



INTERNATIONAL  
PARTNERSHIP FOR  
MICROBICIDES

# Preparing for Access to Microbicides and the Dapivirine Ring for HIV Prevention

*Preliminary Strategy*

International Partnership for Microbicides

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## 1. Abbreviations

<b>AIDS</b>	Acquired Immunodeficiency Syndrome
<b>API</b>	Active Pharmaceutical Ingredient
<b>ARV</b>	Antiretroviral
<b>ART</b>	Antiretroviral treatment
<b>BCC</b>	Behavior Change Communications
<b>BCG</b>	Boston Consulting Group
<b>BMGF</b>	Bill & Melinda Gates Foundation
<b>BMZ</b>	German Federal Ministry for Economic Cooperation and Development
<b>CAPRISA</b>	Centre for the AIDS Programme of Research in South Africa
<b>CCM</b>	Country Coordinating Mechanism
<b>CDC</b>	Centers for Disease Control and Prevention (U.S.)
<b>CHAI</b>	Clinton Health Access Initiative
<b>CSO</b>	Civil Society Organization
<b>CTM</b>	Clinical Trial Material
<b>DFID</b>	Department for International Development (U.K.)
<b>EMA</b>	European Medicines Agency
<b>EOI</b>	Expression of Interest
<b>FCAA</b>	Funders Concerned About AIDS
<b>FDA</b>	Food and Drug Administration (U.S.)
<b>FHI</b>	Family Health International
<b>GAVI</b>	Global Alliance for Vaccines and Immunizations
<b>GFATM</b>	Global Fund to Fight AIDS, Tuberculosis and Malaria
<b>GSK</b>	GlaxoSmithKline
<b>HIV</b>	Human Immunodeficiency Virus
<b>IDA</b>	International Dispensary Association
<b>IEC</b>	Information, Education, and Communications Campaigns
<b>IHP+</b>	International Health Partnership

<b>IPFF</b>	International Planned Parenthood Federation
<b>IPM</b>	International Partnership for Microbicides
<b>MAF</b>	Microbicide Access Forum
<b>MSM</b>	Men Who Have Sex with Men
<b>NCE</b>	New Chemical Entity
<b>NGO</b>	Non Governmental Organization
<b>PAHO</b>	Pan-American Health Organization
<b>PAS</b>	Product Acceptability Study
<b>PDP</b>	Product Development Partnership
<b>PEPFAR</b>	President's Emergency Plan for AIDS Relief (U.S.)
<b>PMTCT</b>	Prevention of Mother-to-Child Transmission of HIV
<b>PQR</b>	Price and Quality Reporting
<b>R&amp;D</b>	Research and Development
<b>RFP</b>	Request for Proposal
<b>SCMS</b>	Supply Chain Management System
<b>SmPC</b>	Summary of Product Characteristics
<b>STI</b>	Sexually Transmitted Infection
<b>SWAp</b>	Sector Wide Approach
<b>TPP</b>	Target Product Profile
<b>UNAIDS</b>	Joint United Nations Programme on HIV and AIDS
<b>UNFPA</b>	United Nations Population Fund
<b>UNICEF</b>	United Nations Children's Fund
<b>USAID</b>	U. S. Agency for International Development
<b>VCT</b>	Voluntary Counseling and Testing
<b>WHO</b>	World Health Organization

## 2. Executive Summary

### Introduction

The International Partnership for Microbicides (IPM) is a non-profit product development partnership with the mission to accelerate the development of, and access to, safe and effective microbicides and other HIV prevention tools for women in developing countries. As of 2010, IPM had royalty-free licenses to develop eight antiretroviral (ARV) drugs for use as microbicides in various forms (vaginal gels, rings, films, tablets, etc.). From among these, *dapivirine ring* and *dapivirine gel* are IPM's most advanced candidates, having been tested in multiple Phase I and Phase I/II clinical safety trials in Africa, Europe and the US. Additionally, IPM holds a co-exclusive license to *tenofovir gel*, along with CONRAD, granted by Gilead Sciences; tenofovir gel demonstrated a 39% protective effect against HIV infection in the CAPRISA 004 trial in South Africa (results released in July 2010).

In 2010, IPM selected *dapivirine vaginal ring* for its microbicide Phase III efficacy program, scheduled to commence in 2011. The vaginal ring has been prioritized for further development because of its long-acting properties (ring can be used for a month or longer), good safety profile, acceptability, ease of use, manufacturing cost, and other factors. It is likely that long-acting products may also achieve good adherence (correct and consistent use of the product), and therefore vaginal rings may have benefits over other dosage forms that would need to be used more frequently (such as vaginal gels, films, tablets, etc.)

To ensure rapid access by women in developing countries to any product that might prove successful in IPM's Phase III trials, IPM initiated an Access Strategy, with *dapivirine ring* as a relevant case study. The plan builds on IPM's Strategic Plan 2011-2015 and will serve as a guide for IPM on how to continue to direct attention to critical-path activities through product development and launch (2011-2018). Much of this work must be done before the final product is ready for production and distribution. Some of this work will remain preliminary until the final product profile is established. This will involve significant work in planning, mobilizing, advocating, and building relationships and partnerships.

### Access to Microbicide Products

"Access" to microbicides refers to people's ability to *obtain and appropriately use good quality, approved microbicide products* whenever and wherever they want and need HIV prevention. Five key concepts are central to understanding and achieving access: architecture, availability, acceptability, affordability, and appropriate use. This Access Strategy is organized around these five concepts.

