• No applicator
• Scalable manufacturing process
  (Listerine Pocket Paks >200,000 million units sold/yr.)
• Low unit dose cost (fractions of a penny/dose)
• Can be used to deliver multiple active agents

Risks
• Duration of use
• Number of doses needed
• Film: Burst release versus slower and steady state IVR or OC release profile
• Drying of vagina
ON THE HORIZON...
OR AT THE FAR EDGE OF KNOWN SPACE

Emerging: A couple of ideas to watch
Electrospun Nanofibers for MPT Delivery

Fiber-based dosage forms:

- MPT compatible sustained and phased release possible for single and combination products
- What will be manufacturing capacity—development of clinical use nanofibers
- Cost of goods and infrastructure needed to make MPT and prevention products
- Current products look like tissue paper—-acceptability and perception for use

Courtesy of Kim Woodrow, Univ. of Washington
Re-engineering the IUD for ARV Delivery

- Very limited volume for drug incorporation—requires highly potent ARV
- Contraceptive IUDs are licensed
- Very early in preclinical development
- Placed in the area of the FRT thought to be a hot spot for transmission, will mild or marginal irritation and subclinical safety findings be of a greater concern?
Co-Administration of HC and ARV

- 2 or more drugs administered to the subject simultaneously

Long-acting Injectable ARVs
- Rilpivirine
- S/GSK ‘744

Depo Provera

Cyclofem

Other HC and non-HC
Co-administration of HC and ARV

Products
Theoretical products only

Advantages
• Co-administration—no need to make a new product

Risks
• Equity of dosing and matching duration of effect
• Limited ARV choices at present: GSK 744 and TMC278
• Number of injection sites and volume
• Dosage form management:
  • Necessity of oral run-in for ARVs?
  • Long duration ARV drug level “tail”
• Injection at same or adjacent sites resulting in tissue mixing leading to novel biophysical and chemical interactions—similar to co-formulation issues—and safety issues
Conclusions

There are a number of MPT options under development, including products poised for clinical testing in the near future.

Many MPT products are still in the early prototype development stage and although each have advantages each could require a significant investment of time resources and dollars to move to a testable clinical product.

From a drug discovery/development point of view:

• Manufacturing and regulatory (path and requirements) are the most critical elements for all MPT products under development.

• It is critical to develop solid Go/No-Go criteria and milestones for each product’s development to identify the MPT products with the most promise, not only as a product, but as a deliverable and implementable strategy after clinical efficacy has been demonstrated.

  e.g. we cannot be afraid of saying development and investment in some products needs to terminated.
Thank you!

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