The Microbicide Pipeline:
A Critical Review

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March 29, 2011
What is the microbicide pipeline and how is it prioritized and progressed?
The Microbicide Pipeline?
Partial Listing of API

**RT Inhibitors:**
- Tenofovir
- Dapivirine
- MIV-150
- UC781
- IQP-0528
- DABO

**Lectins:**
- Cyanovirin N
- Griffithsina
- BanLec
- Actinohivin

**Protease Inhibitors:**
- Darunavir
- Lopinavir
- Ritonavir
- Sequinivir

**Food Products:**
- Praneen
- Green Tea Extracts
- Pomergranate Juice

**Entry Inhibitors:**
- Maraviroc
- Dendrimers (Vivagel)
- Defensins (RC101)
- DS003 (BMS793)
- PSC Rantes
- β cyclodextrin
- IQP-0831 (Isis 5320)
- SAMMA mABs
- HNG-156
- T1249
- C52L
- L’167
- L’872
- L’882
- L’644

**Nucleic Acids:**
- Aptamers
- siRNA

**Food Products:**
- Praneen
- Green Tea Extracts
- Pomergranate Juice

**Other:**
- GML
- Lactobacillus
- Top. Estrogen
- Zinc
- Thiolesters
The Microbicide Pipeline?
Possible Dosage Forms

**Vaginal Rings:**
- Silicone Matrix
- EVA Reservoir
- PU Insert

**Single Use:**
- Gels
- Creams
- Films
- Tablets
- SGC

**Other Devices:**
- Diaphragm
- Duet
- Non-woven
- Female Condom
## The Microbicide Pipeline? Combinations and MPT

<table>
<thead>
<tr>
<th>Combination HIV Prevention Products</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Dapivirine-Maraviroc Vaginal Ring</td>
<td>IPM</td>
</tr>
<tr>
<td>Dapivirine-Maraviroc Gel</td>
<td>IPM</td>
</tr>
<tr>
<td>Maraviroc-Tenofovir Film</td>
<td>IPM</td>
</tr>
<tr>
<td>Dapivirine-Tenofovir Vaginal Ring</td>
<td>IPM</td>
</tr>
<tr>
<td>MIV-150-Zn Acetate-Carageenan Gel</td>
<td>Pop Council</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multi-Purpose Prevention Technologies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir Gel</td>
<td>Gilead</td>
</tr>
<tr>
<td>Tenfovir-Levonorgestrel Vaginal Ring</td>
<td>CONRAD</td>
</tr>
<tr>
<td>ARV-Hormone Vaginal Ring</td>
<td>IPM/Pop Council</td>
</tr>
<tr>
<td>Tenofovir-Acyclovir Vaginal Ring</td>
<td>CONRAD</td>
</tr>
<tr>
<td>CV-N Expressing Lacto/Mucocept</td>
<td>Osel</td>
</tr>
<tr>
<td>Barrier Devices + ARV</td>
<td>Various</td>
</tr>
</tbody>
</table>
Microbicide Pipeline: Conventional Development & Prioritization Criteria

**Quality/CMC**
- Synthetic Process Method Devel. Preformulation

**Safety**
- M of A In vitro cytotox Genotox Acute Tox GPS
- EC_{50} in vitro Explant model Animal model?

**Efficacy**

**Pre-Clin**
- GO

**Phase I/II**
- Remedy
- NO GO
- Remedy
- NO GO
- Remedy
- NO GO

**Phase III**
- Remedy
- NO GO

**Other**
- IP, Development Partners, Regulatory Issues, Cost, Other
- GO
Microbicide Pipeline: Priority Quantification

Axes: Percent Complete with Acceptable Data
What is the microbicide pipeline and how is it prioritized and progressed?

What is available:
• Many API; Often same or similar M of A and/or phys-chem properties
  • Most are early stage
• Multiple dosage form options and device technologies
• Combinations of API and dosage forms
• Intra-organizational prioritization in the absence of field wide prioritization

Consequences to pipeline:
• Independent development of similar or duplicative products
  • Several individual API in multiple dosage form products
  • Independent but similar API in the same dosage forms
• Dilution of resources

Is this an appropriate and feasible approach to the microbicide pipeline?
Critical Review:
What is an appropriate and necessary microbicide pipeline in *current context*?
Current Context for Microbicides: March 29, 2011

ARV Proof of Concept

- CAPRISA 004: 39% reduction in HIV incidence in women using 1.0% TFV gel (Science 329:1168, 2010)
- iPrEx: 44% reduction in HIV incidence in MSM using FTC-TDF (NEJM, 363:2663, 2010)

Resource Limitations

- Global economic downturn yet to fully reverse
- Government and foundation funding adjustments

Placebo Control

- ARV POC establishes new ethical standard of care
- Regulatory agency and ethics committees likely to resist placebo controlled efficacy trial designs

Consequent Challenges

- Without non-ARV POC, no re-dress to ARV limitations
- More complex efficacy evaluations to be conducted within confines of continued resource limitations
Identifying Least Risk/Highest Impact Products in Current Context?

