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Dapivirine Ring: The Roadmap to Licensure

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MTN Regional Meeting

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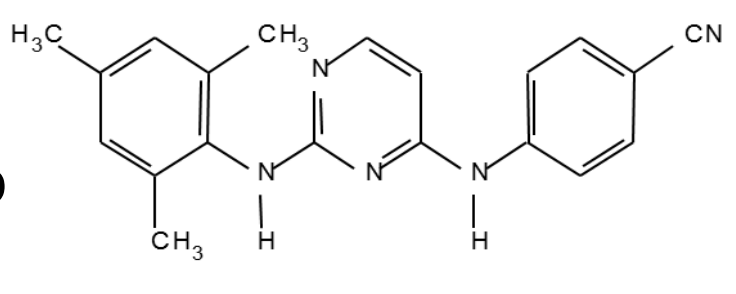
Developing HIV Prevention *Products for* **Women** *worldwide*

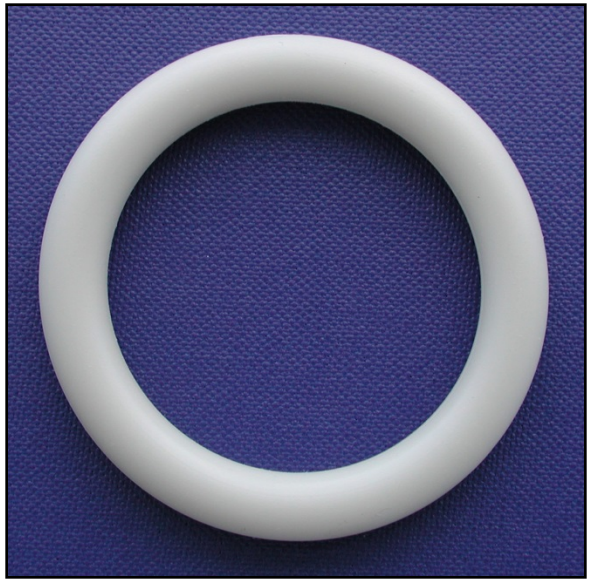
Drug Discovery: Dapivirine



- Highly potent ARV (NNRTI)
  - Acts inside cells in the vagina to block HIV's ability to multiply
- Originally tested by Janssen as therapeutic
- IPM approached Janssen in 2004
  - Negotiated royalty-free license to develop as topical microbicide for HIV prevention in developing countries
  - Expanded to exclusive worldwide rights agreement in 2014

Dapivirine Ring – Early Prototypes

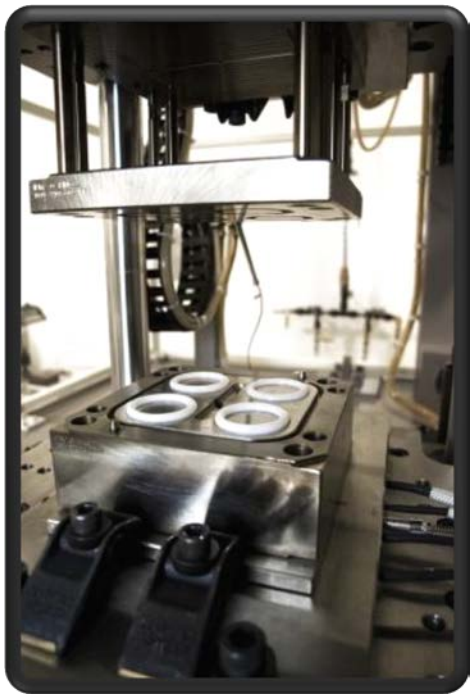
- Advantages: long-acting, easy to use
- Incorporated women's feedback from market research
- Extensive development program to identify:
  - Optimal design for drug release
  - Safe, stable materials
- Three prototypes tested in clinical trials (2004-2008)



Fourth Time's a Charm: Ring-004

- Flexible silicone ring
- Self-inserted every 4 weeks
- Slowly releases drug into cervix and vagina
- Highly acceptable to women and their male partners
- Women are willing to use the ring if it is found effective

Meeting Manufacturing Demands



- 2005: IPM built a clinical trials manufacturing facility for gels, helping to shorten trial time lines
- 2007: Initiated expansion for ring manufacturing
- 2010: Scaled up by transferring technology to partner QPharma (Sweden)

Dapivirine Ring Phase III Program

IPM 027 *The Ring Study*	**Long-term safety and efficacy** study • 1959 participants, ongoing (2012-2016) in Africa
MTN-020 *ASPIRE*	**Safety and efficacy** study • 2629 participants in Africa (2012-2015), in data analysis
Additional safety studies	• Drug-drug interaction (one completed; one ongoing) • Extended use pharmacokinetic profile(completed) • Condom functionality – male (completed); female (clinical study report in finalization) • Safety in women >45 (database lock in process) • Safety in adolescents (ongoing) • Menses and tampon use PK (ongoing)

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MTN microbicide trials network

