MTN 2011 Annual Meeting

Arlington, VA

The Microbicide Pipeline: A Critical Review

J. Romano

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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

Protease Inhibitors:
Darunivir
Lopinavir
Ritonavir
Sequinivir

Lectins:
Cyanovirin N
Griffithsin
BanLec
Actinohivin

Food Products:
Praneen
Green Tea Extracts
Pomergranate Juice

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

Nucleic Acids:
Aptamers
siRNA

Other:
GML
Lactobacillus
Top. Estrogen
Zinc
Thiolesters

The Microbicide Pipeline?

Possible Dosage Forms

Vaginal Rings:

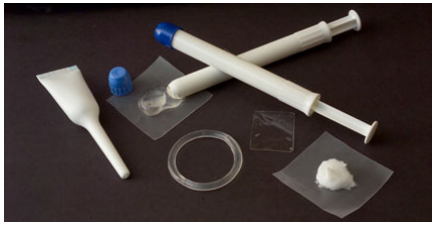
Silicone	Matrix
EVA	Reservoir
PU	Insert

Single Use:

Gels
Creams
Films
Tablets
SGC

Other Devices:

Diaphragm
Duet
Non-woven
Female Condom

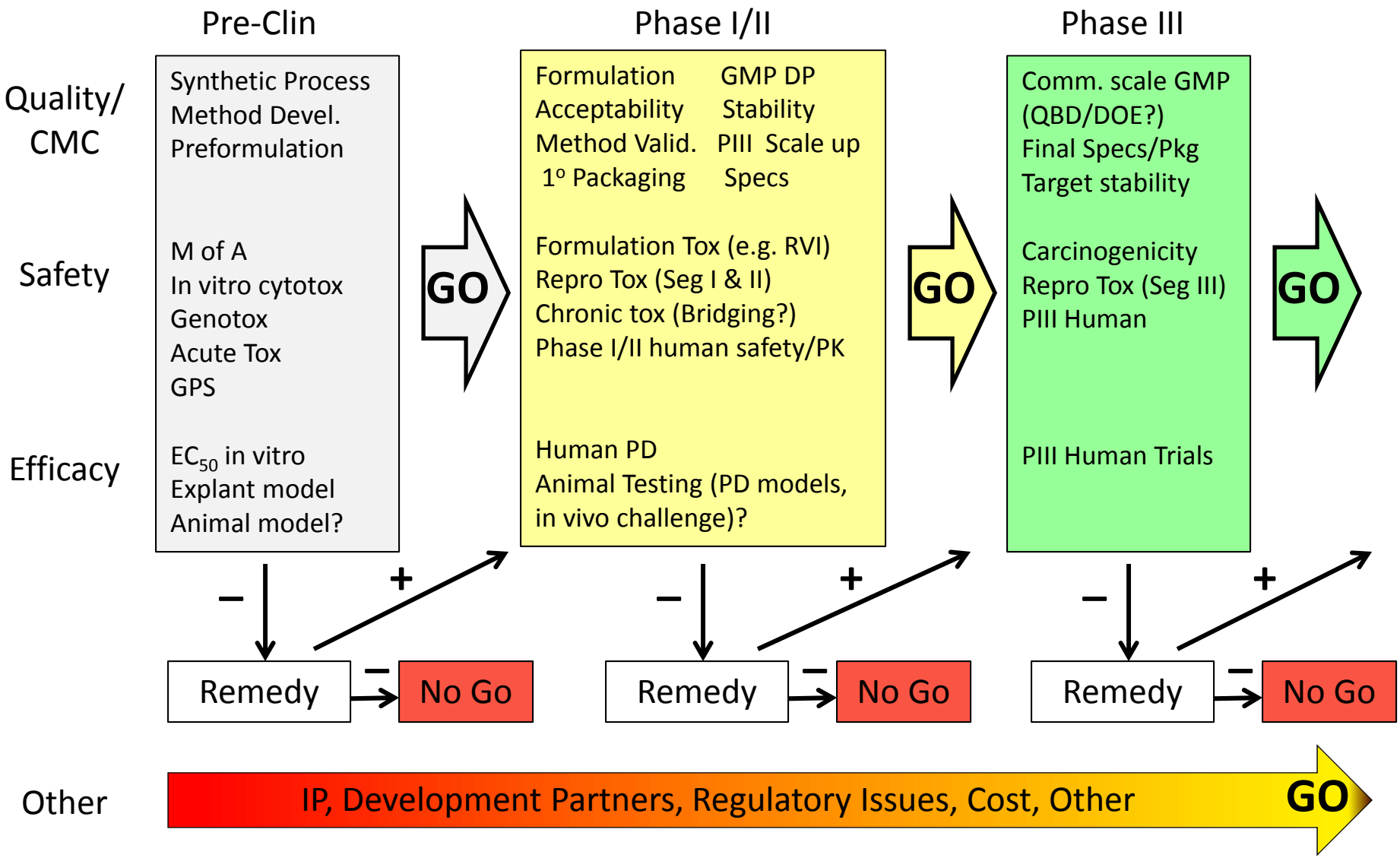


The Microbicide Pipeline?
Combinations and MPT

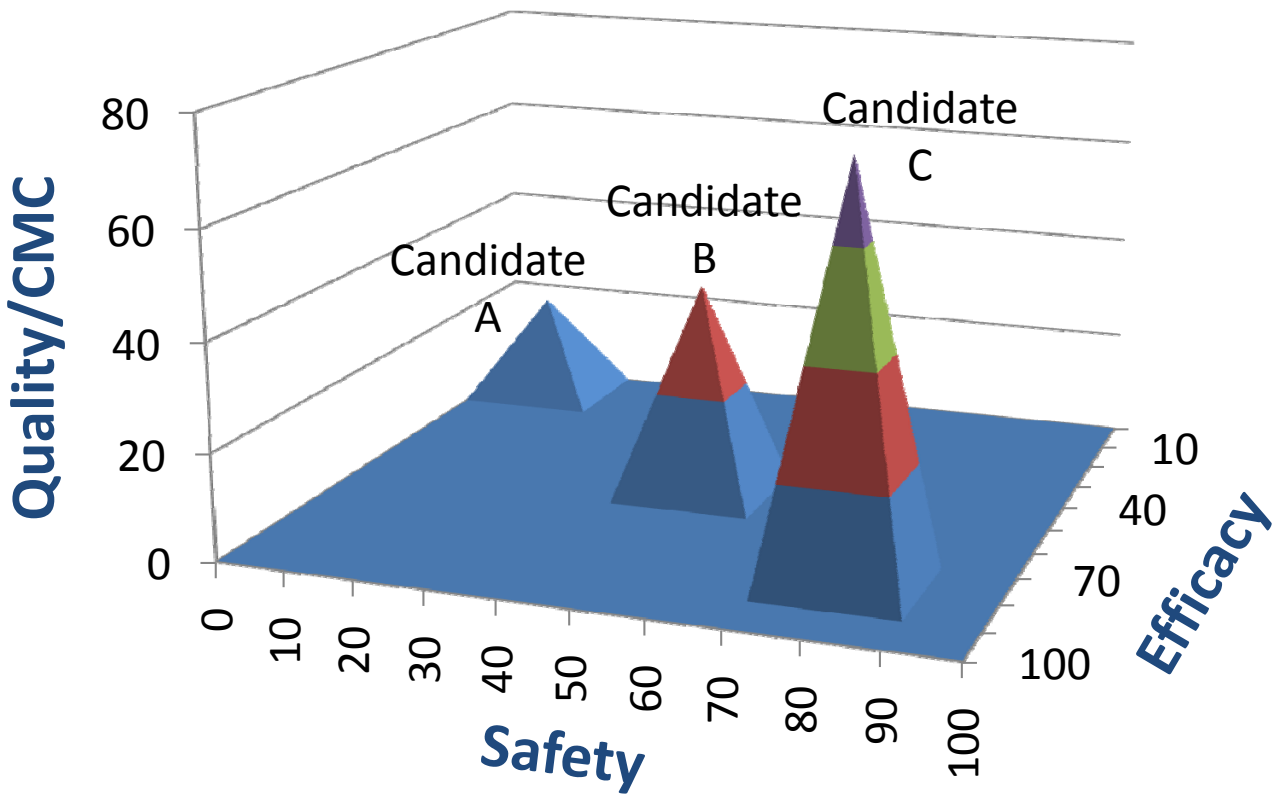
Combination HIV Prevention Products	
Dapivirine-Maraviroc Vaginal Ring	IPM
Dapivirine-Maraviroc Gel	IPM
Maraviroc-Tenofovir Film	IPM
Dapivirine-Tenofovir Vaginal Ring	IPM
MIV-150-Zn Acetate-Carageenan Gel	Pop Council