**One Extreme...**

- HIV Only
- Early stage API in applicator based gel
- Similar MoA/equal potency to advanced products
- Vaginal only
- Minimal pre-clinical tox/pharmacology
- Minimal CMC
- Expensive
- No human experience
- Manufacturing unknown
- No Regulatory input
- Lengthy timeline to market

**...or the Other**

- HIV + Other Indication(s)
- Later stage API in known high adherence formulation
- Significantly more potent/Distinct MoA
- Achieves vaginal & rectal protection
- Advanced CMC/PreClin packages
- Cheap
- Established manufacturing
- Strong clinical package
- Clear, positive Regulatory input
- Short timeline to market

Never this clear!

Standard application of conventional criteria is of limited utility
For Consideration:

*Application of a Critical View Across the Field*

- Current context is not consistent with advancing the entire microbicide pipeline
- Additional criteria must be derived and applied to:
  - Identify products with maximum potential for impact
  - Achieve development in most efficient manner

**Likely Consequence:**
- Pooled resources applied to a more focused pipeline
  - “Big” ≠ “Robust” or “Necessary”
- Less “me too” development
- *More efficient development of higher impact products*
1. How likely is it that a candidate product will achieve a meaningfully higher level of effectiveness than what is currently available?
   a. How much more effective via higher potency or broadness of spectrum will the candidate product be?
   b. Can the product achieve greater adherence or acceptability in at risk populations relative to current POC product, thereby increasing effectiveness?

<table>
<thead>
<tr>
<th>1.0% TFV Gel</th>
<th>39% Efficacy</th>
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<tbody>
<tr>
<td>?</td>
<td>?</td>
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<tr>
<td>Other TFV Dosage form</td>
<td>??? % Efficacy</td>
</tr>
<tr>
<td>TFV combo with RTI? Vs. TFV combo with EI, PI?</td>
<td>or</td>
</tr>
<tr>
<td>Combination w/o TFV?</td>
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Critical View of the Microbicide Pipeline in Current Context: Beyond Conventional Approaches

2. Can a single product be developed for both vaginal and rectal use thus expanding effectiveness to new populations (eg. MSM), and expanding broadness of effectiveness in women?
   a. Or, what is the magnitude of development difference required to achieve use in both compartments?

<table>
<thead>
<tr>
<th>1.0% TFV Gel</th>
<th>Identical formulation/same volume for both compartments?</th>
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<tr>
<td>4 mL Vaginal Dose</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TFV Vaginal Ring</th>
<th>Both compartments in women?</th>
</tr>
</thead>
</table>

1.0% TFV Gel
4 mL Vaginal Dose

Identical formulation/same volume for both compartments?

Both compartments in women?
3. Is a product a “me too” version of an alternative product that is later stage?

- Similar Mechanism of Action
- Similar Potency/Resistance Profile/SI
- Similar Phys/Chem Properties
- Same Dosage Form

Product A

~ 2 yrs to Phase I

Product B

< 18 mos to phase III
4. Does a product address other user needs, such as contraception or the prevention of other STI’s (particularly those serving as cofactors for HIV infection)?

5. Does a product option, in addition to satisfying the efficacy standards set by current POC products, also provide distinct advantages from an access perspective?

   e.g. Stability, cost, easier to ship, easier to store, easier to manufacture and package, less waste generating, etc
6. How amenable is a product to achieving licensure, particularly in a post-placebo controlled efficacy study regulatory environment, by means of innovative trial designs and strategies?
Critical Review of Pipeline Candidates
E.g. Tenofovir Film

- Quality/CMC
- TFV Gel
- Safety
- Efficacy

TFV Film

- Increased Potency ✓?
- Vaginal and Rectal ✓?
- Not “Me Too” ?
- MPT Potential ✓
- Access Advantages ✓
- Approval Prospects ✓
Summary and Conclusions:

- Present microbicide pipeline is large
  - Prioritized and advanced from within development organizations via conventional processes
  - Duplication ("me too") exists; Dilution of resources

- Present pipeline and its management are likely inconsistent with current context
  - Resource limitations; complex regulatory environment

- Cross-field critical review beyond conventional criteria is needed for identification of highest impact opportunities
  - Increased focus: "Big" is not "Robust" or "Necessary"
  - Requires use of context-based criteria (which is dynamic!)
  - Could result in long or short term prospects

**Goal:** Highest impact products, developed with greatest efficiency
Thank You