International Partnership for Microbicides

Update on Microbicide Development

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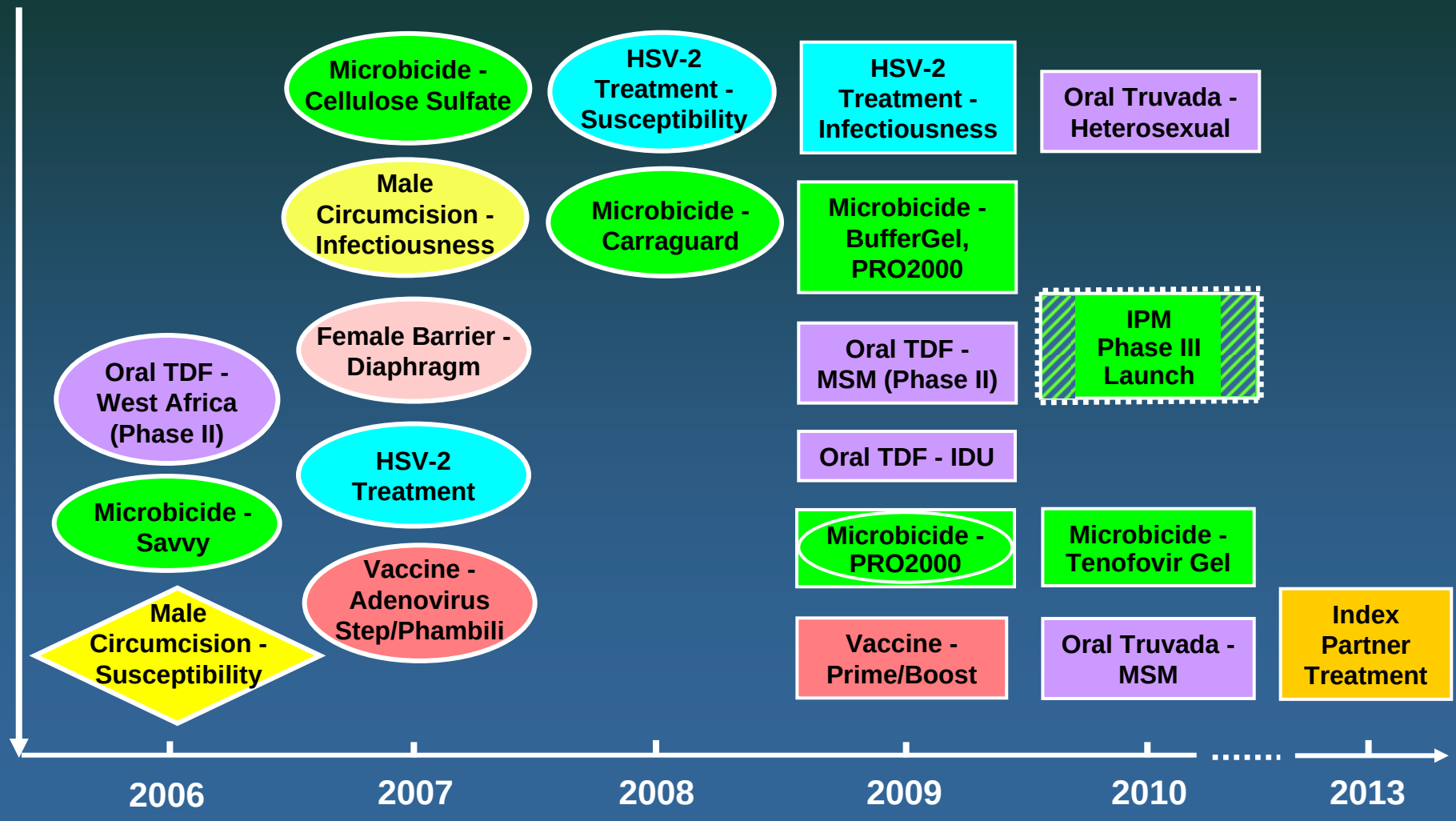
Presentation Overview

- Microbicides in context
- Products in the pipeline
- Laying the foundation for access

HIV Prevention Trial Results



Microbicides

- Topical products to prevent HIV transmission
- Could be delivered in many forms:

Gel applicator

Ring

Tablet, capsule, film

- Ideally safe, effective, low cost, user friendly

Early & Next Generation Microbicides

Early Generation	Next Generation
• First microbicides tested, some still in efficacy trials	• Newer products in different stages of preclinical and clinical research
• Not HIV specific	• Specific to HIV (ARV-based)
• Gel formulations	• Various forms: gel, ring, film, tablet
• To be applied vaginally within a few hours before sex	• Longer duration of action: daily gels, monthly rings, etc.
• No concern about potential resistance	• ARV resistance is a possible issue that needs to be investigated

Early Generation Microbicides: Ongoing Efficacy Trials

Product / Study	Phase	Mechanism of Action	Sponsor / Developer	Countries	Estimated Completion
BufferGel & PRO 2000 (0.5%) HPTN 035	2/2B	Defense Enhancer & Entry Inhibitor	NIAID / HPTN (MTN)	Malawi South Africa Zambia Zimbabwe USA	July 2008 Results 2009
PRO 2000 (0.5%) MDP 301	3	Entry Inhibitor	UK MRC, DFID / MDP	South Africa Tanzania Uganda Zambia	March 2009 Results 2009

Next Generation Microbicides: Ongoing/Planned Efficacy Trials

Product / Study	Phase	Mechanism of Action	Sponsor / Developer	Countries	Estimated Completion
Tenofovir CAPRISA 004	2B	ARV (NRTI)	DST (SA), USAID / CONRAD, CAPRISA	South Africa	Q1 2010 Results 2010
Tenofovir MTN 003/VOICE (Planned)	2B	ARV (NRTI)	NIAID / MTN	Malawi Uganda Zambia Zimbabwe South Africa	Q2 2011 Results 2011

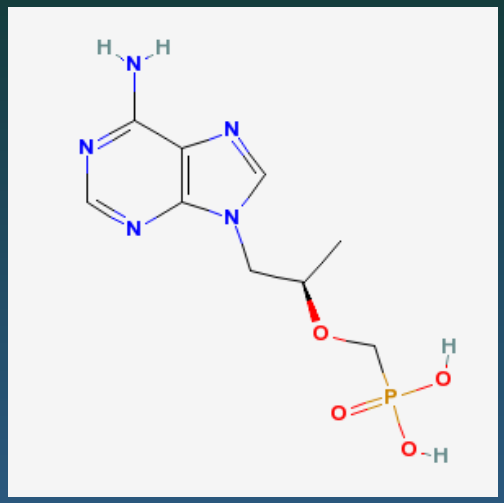
ARV-Based Microbicides in Development

Class	Drug	Developer	Development Stage
NNRTI	Dapivirine * UC-781 * PC-815 Pyrimidinediones S-DABO	IPM CONRAD Population Council ImQuest Idenix	Phase 1/2 Phase 1 Phase 1 Preclinical Preclinical
NRTI	Tenofovir *	IPM / CONRAD	Phase 1/2B
CCR5 blocker	Maraviroc * Merck L-167, 872, 882 RANTES analogs	IPM IPM Mintaka Foundation	Preclinical Preclinical Preclinical
gp41 binder	Merck L-644	IPM	Preclinical
gp120 binder	BMS-793 Cyanovirin-N	IPM Osel	Preclinical Preclinical
Zinc finger inhibitor	NCp7's	ImQuest	Preclinical

** Also being developed in combination*

Topical Tenofovir

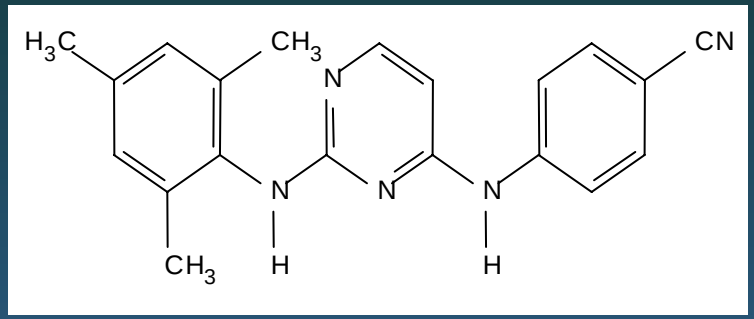
- NRTI
- Most advanced ARV microbicide in the pipeline
- Preclinical development began in late 1990s



- Proof-of-concept efficacy trials ongoing/planned
- Gilead license to CONRAD and IPM
- Viread® marketed as AIDS therapeutic

Dapivirine (TMC120)