### *Architecture*

“Architecture” refers to the network of organizations at the global, national, and local levels that support, connect and implement all access activities. IPM will continue to build the architecture for microbicide access by identifying and evaluating potential partners for manufacturing, national regulatory activities, pharmacovigilance, advocacy, and communication. An early decision point for IPM will be determining who will hold market authorization in the countries where the product(s) will be launched. The market authorization holder has responsibility for submission of dossiers at the national level and pharmacovigilance.

### *Availability*

“Availability” ensures that there is sufficient high-quality production and supply of the microbicide product, and reliable channels for distribution, to meet user demand. IPM’s focus will be on identifying suitable partners to manufacture the product for access. It will also continue to develop a regulatory strategy that mitigates the risk of time delays in national-level registration and ensures eligibility for donor financing. As Phase III trials proceed, IPM will prioritize launch countries and will identify potential synergies with national and regional partners.

Throughout the Phase III program, IPM will analyze the anticipated demand and reevaluate the current forecast against the existing target product profile to determine if and when additional product supply capacity is required.

### *Acceptability*

“Acceptability” refers to whether microbicides — in various forms — are satisfactory to end-users (women and their sexual partners) and to any gatekeepers who control availability.

To gain an understanding of product acceptability, IPM and others have conducted a range of acceptability studies in Africa and elsewhere, including market research studies with placebo vaginal gels, films, tablets and soft gel capsules as well as a clinical trial with placebo vaginal rings; these studies conclude that these products are acceptable and their likelihood of use is high in various countries and communities in Africa; the products were assessed after actual use by women evaluating a variety of characteristics including product size, texture, color, odor, leakage, insertion ease, sexual pleasure for them and their partners, etc. Some male partners also expressed their preferences as part of the studies. These initial findings are informative and are being incorporated into ongoing product development. Identification of appropriate partners for advocacy, branding, social marketing, and communications is also under

way. Additional acceptability, adherence, and other social-behavioral data are being collected as part of ongoing microbicide clinical trials. A summary of existing acceptability data is included as an appendix to this strategy.

### *Affordability*

“Affordability” directs attention to the costs of microbicide products, and programs to deliver them, and seeks to ensure products are affordable to purchasers, funders and end-users. IPM has acquired licenses to intellectual property rights for all the ARV drugs in its product portfolio (to ensure the products can be made available at low or no cost in developing countries) and is prioritizing APIs with lower production costs. IPM is also focusing on another key strategy—securing financing for access. IPM will maintain and strengthen its relationships with current donors through ongoing dialogue, transparency and accountability. Specifically, IPM will continue to reach out and engage potential new donors, gaining an in-depth understanding of their funding priorities and procedures to determine whether they might be able to provide financing for access.

### *Appropriate Use*

Attention to critical-path activities in the area of “appropriate use” ensures that microbicides are used properly in order to achieve the desired health outcome: preventing HIV transmission. To this end, IPM will identify partners who can conduct medical education activities targeted to health care providers and awareness campaigns for end-users. The design of packaging and instructions in appropriate languages and with visual aids is another strategy that IPM will employ to better ensure appropriate use of the products. IPM and its access partners will begin planning for work in these areas before launch of the product.

### Timeline

The timeline for IPM’s critical-path activities is separated into three key stages of implementation. The first implementation stage occurs before IPM forms partnerships for access. In this stage, IPM will continue its microbicide clinical development program. Phase I/II and III clinical trials will move forward and serve to inform broader access issues. IPM will also continue to develop a strategy to obtain licensure with EMA and/or FDA as well as African regulatory agencies. During this period, IPM will conduct country studies to look for synergies at national and regional levels that can inform a launch strategy in the initial clinical trial countries.

IPM’s second stage of implementing critical-path activities focuses on selecting and securing partnerships for access. Building the architecture for access is one of the most important actions IPM will take in the overall development cycle for microbicides. IPM will seek partnerships with product manufacturers who also have competencies in managing regulatory product approval, pharmacovigilance, medical education, and

communication functions. If a single partner cannot be identified to take on all of these functions, then IPM will partner with a mix of highly competent organizations in order to achieve the desired goal of access implementation. In terms of financing, IPM will continue to engage existing donors as well as seek new donors.

The final stage of implementation occurs after the partnerships are in place. During this stage, IPM will determine its level and depth of engagement. IPM and its access partners will develop operational work practices to enable the partnerships to reach their goals. The access partnerships will engage in medical education for health professionals and end-users in target countries to generate demand for the product. At this stage, local partners will take on the majority of implementation activities.

### Maintaining the Access Strategy

This Access Strategy was developed in 2010, before formal initiation of IPM's microbicide Phase III program, and presents both potential access barriers and strategies based on the best information available about current product characteristics and the contexts in which microbicides will be made accessible to women.

In particular, the Access Strategy is using *dapivirine vaginal ring* as a case study of a microbicide product that will eventually reach the market. As this information changes, IPM will update and revise the Access Strategy accordingly.



### 3. Introduction to the Access Strategy

IPM is a non-profit product development partnership with the mission to accelerate the development of, and access to, safe and effective microbicides and other HIV prevention tools for women in developing countries.

Established in 2002, IPM raises funds and implements strategic efforts to fulfill the promise of microbicides, which have the potential to be critically important components of a comprehensive global response to the HIV/AIDS epidemic. Widespread use of microbicides, once proven safe, effective, and acceptable, could help *prevent* further spread of the HIV virus—and save many lives.