National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

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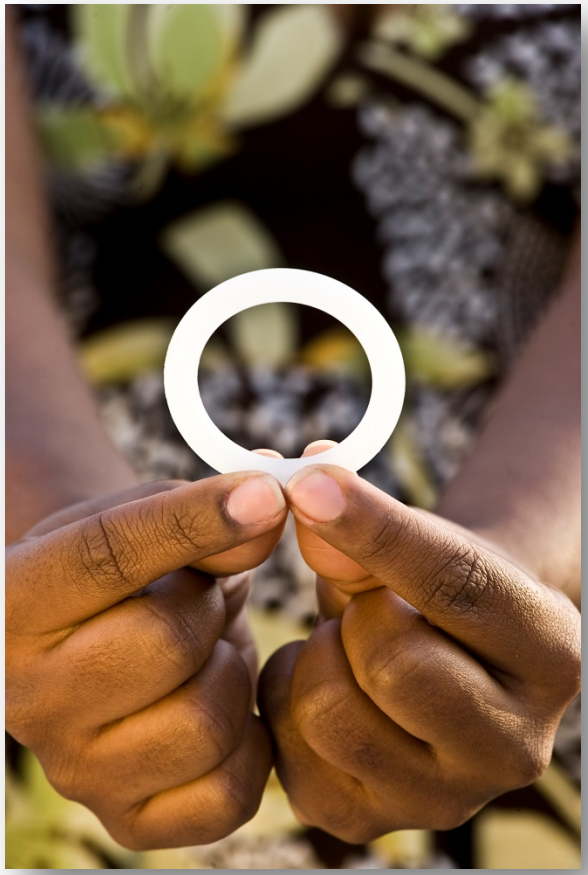
Why Two Parallel Phase III Trials?

- Regulatory approval usually requires results from at least two Phase III clinical trials
- One Phase III trial can take 4-6 years, from design to data analysis

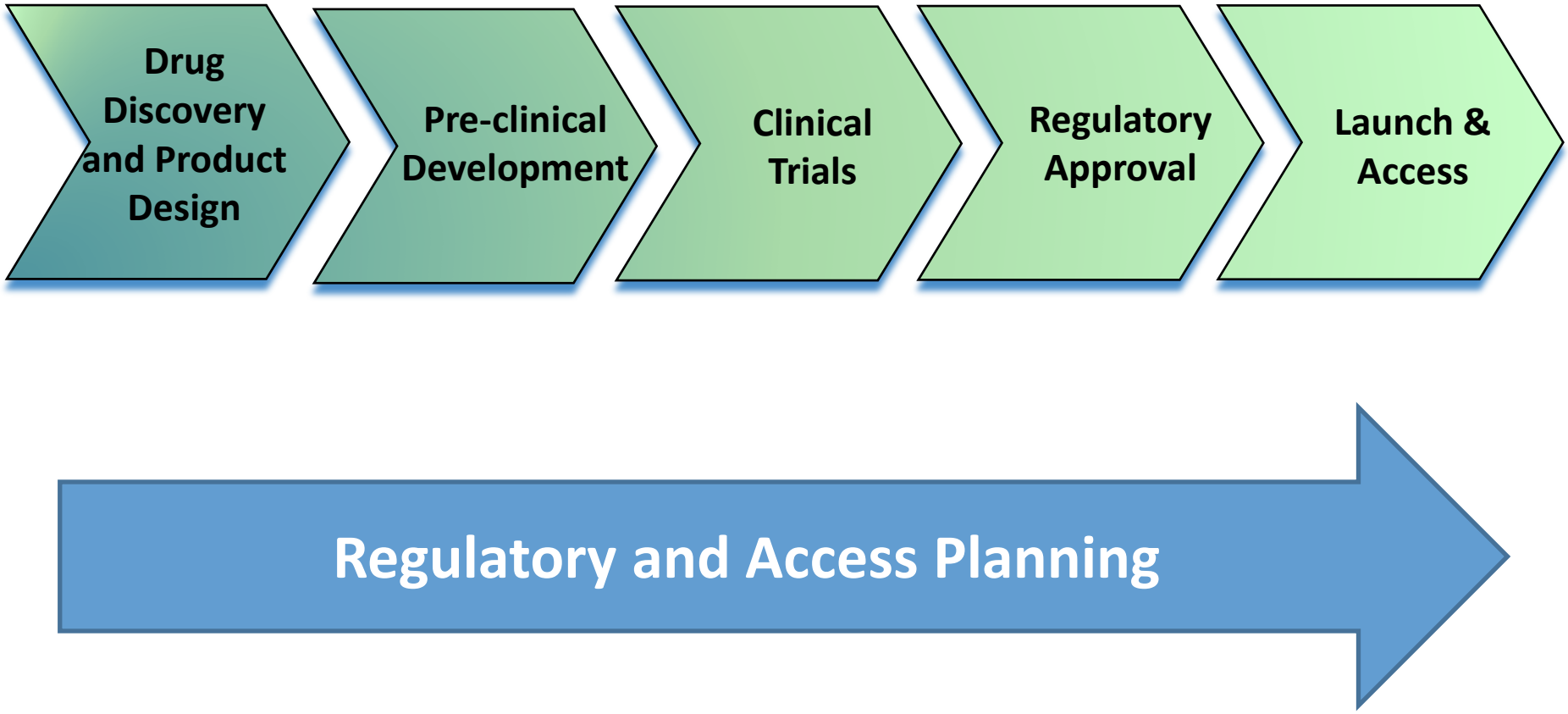
Running two clinical trials in parallel ***saves time***— enabling rapid regulatory submission if the dapivirine ring demonstrates safety and efficacy

Looking Ahead to Results



First efficacy results expected as soon as early 2016

From Development to Access



Timeline to Roll-out

2015	2016	2017	2018	2019

IPM 027
The Ring Study

Results?

