INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

The Path to Licensure for the Dapivirine Ring

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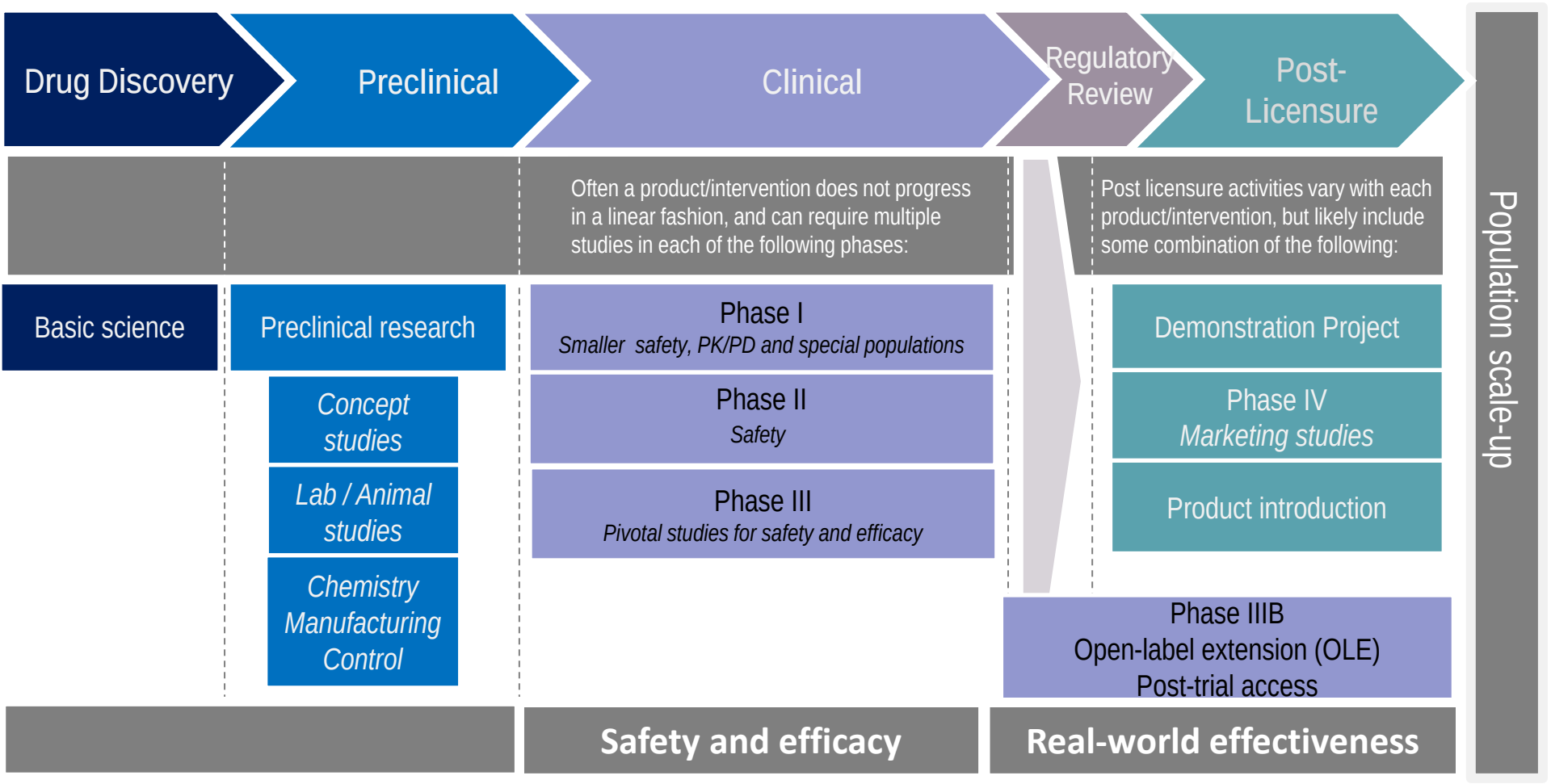
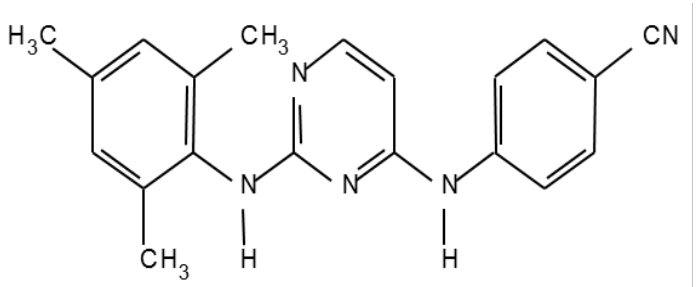
MTN Regional Meeting
Westin Cape Town Hotel, Cape Town, South Africa
25 October 2014