To illustrate the potential importance of microbicides containing ARV drugs, in an important milestone for HIV prevention, the CAPRISA 004 microbicide Phase IIB trial found a *39% protective effect* against HIV infection among women using 1% *tenofovir gel* (the first ARV-based microbicide to be tested in an efficacy trial).<sup>1</sup> Tenofovir gel also demonstrated a good safety profile. In addition to showing efficacy against HIV, the trial showed that tenofovir gel provided 51% protection against infection with herpes simplex virus type 2 (HSV-2). With successful proof-of-concept for an ARV-based microbicide, it is hoped that ARV approaches to prevention have the potential to transform the response to the HIV/AIDS epidemic.

In addition to confirmatory work on tenofovir gel, research is urgently needed to develop additional drugs and formulations that hold promise for increasing efficacy and addressing product adherence concerns, such as the sustained-release dapivirine vaginal ring being developed by IPM that is ready to move into efficacy trials in 2011.

The impact of the AIDS epidemic underscores the importance of this research. Since the inception of the AIDS epidemic in the early 1980s more than nearly 30 million people worldwide have died of HIV-related causes. Two-thirds of people currently living with HIV are in sub-Saharan Africa—where women make up approximately 60% of people living with HIV/AIDS. Stemming and reversing the AIDS epidemic would represent a major milestone of global leadership, helping to achieve promises such as the Millennium Development Goals and the 2001 United Nations General Assembly Special Session's Declaration of Commitment on HIV/AIDS. Developing and making microbicides accessible to women who are most at risk for HIV infection could contribute to the achievement of commitments to the human rights and well-being of women, their families and their communities.

While the primary focus of IPM has been on developing and testing effective microbicide products, IPM has also devoted increasing attention and resources to preparing for distribution and use of a microbicide product once one is licensed for use. In its organizational Strategic Plan, IPM notes a serious risk faced by many new medical

products: an extended time lag between registration and availability of product. This Access Strategy is one link in a long chain of activities that will contribute to minimizing that time lag by promoting access to microbicides for women who need them as soon as a product is available. Among the various outputs of these activities are:

- Meticulous planning, as embodied in the “pathway to access” outlined in IPM’s organization-wide Strategic Plan<sup>2</sup> and the development and costing of models of alternative distribution strategies<sup>3</sup>
- Research on lessons from comparable initiatives, such as the roll-outs of new contraceptive technologies<sup>4</sup> and ARVs<sup>5</sup> to treat AIDS
- Solidifying support among partners and potential stakeholders through events such as an annual Microbicide Access Forum “to share information and discuss timely issues and new research that can inform the future introduction and use of microbicides.”
- Participating in inter-sectoral initiatives such as the PDP Support Project established in 2009 by the Bill & Melinda Gates Foundation and Boston Consulting Group, for which IPM serves on the Design Team, studying Regulatory, Policy & Financing.<sup>6</sup>

These and many other similar IPM activities are outlined in greater detail below. They represent IPM’s efforts to prepare for the success of a microbicide product and to ensure prevention of new HIV infections among women throughout the world.

### **3.1 IPM’s Dapivirine Ring**

This Access Strategy focuses on one of IPM’s microbicide formulations currently under development: a flexible vaginal ring made of silicone-elastomer that delivers the ARV drug dapivirine over the course of one month or longer. As of late 2010, dapivirine rings had been tested in five Phase I and I/II clinical safety trials in Europe, with one additional trial ongoing in Africa, and plans for further testing in IPM’s Phase III efficacy trials beginning in 2011. An application for registration to regulatory agencies is anticipated to occur in 2014 (EMA and/or FDA) and 2015 (national regulatory agencies) with approvals by 2015-2016, respectively. Phase IV activities and subsequent launch will occur shortly thereafter. IPM will utilize a staggered launch strategy with the initial launch occurring in those countries where IPM Phase III clinical trials will be conducted. These countries could include South Africa, Malawi, Rwanda, Kenya, and Zimbabwe, among others.

Dapivirine is one of many possible active ingredients for a microbicide product being developed and tested; likewise, the ring is one of many possible delivery mechanisms for a microbicide—others include gels, films, vaginal tablets, soft gel capsules, etc. IPM has noted that given the number of active ingredients and delivery mechanisms being developed and tested, there are over two dozen possible single product configurations and hundreds of possible combination products. While IPM’s future efforts continue to be informed by emerging safety, pharmacokinetics and pharmacodynamic data from the

current Phase I/II trials of both gels and rings, this Access Strategy focuses on the dapivirine-based ring due to several possible advantages for a sustained-release product. Potential advantages with a ring formulation include a higher probability of product stability in conditions found in Africa, ease of use, likelihood for increased adherence (correct and consistent use of product) due to a monthly formulation versus a once-daily application or around each sex act, and distribution advantages of supplying 12 rings per year per user versus hundreds of gel applicators per year per user.

Ensuring access to microbicides, once proven to protect against HIV, is a responsibility that must be shared by trial sponsors, research teams, donors, multilateral and bilateral agencies and, ultimately, national governments. IPM is committed to the principle that participants in an IPM clinical trial should have access to the product studied if the product has been proven to be safe and effective; this goal could be achieved through the conduct of follow-up studies (operational and implementation research) that would gain more information on the use of the product in the context of a research setting, happening in tandem with strategies for regulatory approval. More broadly, IPM will partner with global and national stakeholders to ensure that the population in the countries where the research took place will have access to the product once it has been licensed for domestic use.