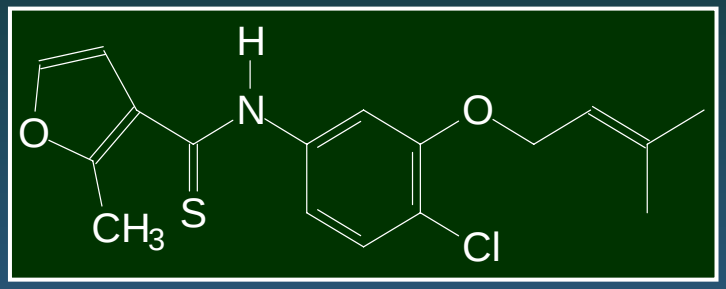
- Highly potent NNRTI
- Developed by Tibotec, licensed to IPM
- Originally tested as oral therapeutic (11 studies)



- Multiple vaginal dosage forms in development (gels, rings, films, tablets, other)
- Phase 1/2 studies completed and ongoing; Phase 3 planned 2010

UC-781

- Highly potent NNRTI
- 4 Phase 1 studies completed or in data analysis (Thailand, US) – vaginal and rectal



- 2 Phase 1 studies ongoing – vaginal and male tolerance
- 2 studies planned:
  - Single agent PK and expanded safety – planned early 2009
  - Combination UC-781/tenofovir safety – planned early 2010

Source: CONRAD

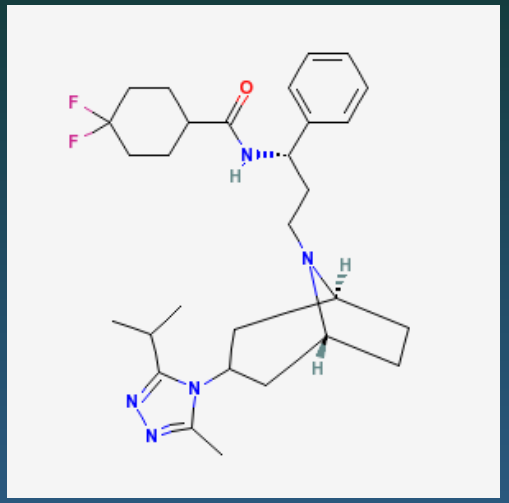
PC-815

- Carraguard + MIV-150 (NNRTI)
- In vitro activity
  - MIV-150 inactivates cell-free virus
  - MIV-150 and Carraguard are additive
  - EC50 of PC-815 is ~10X stronger than Carraguard
  - PC-815 is active against wide variety of HIV isolates
  - Seminal fluid does not impede activity
- HIV prevention studies ongoing in primate model
- Phase 1 clinical trials being planned

Source: Population Council

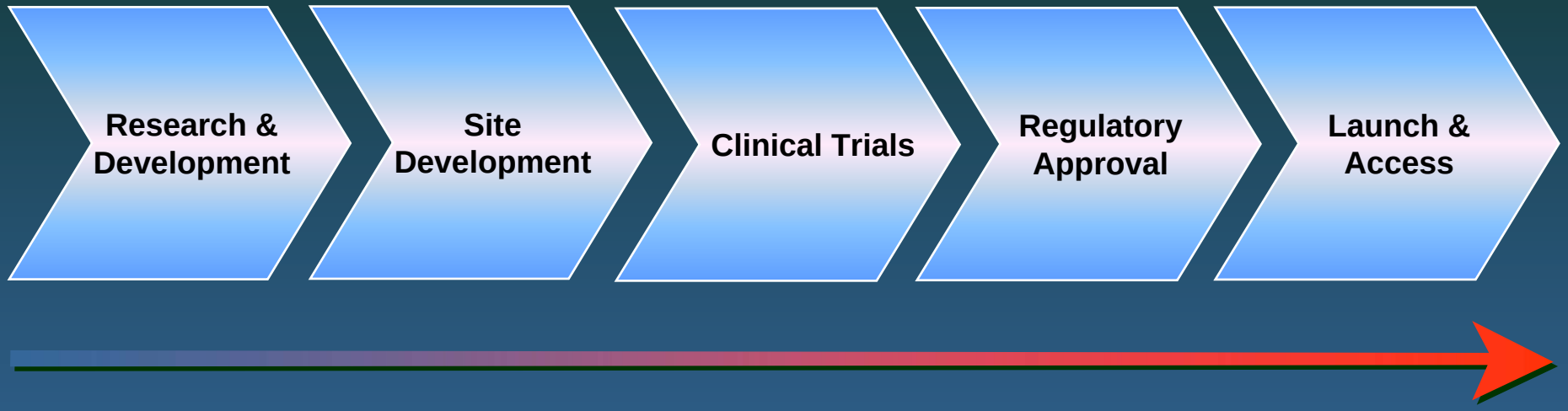
Topical Maraviroc

- CCR5 blocker
  - Pre-formulation ongoing
- Combination dapivirine/maraviroc
  - Silicone & EVA ring feasibility initiated
  - Gel initiated
  - Film to be initiated
  - Virology ongoing