Developing HIV Prevention *Products for* **Women** *worldwide*

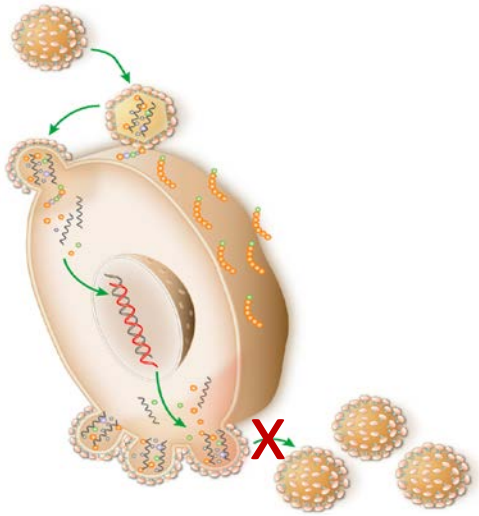
Dapivirine Development Pathway



Dapivirine



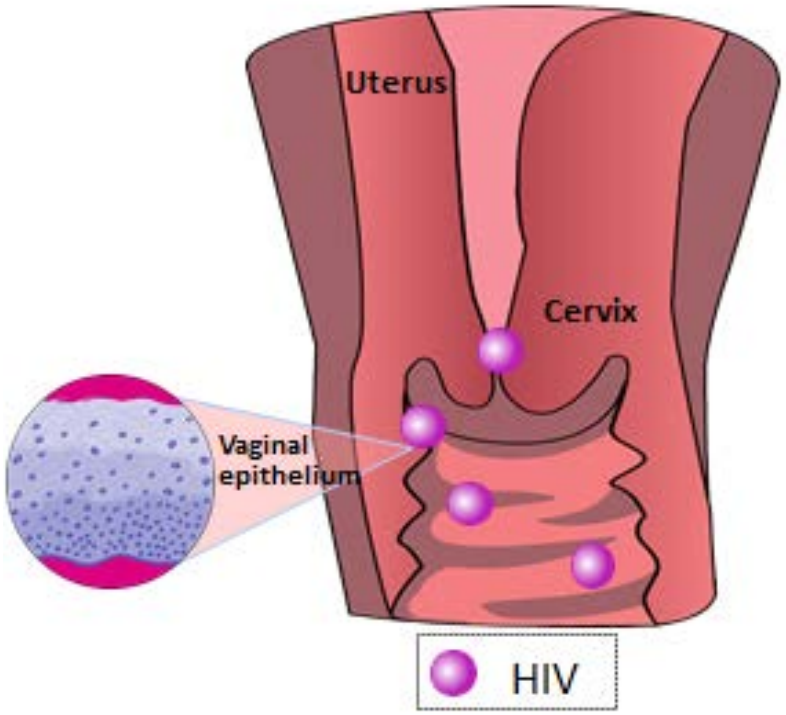
- Highly potent ARV (NNRTI)
- Developed by Janssen
  - Evaluated in preclinical and clinical studies as oral therapeutic
- Licensed to IPM in 2004
  - Royalty-free license to develop as topical microbicide for HIV prevention in developing countries
- Acts inside cells in the vagina to block the ability of HIV to multiply



HIV Prevention Method: Microbicides

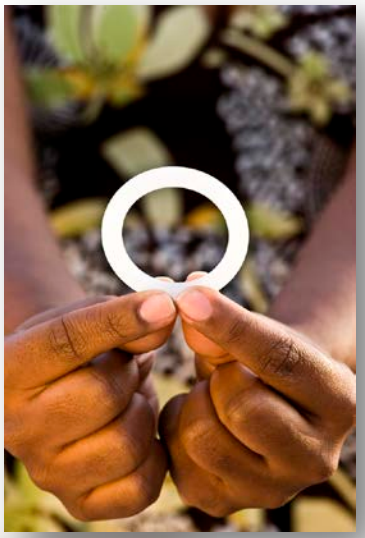
Critical to deliver:

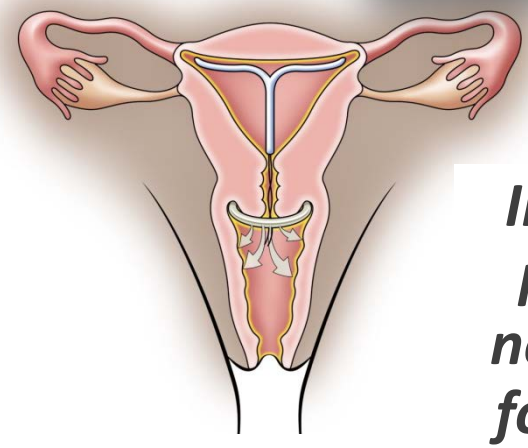
- the right ***drug*** to
- the right ***place*** at
- the right ***time***



Microbicide Vaginal Rings

- **Long-acting: monthly or longer**
  - Could potentially improve adherence
  - Better adherence → better effectiveness
- **Easy to use, comfortable**
  - Flexible ring, can be self-inserted
  - Rarely felt by women or male partners
  - Little or no impact on sexual activity
- **Suitable for developing world**
  - Relatively low manufacturing cost
  - Good safety and acceptability data

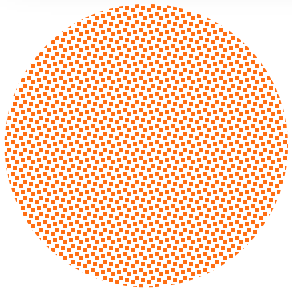




Important potential new option for women

Dapivirine Vaginal Ring-004

- Off-white flexible platinum-cured silicone matrix ring (56mm x 7.7mm)
- Manufactured by mixing dapivirine into liquid silicone
- The mixture is put into a ring mold and heated
- The solid ring can slowly release drug into vaginal tissue



Cross-sectional profile

Preclinical

Preclinical Studies

- **Primary Pharmacology**
  - *In vitro*
    - Lab adapted isolates, cell-associated isolates, primary HIV-1 strains across clades, against drug-resistant strains
    - In cell lines & primary cells
    - In relevant physiological fluids and across pH
  - Mode of action studies
  - Development of resistance
  - *Ex vivo* – in tissue explants
  - *In vivo* – in mice

- **Secondary & Safety Pharmacology**
  - Receptor, enzyme & ion channel screens
  - Central & peripheral nervous system
  - Respiratory system
  - Cardiovascular system

- **Pharmacokinetics**
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
  - Drug interactions

- **General Toxicology**
  - Acute - mice and rats
  - Sub-chronic - Rodent and non-rodent
  - Chronic - rodent (6 months) & non-rodent (9 months)

- **Reproductive Toxicology**
  - Fertility & reproductive performance (rat)
  - Embryofetal development (rat & rabbit)
  - Peri- & post-natal development (rat)

- **Genotoxicity**
  - *In vitro* – microbial & mammalian cell
  - *In vivo* – micronucleus test (mouse or rat)

- **Carcinogenicity**
  - 2 years (rat)

- **Other**
  - Sensitization assay
  - Sperm toxicity
  - Compatibility with vaginal flora
  - Biomarkers (pro-inflammatory/ innate immunity)
  - Biocompatibility (medical device)

Clinical

Phase I: Safety and PK

Dapivirine Ring-004

Single and

Multiple Rings

- Multiple dosing of monthly rings well tolerated, no safety concerns
- Supported sustained-release over 28-days and 35-days
- Vaginal fluid levels on Day 28 were at least 4000 times higher and on Day 35 at least 3000 times higher than the *in vitro* 99% inhibitory concentration (3.3 ng/ml) in cervical tissue
- The potential for the ring to be effective for a period of at least 35 days was supported by *ex vivo* experiments in which viral replication in susceptible cells challenged with HIV-1 in the presence of fluids collected by cervicovaginal lavage showed protection
- The lavage procedure meant that the fluids were substantially diluted during collection, but high levels of inhibition were seen even when the fluids were diluted by a further 10-fold
- Plasma levels < 1 ng/ml

Phase I: Safety and PK cont.

Dapivirine Ring-004
Extended Use
(up to 12 weeks)
of a Single Ring

- Dapivirine plasma and vaginal fluid concentrations decreased after 4 weeks with the duration of ring use
- The minimum vaginal fluid level at 12 weeks was at least 300 times higher than the *in vitro* 99% inhibitory concentration (3.3 ng/ml) in cervical tissue
- Dapivirine ring residual levels indicate that ≈4 mg dapivirine is released from Ring-004 over 4 weeks and ≈10 mg dapivirine over 12 weeks

Clinical

Phase I cont.