### **3.2 The Dapivirine Ring and Access**

In this strategy, access to microbicides refers to more than just whether microbicides are available from a health care clinic or in a local pharmacy. Access in its fullest sense is women's ability to *obtain and appropriately use good quality microbicides* whenever and wherever they want and need HIV prevention.<sup>7</sup> Creating—and then sustaining—access is a complex process.

Five concepts are central to understanding and achieving access to microbicides:

- *Architecture: The network of organizations at the global, national, and local levels that will support, connect and implement all microbicide access activities.*
- *Availability: Sufficient high-quality production and supply of microbicide products, and reliable channels for distribution, to meet user demand.*
- *Acceptability: A microbicide product and how it is provided need to be satisfactory to end-users (women and their sexual partners) and to gatekeepers who control and facilitate availability.*
- *Affordability: The costs of microbicides and programs to deliver them must be affordable to purchasers, funders and end-users.*

- *Appropriate use: Microbicides need to be used properly as part of personal and programmatic strategies to achieve the desired health outcome: preventing HIV transmission.*

Research on access issues shows that the existence of a good quality health technology alone does not guarantee that the technology will be delivered or used; many potentially useful technologies fail to contribute to achieving health improvements.<sup>8</sup> Indeed, the World Health Organization estimates that approximately one third of the world's population does not have regular access to essential medicines and vaccines.<sup>9</sup>

Potential barriers that could contribute to limited access for microbicides when a product becomes available may include (and are not limited to):

- Lack of manufacturing partners
- Limited distribution capacity in existing health systems
- Unrealistic product costs
- Lack of political commitment to HIV prevention technologies
- Stigma associated with HIV and sexual behavior
- Gender inequalities (particularly patriarchal social and political structures)
- Need for users to undergo frequent HIV counseling and testing prior to use
- Need for a physician prescription to acquire the product
- Challenges in communicating the benefits and risks of a new vaginal product
- Partial effectiveness in the context of other HIV prevention methods
- Determining optimal strategies for delivering ARVs to HIV-negative individuals
- Resistance monitoring

IPM began to address the complex problems involved in creating access during the product development phase. This Access Strategy is the next step in the chain of activities that will contribute to seeking to ensure access to the dapivirine ring without significant delays after the product has completed clinical testing. It will serve as a guide for IPM on how to direct its continued attention to potential barriers and critical-path activities through product development and launch (2011-2018).

An Access Strategy is both a *statement of strategy* and a *tool*. Based on the access goals for a product, and the context in which it will be introduced, an Access Strategy offers an operational guide for creating the architecture, acceptability, availability, affordability and appropriate use of the product. A good Access Strategy provides a concrete frame for activities, offers a map of the position and power of various stakeholders, identifies existing and potential obstacles and opportunities, and offers strategies to promote access. At the same time, an Access Strategy is flexible and dynamic, as different stakeholders respond to changes in the product and the context.<sup>10</sup>

This Access Strategy has been prepared to help IPM navigate the process of creating access to the dapivirine ring when it becomes available. The Strategy provides an overview of the current status of IPM's access work and the steps that will be necessary to achieve access to the product once it is ready for distribution. Each individual section of the Strategy goes in-depth on issues that need to be considered, as well as steps for action.

IPM will use the Access Strategy to guide efforts in creating a pathway to access. Much of this work must be done before the final product is ready for production and distribution in order to ensure that there is a minimal amount of lag time between the development of a viable dapivirine ring and its dissemination to those who need it. This will involve significant effort in planning, mobilizing, advocating, and building relationships. Throughout this process, IPM will also regularly revisit the assumptions underlying the Access Strategy. As these assumptions and other aspects of the context change, revising the Access Strategy may become necessary. Likewise, after the product is introduced, ongoing evaluations of the success of IPM's access efforts will be conducted and accounted for in future activities.

The Access Strategy is organized into sections addressing five components of access for the dapivirine ring: architecture, availability, acceptability, affordability, and appropriate use. Each section begins by detailing IPM's actions to-date. After documenting what has already been accomplished, the Access Strategy presents a set of issues and questions under consideration by IPM.

In the development of this Strategy, key assumptions were made about the dapivirine ring and the contexts in which it will be made available to women. If these assumptions change, IPM will revise the Access Strategy accordingly.

The main assumptions focus on the product itself. This Access Strategy focuses on the introduction of a microbicide delivered through the mechanism of a vaginal ring. The active ingredient in the ring is assumed to be dapivirine. This product will initially only be available through prescription to women who have tested HIV-negative. The product would be manually self-inserted and would remain in place for a minimum of one month. Rings would have a shelf life (proven stability) of 24 months.

Other assumptions about the product include: the product is proven effective by 2015; the product is developed under the auspices of IPM; and cost estimates will remain somewhat similar to a marginal cost of production. Submission to EMA and/or FDA will occur by 2015 with regulatory review at the national level in Africa beginning approximately twelve months later, in 2016. Manufacturing will be optimized and scaled during Phases III and IV to meet projected market demand.

Similarly, assumptions were made about the global and national contexts in which a microbicide will be introduced: 1) the product will initially be launched in the countries

where it was tested in clinical trials; 2) financing structures such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the President's Emergency Plan for AIDS Relief (PEPFAR) and foundations currently involved remain key players in global health; and 3) other new HIV prevention technologies will be introduced to the market in the intervening years given recent data showing an ARV-containing gel or pill can prevent HIV.