- Preclinical assessment
  - 28-day vaginal rabbit dosing study ongoing
- PK and safety studies planned 2009-10
- Selzentry™ marketed as AIDS therapeutic

Microbicide Development Process



- IP rights
- Formulation
- Lab safety

- Community engagement
- Capacity building
- Incidence studies

- Safety
- Efficacy
- Acceptability

- Clinical trials
- Licensure
- Post-licensure studies

- Manufacturing
- Service delivery
- Marketing

Criteria for Moving Forward: Pre-Clinical

- Compounds assessed to identify best candidates for clinic

MECHANISMS OF ACTION

- Earlier in life cycle is better
- New mechanism of action
- Comparison with other candidates with same mechanism of action

LABORATORY STUDIES

- Toxicity / Potency
- Pre-formulation

COST & AVAILABILITY

- IP access to compound
- Drug synthesis process
- Ease of manufacture

Criteria for Moving Forward: Early Clinical Trials

- Candidates assessed in small numbers of volunteers

PHARMACOKINETICS

- Where drug goes in body, concentration, duration
- Preferred dosage:
  - Wide distribution in genital tract
  - Long duration
  - Sufficient concentration

ACCEPTABILITY

- Placebo formulations assessed in diverse populations
- Acceptability measured in all clinical trials

SAFETY

- Drug, formulation, delivery assessed for prolonged use
- Product safety evaluated in diverse populations
- Early clinical trials cannot fully predict risk of enhancing HIV transmission

Criteria for Moving Forward: Efficacy Trials

- Top candidates move into efficacy trials

BEST-IN-CLASS

- Essential criteria:
  - Potency
  - Safety
  - PK
  - Acceptable formulation
- Secondary criteria:
  - Mechanism of action
  - Cost
  - Ease of manufacture
  - Access / IP

Access Principles: Planning for Success

- Affordability
- Availability
- Accessibility
- Acceptability

Partnerships with Industry

Compound	License	Year	Type/Stage	Development Status
Dapivirine	Tibotec	2004	NNRTI	Phase I/II (vaginal gel, ring)
M167, M872, M882	Merck	2005	CCR5 blockers	Pre-clinical
BMS793	BMS	2005	gp120 binder	Early pre-clinical
Tenofovir	Gilead	2006	NRTI	Phase I PK (CONRAD / IPM) Phase IIB (CONRAD / CAPRISA) Phase IIB (MTN, planned)
Maraviroc	Pfizer	2008	CCR5 blocker	Pre-clinical
L'644 peptide	Merck	2008	gp41 binder	Early pre-clinical

Intellectual Property

- Non-exclusive royalty-free licenses to develop, manufacture and distribute antiviral compounds as microbicides in developing countries
- License provide for distribution on an affordable basis

Capacity Building at Research Centers

- Community engagement
- Referral networks for medical care/support
- Infrastructure and equipment
  - Build/purchase/lease and renovate space
  - Acquire medical and office equipment
- Staff development
  - Hire 15-20 per site with diverse expertise
  - Provide GCP, GCLP & study-specific training
- Communications, messaging and tools
- Financial management support
- HIV incidence studies