Dapivirine Ring-004 Vaginal Miconazole (1200mg capsule)

- Concomitant use of Dapivirine vaginal ring and miconazole nitrate was safe and well tolerated
- Dapivirine release from Ring-004 was similar in the presence and absence of miconazole nitrate
- Changes in local and systemic exposure of both compounds were observed but considered unlikely to adversely affect the efficacy of either drug (HIVR4P 2014, Poster P15.09)

Placebo Ring Male & Female Condom Functionality Studies

- Male and Female condom use was safe and well tolerated with vaginal ring use
- The presence of the ring did not negatively affect the total clinical failure rate of neither male nor female condoms (Male Condom Study Poster: HIVR4P 2014, Poster P53.01)
- No ring expulsions or removals during intercourse were reported with the female condom

Clinical

Phase I : Planned

Menses and Tampon use impact on Dapivirine PK levels

- Objective:
  - To determine if menses and tampon use have an effect on local and systemic dapivirine concentrations
- Design:
  - Open-label, randomised, crossover trial
  - Two cohorts of 16 healthy HIV-negative women

Clinical

Phase II

Dapivirine Ring-004

Safety

Acceptability

- Multiple ring use (3 consecutive rings inserted monthly) was well tolerated with no safety concerns in healthy, HIV-negative African women
- High acceptability was reported by women and their partners
- Self-reported adherence was good
- Ring was highly acceptable to women in Africa
- Progressed to Phase III clinical program

Special Populations:

- Adolescents
- Post-Menopausal

- Objective:
  - Safety , PK and acceptability of dapivirine ring
- Design:
  - Double-blind, randomised, placebo-controlled trials
  - 96 participants each, 3:1 randomisation
  - Three consecutive rings inserted monthly

Regulatory Review

Regulatory: Authority Consultations

Scientific and regulatory advice on Phase III trial design and requirements:

- US Food and Drug Administration (FDA)
- European Medicines Agency (EMA)

Country-specific requirements from national regulatory authorities (NRAs):

- Kenya
- Malawi
- South Africa
- Tanzania
- Uganda
- Zambia
- Zimbabwe

Clinical

Phase III

	IPM 027 (The Ring Study) V1.0 Amendment 3.0	MTN-020 (ASPIRE)
Primary Objective	Safety & Efficacy	Safety & Effectiveness
Design	fixed time	endpoint driven
Endpoints: confirmed HIV-1 seroconversions	expected 96	≈120
Number of participants	Total 1950 Active arm 1300	Final Enrolled 2629 (planned ≈ 3476) Active arm ≈1315 (planned ≈1738)
Randomization	2:1 Double-blind; Placebo-controlled	1:1 Double-blind; Placebo-controlled
Power	81% power to detect 50% treatment effect	90% power to detect 60% treatment effect with a lower bound of 25% treatment effect
Age	18-45 yrs	18-45 yrs
Product use period	24 months fixed	until end of study (12 months min)

Regulatory Review

Regulatory: Application Requirements

- Each country has a different application format
- However, each country requires the same types of data from early preclinical tests in the lab through efficacy studies
- For the dapivirine ring, this means that IPM will have organized **13 years of data and findings from nearly 250 studies** into each application
- The average length of a dossier is approximately **500,000 pages** and could fill a **3x3 meter room**

Regulatory Review

A Peek Inside a Regulatory Application

- Index
- Summary
- Chemistry, manufacturing and control (CMC)
- Samples, methods validation package and labeling
- Nonclinical pharmacology and toxicology
- Human pharmacokinetics and bioavailability
- Microbiology (for anti-microbial drugs only)
- Clinical data
- Statistics

- Integrated Safety update report
- Case report tabulations
- Case report forms
- Patent information
- Patent certification

Regulatory Review

Ongoing

IPM is actively assembling a **global dossier** of all the data on dapvirine ring's development:

- Product quality (CMC)
  - Janssen and IPM preclinical study data
- Safety and Pharmacology
  - Janssen and IPM preclinical study data
  - IPM clinical safety study data
  - IPM pharmacokinetic study data
  - Integrated safety data of Phase III clinical studies
- Efficacy (The Ring Study and ASPIRE)
  - Integrated efficacy data of Phase III clinical studies