## **4. Architecture**

Architecture refers to the network of organizations at the global, national, and local levels that will support, connect, and implement all access activities for the dapivirine ring. This section summarizes IPM's strategic decisions and next steps in Partnering for Access.

### **4.1 Access process for the dapivirine ring**

The process of creating access for dapivirine rings will be complex due to the multiple activities required and the many different actors involved. Figure 1 provides an illustration of this process for the dapivirine ring in a typical country in sub-Saharan Africa.<sup>11</sup> The process will differ in each country, depending on the health system and the implementation strategy.

As shown in Figure 1, the process begins with manufacture. For dapivirine rings, manufacturing will likely be conducted by generic manufacturer(s) and production will occur at central or regional facilities. Procurers will purchase the ring from these manufacturers, in order to ensure availability. Illustrative procurement agents for HIV/AIDS products include organizations such as UNICEF, IDA, Mission Pharma, Crown Agents, and the PEPFAR-funded SCMS. These agencies procure drugs on behalf of ministries of health, NGOs, the faith-based sector, and private importers. They could act as a key link between the dapivirine ring manufacturer and purchasers of the product in many developing countries. The products will flow from these buyers to the point of prescribing through a distribution channel consisting of regional warehouses and wholesalers. There are a variety of potential dispensing points for dapivirine rings, including public hospitals and health facilities, faith-based clinics and hospitals, other private clinics, and pharmacies. Because dapivirine rings will begin as prescription-only products, drug shops and other informal outlets will not be dispensing points, at least initially.

Financing organizations such as bilateral donors, private foundations, and international financing organizations like PEPFAR, the GFATM and UNITAID could play a key role in ensuring affordability of microbicides in developing countries. These funds typically flow directly to manufacturers and more often, to procurement agents. The particular financing flow differs by country, product, and donor agency. In the Kenya PEPFAR

program, for example, SCMS procures rapid test kits and laboratory supplies while the Mission for Essential Drugs procures ARVs.

A range of other global, national, and local agencies will influence the dapivirine ring access process. Global technical agencies such as the World Health Organization set reference standards on product use guidelines. National drug regulatory authorities and policy agencies play key roles in product registration and the adoption of product use guidelines within each country. As product developer, IPM will continue to provide product support and global-level advocacy. A range of agencies in the public and private sectors will steer activities related to prescribing, delivery, and creating awareness of the product amongst policymakers, providers, and end-users.