Multi-Purpose Prevention Technologies	
Tenofovir Gel	Gilead
Tenfovir-Levonorgestrel Vaginal Ring	CONRAD
ARV-Hormone Vaginal Ring	IPM/Pop Council
Tenofovir-Acyclovir Vaginal Ring	CONRAD
CV-N Expressing Lacto/Mucocept	Osel
Barrier Devices + ARV	Various

Microbicide Pipeline: Conventional Development & Prioritization Criteria



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

Never this clear!

Standard application of conventional criteria is of limited utility

…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

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*

Critical View of the Microbicide Pipeline in Current Context: Beyond Conventional Approaches

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?

1.0% TFV Gel= 39% Efficacy

?

TFV combo with RTI?
Vs.
TFV combo with EI, PI?

or

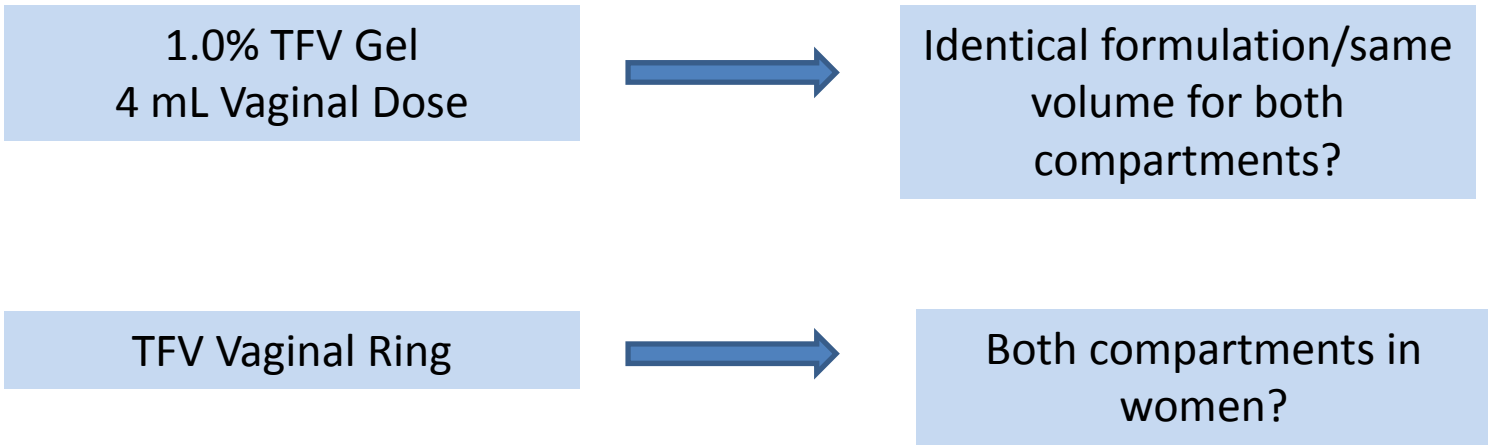
Combination w/o TFV?

?