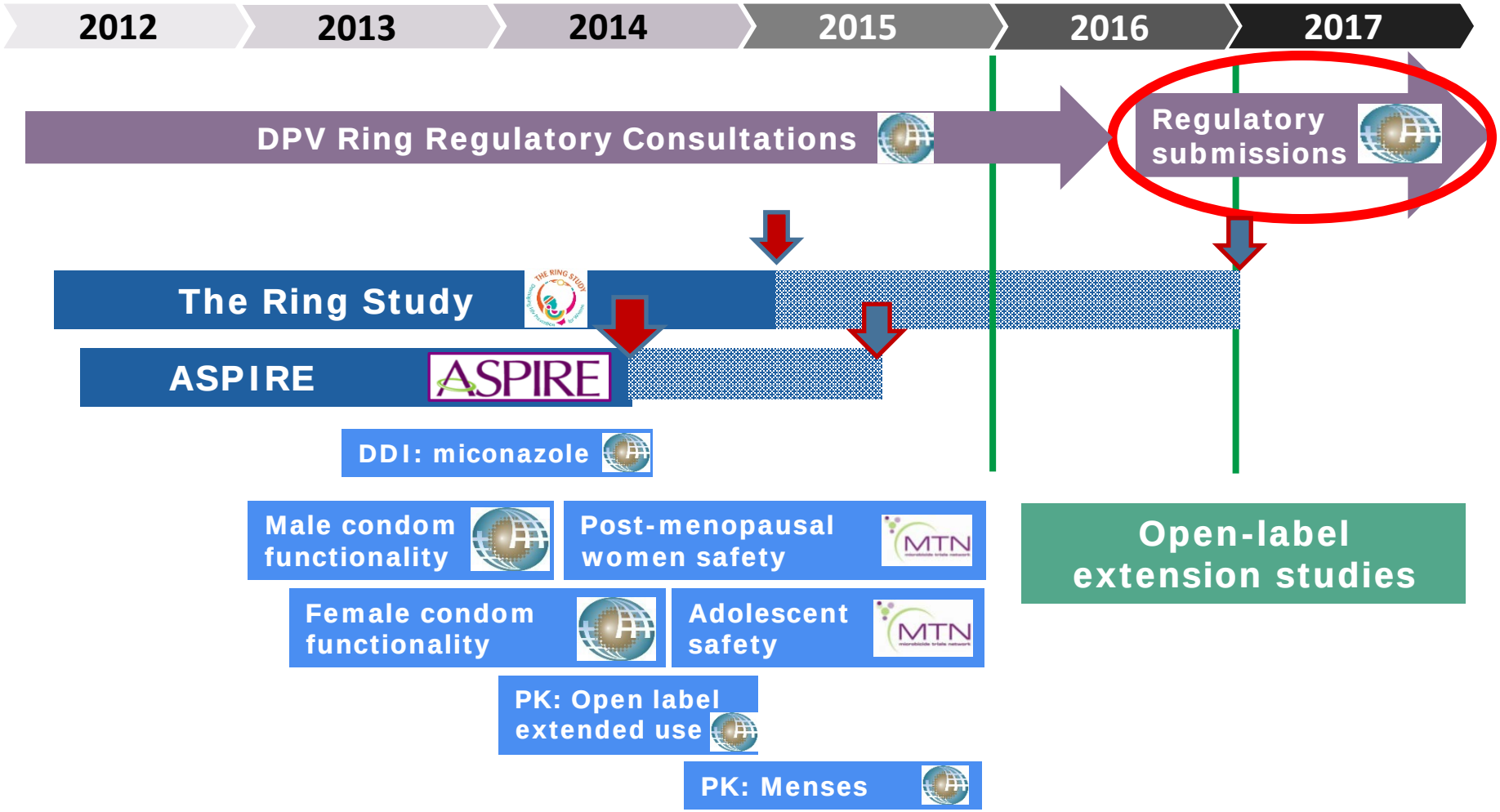
This will allow us to more quickly format specific applications to different regulatory agencies throughout Africa

Clinical: Post Trial Access

Phase IIIB

	IPM 032 A Follow-on Open-label Trial to Assess continued Long-term Safety of and Adherence to Dapivirine (25 mg) Vaginal Ring-004 in HIV-negative women	MTN-025 An Open-Label Follow-on Trial to Assess the Continued Safety of a Vaginal Ring Containing Dapivirine
Primary Objective	Long-term Safety Adherence	Long-term Safety Adherence
Design	Open-label; Randomised	Open-label
Number of participants	Follow-on to IPM 027	Follow-on to MTN-020
Randomization	Open-label	Open-label
Follow-up Schedule	1-monthly 3-monthly (2 additional rings)	1-monthly 3-monthly (2 additional rings)
Treatment Regimen	1-monthly ring replacement	1-monthly ring replacement
Product use period	Approx. 1-year follow-up with option to extend	Approx. 1-year follow-up

Dapivirine Ring Program Timeline



International Partnership for Microbicides

Acknowledgements .....

Thank you to All of You.....