**Figure 1: Access process of a dapivirine ring in a typical country in sub-Saharan Africa<sup>12</sup>**

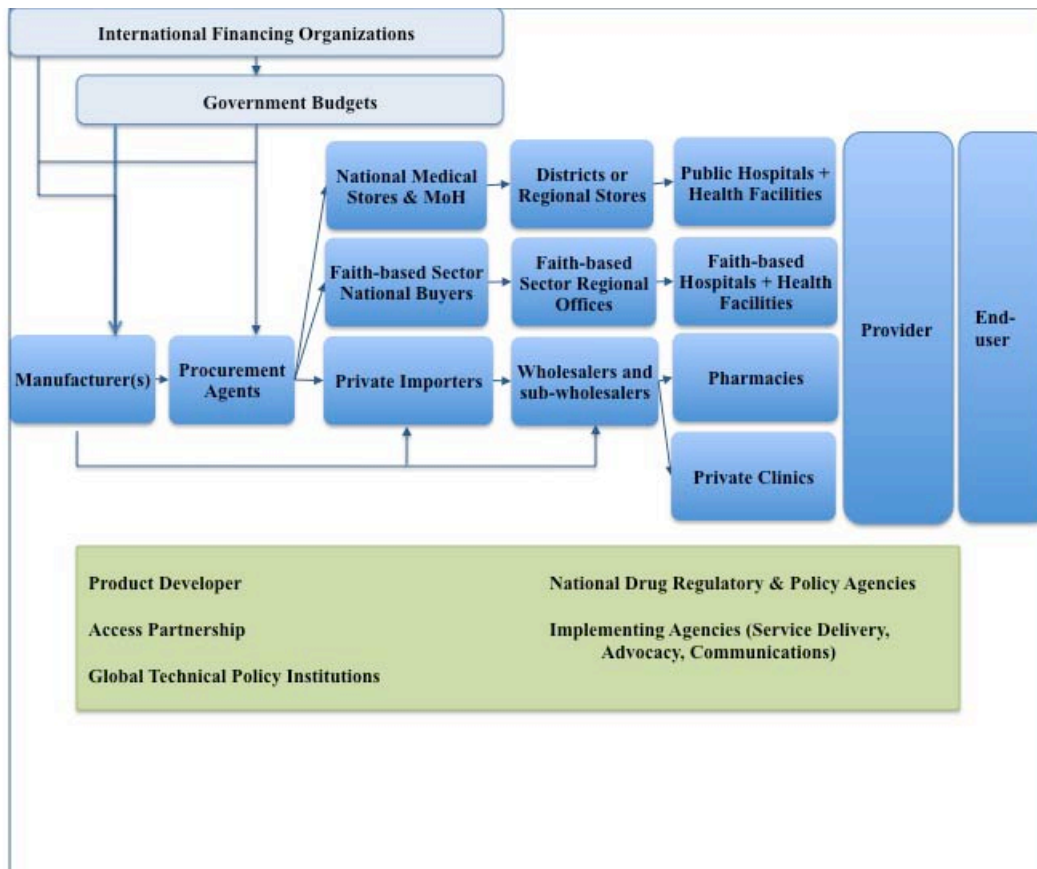
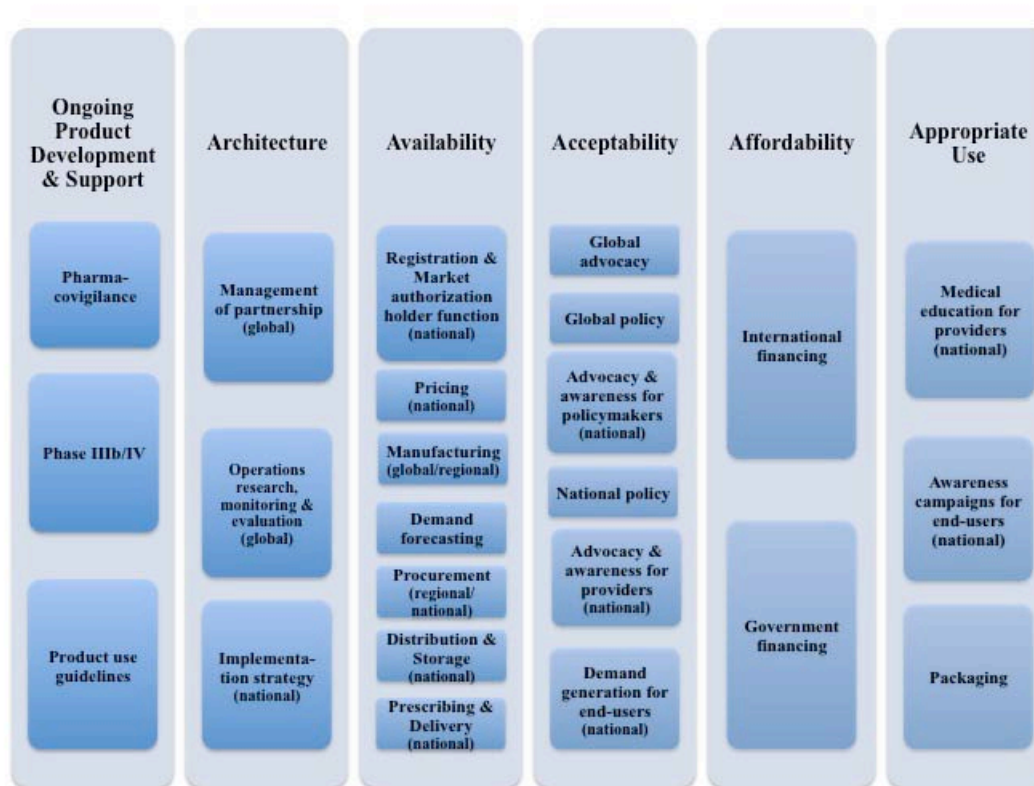


Figure 2 presents the multiple *activities* required for successfully achieving the access process outlined in Figure 1. These access activities are defined as specific events at the national, regional, or global level and are related to IPM’s five A’s of access. Appendix 1 provides definitions for each of these activities.

**Figure 2: Activities for the dapivirine ring access process**



## 4.2 Partnering for Access

As a first step in assessing partnering options, previous experiences were examined to understand how other product developers have handled partnership decisions. This survey included pharmaceutical company experiences presented in the IPM-commissioned study “Access to Medicines in the Developing World: Lessons Learned from Antiretroviral Access Programs.”<sup>13</sup> The survey found five general models of partnering for access that IPM could adopt:

- *Model #1:* Create partnerships with several types of organizations (for-profit companies, non-profit agencies, UN agencies, multilaterals, governments, etc.) to handle access responsibilities on national or regional levels.
- *Model #2:* Hand off all activities to a for-profit company including pharmaceutical companies. The for-profit company in this instance would market the drug at a set margin or highly subsidized final price rather than a commercial price.
- *Model #3:* Hand off most access responsibilities to a UN agency, multilateral, or other non-profit entity including governments.
- *Model #4:* Create a new, unique legal entity with partners to handle access responsibilities.



- *Model #5*: Build internal IPM capacity for handling all product and access related processes.

After discussion of the strengths and limitations of each model, and applicability to the dapivirine ring, at this time IPM considers *Model #1* the most likely appropriate option but that the other models in whole or part will need to be reconsidered, should the right opportunities arise or as circumstances change. In creating a *Model #1* partnership, IPM is faced with a wide range of potential partners and many decisions about specific approaches along the following dimensions:

- Number of partners (including number of manufacturing partners)
- Whether partners are selected according to access activity (such as manufacturing, local registration, distribution, medical education, or pharmacovigilance) or location (sub-Saharan Africa, Latin America, Asia, or on a country-by-country basis).
- Where the partnership management functions are located (in the product development organization as in the case of Norplant and the Population Council; in the manufacturing company as is the case of Gilead's Tenofovir and Aspen Pharma; or in a specialist for-profit or non-profit entity like Boehringer Ingelheim's Nevirapine Program and Axios).
- The role of the product developer in access. The product developer can retain a small or large role in access, with examples showing a wide variation in practice. At a minimum, the product developer usually maintains broad regulatory oversight (at the FDA or EMA level) and responsibility for ongoing product development, and often takes responsibility for additional activities such as advocacy, communications, and partnership management.