Other TFV Dosage form =
??? % Efficacy

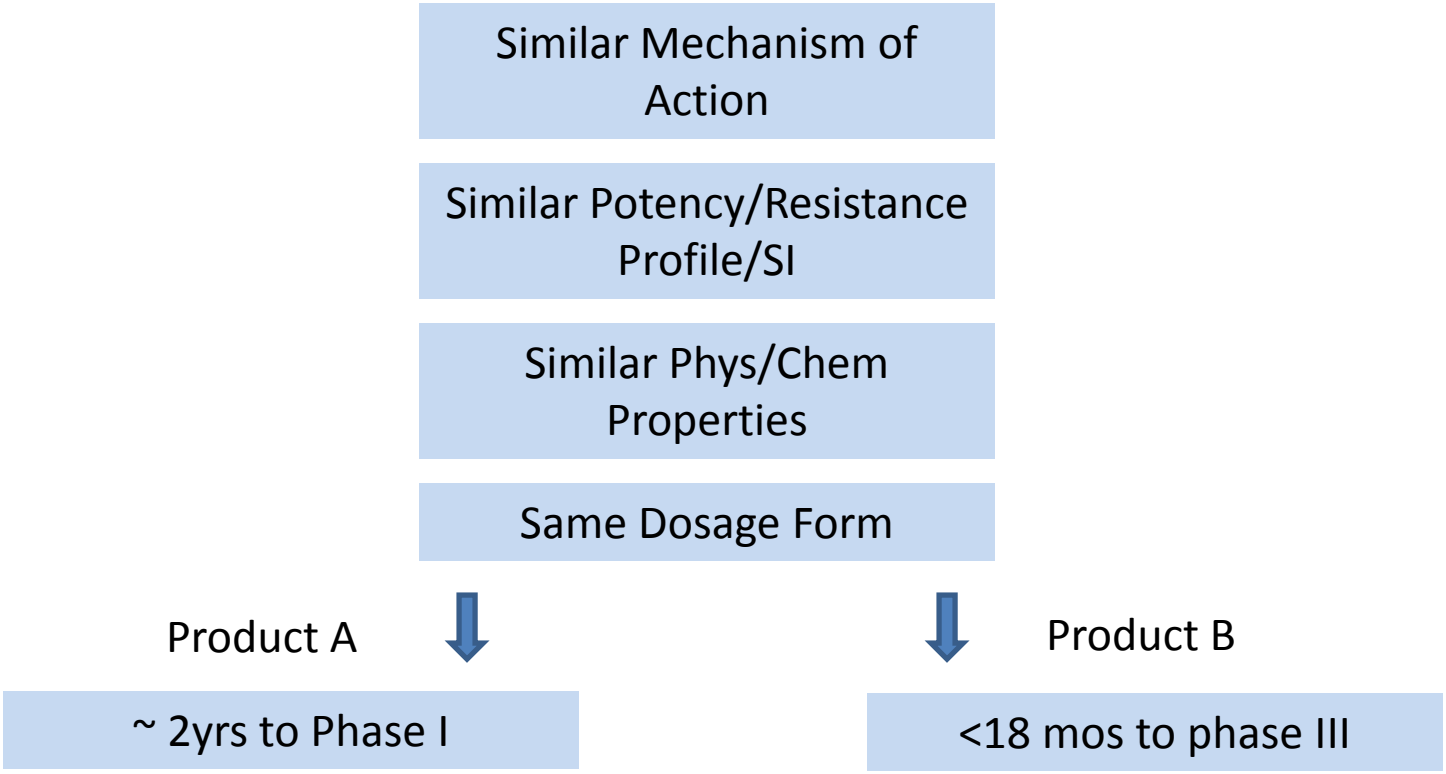
Critical View of the Microbicide Pipeline in Current Context: Beyond Conventional Approaches

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?



Critical View of the Microbicide Pipeline in Current Context: Beyond Conventional Approaches (continued)

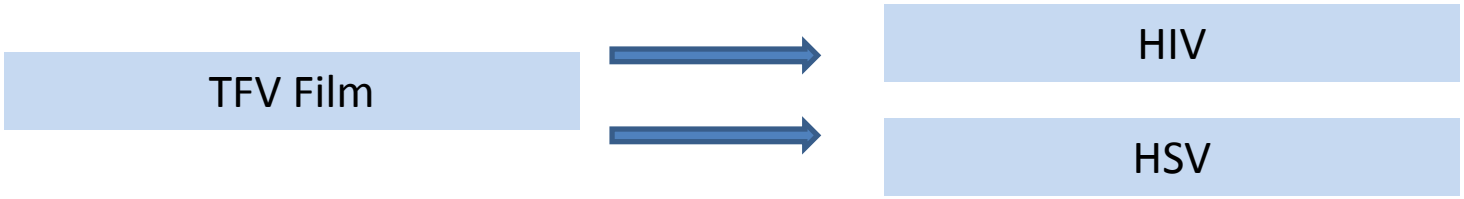
3. Is a product a “me too” version of an alternative product that is later stage?