MTN-020/ ASPIRE

Results

Open-label extension studies: IPM 032 & MTN-025

Supporting Safety and PK Studies

Dapivirine Ring Regulatory Consultations

EMA Art 58

WHO PQ → African NRAs (submission & approval)

US FDA

S. Afr. MCC

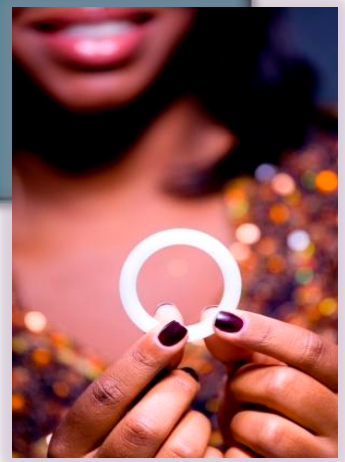
Planning for Product Introduction

From…

- Phase III clinical trials (The Ring Study and ASPIRE)
- Small-scale manufacturing
- Regulatory dossier preparation

To…

- Regulatory approval
- Post-efficacy access
- Affordable and sustainable commercial manufacturing
- WHO pre-qualification and guidelines for product use
- Optimized supply chain
- HIV and product awareness



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Regulatory Planning

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Regulatory Considerations: Dapivirine

- Dapivirine is a new chemical entity (NCE)
- Approval pathway for a NCE for HIV prevention is more complex than for an already approved treatment drug being used for prevention (like Truvada for PrEP use)
- Need to include more comprehensive safety and quality data

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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

WHO Prequalification (PQ)

- Process to evaluate whether a drug meets global standards of:
  - Quality, safety, efficacy
- Many African regulators use WHO PQ to determine which new products to approve, and also review FDA and EMA decisions

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 is organizing **13 years of data and findings from nearly 250 studies** into each application

Preparing for Regulatory Submission

IPM is assembling a **global dossier** of all data on dapivirine ring:

- Product quality (CMC)
  - Janssen and IPM preclinical study data
- Safety and Pharmacology
  - Janssen and IPM preclinical study data
  - IPM and MTN clinical safety study data
  - IPM pharmacokinetic study data
  - Integrated safety data of 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

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Post-Efficacy Access

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Phase IIIb Open-Label Follow-on Studies

- When Phase III trials show efficacy, open-label follow-on studies would be conducted to:
  - Give women who were enrolled in The Ring Study and ASPIRE pre-licensure access to the dapivirine ring
  - Collect additional information on safety and adherence to support broad product roll-out


DREAM
Dapivirine Ring Extended Access and Monitoring


HOPE
Out of ASPIRE, there is HOPE

Dapivirine Ring Phase IIIb Studies: DREAM & HOPE

	DREAM (IPM 032)	HOPE (MTN-025)
Primary Objective	Long-term safety and adherence	
Design	Open-label	
No. of participants	Follow-on to IPM 027	Follow-on to MTN-020
Follow-up Regimens	1-monthly (no additional rings) 3-monthly (optional: 2 additional rings)	
Treatment Regimen	1-monthly ring replacement	
Product use period	Approx. 1-year follow-up with option to extend	
Expected start	2016 or 2017, pending The Ring Study efficacy	2016, pending ASPIRE efficacy

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Manufacturing

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Commercial Manufacturing Summary

- QPharma will be commercial launch partner
- IPM working with Trelyst as potential long-term, low-cost commercial supply partner
  - IPM and Trelyst are developing a bridging strategy to support transfer to Trelyst as a commercial manufacturer
- Capacity in place to meet commercial demand with ability to scale up
- COGS at launch of ~$5/ring with potential to reduce to ~$2/ring

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Global Dapivirine Ring Access

Developing HIV Prevention Products for Women worldwide

Key Elements for Ring Introduction

Commercial Manufacturing & Supply	• Engage potential commercial manufacturing partners • Explore commercial procurement and distribution options (supply chain)
Economics & Financing	• Cost-effectiveness and willingness-to-pay studies • Understand access-related funding requirements and opportunities
Country Strategy, Planning & Implementation	• Demand forecasting, stakeholder and social network mapping • Meet with country-specific stakeholders • Product awareness, education and demand-generation/marketing • Demonstration projects and implementation research
Public Affairs, Policy & Communications	• Engage in policy discussions and knowledge building with key global, regional and local partners, donors and advocates • Develop strategy to influence WHO guidelines for HIV prevention using vaginal rings

Timeline to Roll-out

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★ ***Earliest possible launch***

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