The partnering approach that IPM takes will depend on the expertise of potential partners and which organizations show an interest in partnering for dapivirine ring access. As shown by Keller,<sup>14</sup> partnerships with a few organizations tend to make the process more manageable. In addition, IPM will likely seek partners that have:

1. Existing activities in high priority, target countries, particularly in first-launch countries.
2. Competencies in a range of access activities (see Figure 2) rather than just one or two areas.
3. Demonstrated experience and credibility in HIV/AIDS and/or family planning access programs.

### **4.3 Action Plan for Partnering**

IPM's action plan for partnering explains next steps and potential challenges.

Action 1: IPM will continue to identify and evaluate potential partners for *manufacturing* of the dapivirine ring and for *national regulatory activities* (including *pharmacovigilance*). Depending on the competencies of the parties, one partner may be able to fulfill all these functions or several partners may be required. An early decision point for IPM will be determining who will hold market authorization in the countries where the product will be launched. The market authorization holder has responsibility for submission of dossiers at the national level and pharmacovigilance. IPM can transfer market authorization to partners that can fulfill these national-level activities as well as manufacturing, and will prioritize partnerships with those organizations who can assume those duties.

Once IPM has identified suitable partners, IPM's workplan will include:

*1.1 Detailed discussions with interested partners:* Discussions will focus on:

- Objectives of the partnership, including agreement on the benefits of collaboration and what the partners have to do to capture these sources of value.
- Roles and responsibilities as defined in terms of geography, target populations, functional activities, and timeline.
- An appropriate governance structure for working together, including decision-making, regular meetings, and assurance of enough dedicated staff time for the work.

*1.2 Creation of working agreements and contracts:* Following the discussions in the previous step, working agreements and contracts can be negotiated and executed. These should include commitments on both sides and "operating minimums" at different phases of the partnership life cycle.

*1.3 Establishment of cross-partner project teams:* As agreements are finalized between partners, cross-partner project (or product implementation) teams will need to be established. The structure of these teams and their governance processes would be included in the working agreements and contracts such that the role and responsibilities of the team Chairmen are clearly assigned and defined. The agreements could also stipulate which functions from each organization would sit on the cross-project teams. These teams would be the place where decisions regarding the further development and implementation of the dapivirine ring would be discussed and made.

Action 2: Concurrent with Action 1, IPM will continue to form partnerships for *advocacy* and *communication* in order to educate and raise awareness about microbicides among policymakers (global and national), donors, providers, and potential end-users. Partnerships will be formed with organizations at the global HIV-prevention advocacy level and within countries.

**Action 3:** As Phase III efficacy data becomes available for the dapivirine ring, IPM and its partners will identify additional suitable and interested parties with specific expertise needed for the access partnership (for example, partnership management, procurement, operations research, communications, etc.). The partnership will also begin collaborating with governments in first-launch countries, key donors, and implementing organizations. Together these organizations will design an implementation strategy for dapivirine ring access, specific to each country.

## **5. Availability**

Availability refers to sufficient high-quality production and supply of the dapivirine ring, and reliable channels for distribution, to meet user demand. Activities to ensure availability include manufacturing, demand forecasting, registration and pricing in countries where the dapivirine ring will be made available, procurement, distribution and storage, and prescribing and delivery (see Figure 2). IPM's early focus will be on finding suitable partners for manufacturing for access, and identifying the appropriate regulatory strategy for the product. Decisions made in these two areas have direct implications for the access timeline, structure of the access partnership, launch scenarios, and the financing for access strategy.

### **5.1 Summary of IPM's work in Availability**

IPM is engaged in many activities to build the foundation for manufacturing for access. IPM's manufacturing activities fall into three general categories: planning, primary manufacture, and secondary manufacture.

#### *Product Development Planning*

IPM has a comprehensive development plan for the dapivirine ring which extends through 2017. This document discusses regulatory, preclinical, clinical, chemistry, manufacturing and controls/analytical development, pharmaceutical development, and the manufacturing plan. In addition it identifies development milestones, outlines the clinical trial plans, identifies key project drivers, and lays out a risk management plan for product development. A target product profile (TPP) is in place that can be used as a reference for review at scheduled intervals or concurrent with pivotal decision points during the microbicide development process.

#### *Drug Substance (Primary) Manufacturing Capabilities*

The manufacture of the dapivirine drug substance, referred to as dapivirine API or primary manufacturing, is conducted at a contract manufacturer, OmniChem in Belgium. Current batch size is 15-20 kg. This capacity is considered sufficient to cover the amounts required for Phases III and IV. Access implementation will require slightly larger API volume to fulfill the proposed staggered-launch strategy in countries where Phase III clinical trials have been conducted. IPM has created initial forecasts evaluating three

market uptake scenarios at the time of launch. According to these forecasts, with low market uptake (0.5% growth rate) an estimated 786,000 rings would be required in the first year, requiring approximately 60 kg of API.

#### *Drug Product (Secondary) Manufacturing Capabilities*

Secondary manufacturing refers to the production of silicone rings containing dapivirine. Following a competitive bidding and evaluation process, IPM contracted in June 2010 with QPharma for Phase III ring manufacturing. Based in Malmö, Sweden, QPharma has more than 35 years of manufacturing experience and the capability to scale up quickly for IPM's Phase III research program. QPharma has worked with the Population Council, Pfizer and other organizations on manufacturing and analytical testing of vaginal ring products for clinical trials. Additional factors considered in the evaluation process were the availability of facility manufacturing space, strong quality control systems, and cost.