Critical View of the Microbicide Pipeline in Current Context: Beyond Conventional Approaches (continued)

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

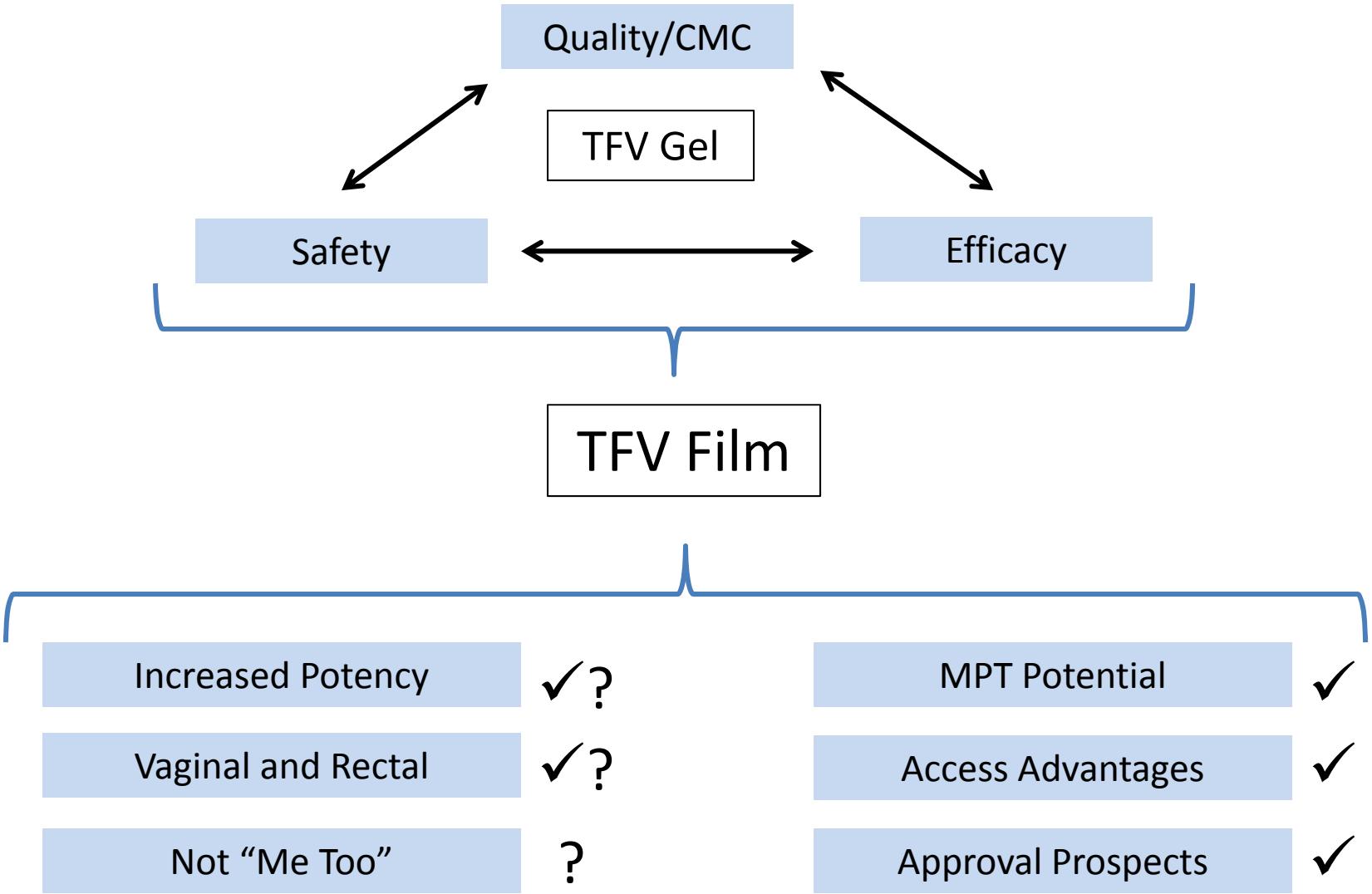


Critical View of the Microbicide Pipeline in Current Context: Beyond Conventional Approaches (continued)

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?

Approved TFV Gel →  → *Approvable* TFV Film

Critical Review of Pipeline Candidates
E.g. Tenofovir Film



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