Ethical Guidelines for Clinical Trials

- Many studies taking place in developing countries

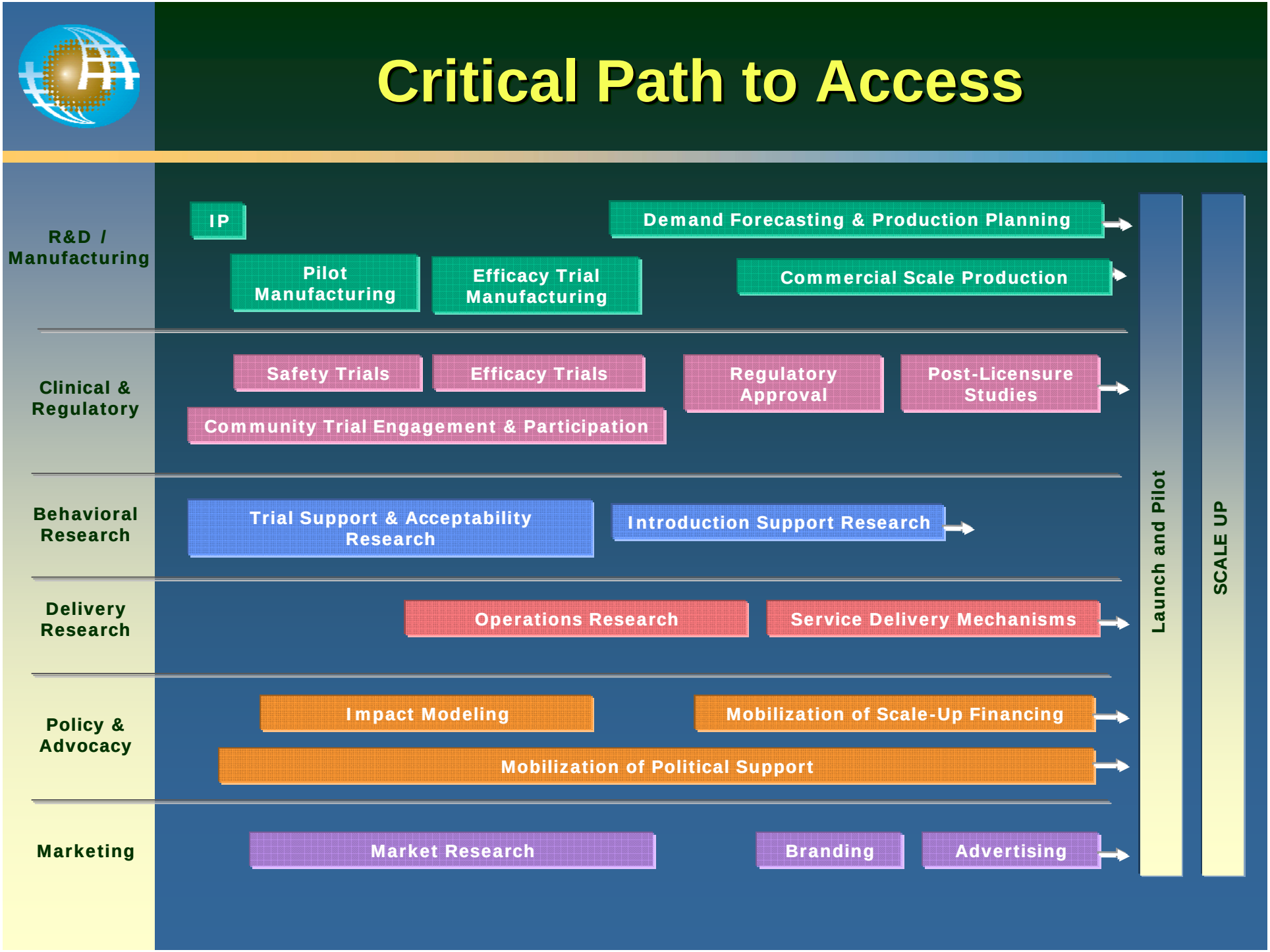
Key issues

- Community engagement
- Monitoring social harms
- Informed consent process
- Risk reduction counseling
- Family planning / condoms
- Management of pregnancy
- STI screening and treatment
- Testing positive at screening
- Participants who seroconvert
- Treatment for physical harms
- Post-trial access to products

Guidelines

- UNAIDS/WHO ethical guidelines in HIV prevention trials, 2007
- UNAIDS/AVAC good participatory practices, 2007
- South Africa GCP guidelines, 2006
- IPM ethical guidelines, 2006
- Nuffield Council on Bioethics, 2005
- GCM consensus points, 2005
- CIOMS biomedical guidelines, 2002
- WMA Declaration of Helsinki, 2000
- ICH GCP, 1996

Critical Path to Access



Illustrative Access Activities

- Acceptability studies
- Global manufacturing survey completed
- LSHTM modelling of microbicide introduction
    - India, South Africa, Tanzania
- Pharma lessons learned ARV treatment introduction

Discussion