#### *Regulatory Environment*

Approval by the FDA is necessary for obtaining PEPFAR and other U.S. government funding for microbicide access. Unlike with generic drugs, there are no known instances of the FDA approving a New Chemical Entity (NCE) for use exclusively outside of the USA. IPM is engaged in discussions with the FDA to develop a strategy for seeking FDA approval of a microbicide.

In Europe, IPM has entered into the EMA Article 58 process. As in the U.S., this process has not previously been employed for the review of an NCE. A positive EMA review would potentially expedite subsequent submissions to national regulatory authorities in Africa. However, this strategy does not negate the necessity of obtaining approval from the FDA in order to obtain PEPFAR funding.

## **5.2 Challenges to IPM's Manufacturing and Launch Strategies**

IPM has set 50% as an acceptable target efficacy. Assuming the dapivirine ring reaches or exceeds that level of efficacy, at the completion of the Phase III clinical trials, IPM will be in a position to model public health impact based on observed efficacy. At that point, IPM can project more accurate timelines and product demand. Until that time, IPM will move forward with the understanding that initial launch will occur in countries where Phase III trials were conducted using the current market forecasts. Even among those countries there will likely be a staggered release of product across 9-12 months given local regulatory approval timelines. This will allow for a definition of scale requirements for both primary and secondary manufacturing and allow scale up efforts to occur during Phase III studies.

During the time period of 2012-2016, IPM will evaluate prioritization of launch countries beyond those conducting Phase III clinical trials. A set of criteria will be used by which countries can be compared incorporating data such as incidence, target population, and

the country's ability to implement access via local and regional partnerships. Country studies will best inform these decisions and allow for the highest quality of input into any prioritization exercise.

### **5.3 Action Plan for Availability**

IPM's action plan for its manufacturing and launch strategies explains next steps and potential challenges.

Action 1: IPM will identify manufacturers who can manufacture sufficient quantity and quality supply for access. Finding suitable manufacturers to enter into long-term partnerships is an essential piece of the launch. To find suitable partners, IPM will: 1) conduct a new survey of potential partners in South Africa; 2) reevaluate existing and potential partners; and 3) revise and re-issue EOI and/or RFP to capture more commercial scale partners no later than 2013.

Action 2: IPM will continue discussions with regulatory agencies. Discussions with the US FDA will focus on whether the Agency will agree to approve dapivirine vaginal ring on the basis of IPM's product development program. As has been noted, at this time FDA approval is necessary to ensure eligibility for PEFPAR funding, a key source of financing in many of IPM's potential first-launch countries. IPM's discussions with the EMA are focused on whether the Article 58 process is the appropriate regulatory pathway for the dapivirine ring marketing application.

Action 3: IPM will prioritize countries beyond those conducting Phase III clinical trials. This prioritization will be informed by a series of country reviews that will provide data including incidence, target population, and the country's ability to implement access via local and regional partnerships.

Action 4: IPM will assess potential product demand throughout the Phase III program when a more focused product profile can be refined taking into account interim efficacy data.

Action 5: Once Phase III efficacy data are available, IPM will investigate public health impact based on observed efficacy ( e.g. modeling, Phase IV studies, and observational cohort studies).

## **6. Acceptability**

Activities in the area of Acceptability ensure that the dapivirine ring—and how it is distributed—is satisfactory to end-users and to any gatekeepers who control and facilitate availability. This involves two parallel processes: gauging existing perceptions

of the product and then working to influence user opinions. For the dapivirine ring, IPM must ensure acceptability of the product to women, their sexual partners, and implementing and distributing agencies.

### **6.1 Summary of IPM's work in Acceptability**

IPM has thus far conducted a safety and acceptability study with placebo vaginal rings (IPM 011) at four sites in Africa, and study findings indicate that placebo vaginal rings are safe and acceptable to women and their partners, and likelihood of use (for HIV prevention) is high. Additionally, IPM is assessing acceptability, adherence and other behavioral data on dapivirine rings as part of the IPM 015 Phase I/II safety trial; the planned IPM Phase III trial will also include a significant social-behavioral component.

In addition, IPM is pursuing the second process of capturing and analyzing user opinions. A branding and marketing project is underway with the project focused on "preparing the marketplace for microbicides with the goals of raising awareness of microbicides as potential new tools in reducing women's vulnerabilities to HIV and building support for product development and eventual access to microbicides." Following an initial market assessment study, developing tailored messages and brands as well as an education and advocacy campaign are being finalized. As product details become clarified, IPM will intensify these efforts.

### **6.2 Action Plan for Acceptability**

IPM's action plan for acceptability explains the next steps and potential challenges. The timing of these activities is presented in the Access Timeline in Section 9.

Action 1: IPM will apply the results of its acceptability and market assessment studies to inform product development, and help to prepare for branding and marketing activities.

Action 2: As IPM forms its access partnerships, it will involve partners with competencies in advocacy, branding, social marketing, information, education, and communications (IEC), and behavior change communications (BCC).

Action 3: Once partnerships are in place, partners will agree on roles and responsibilities, timeframe for work, working agreements, and contracts.

Action 4: IPM and its partners will engage in intensive marketing and promotion to end-users and to opinion leaders in target countries to generate demand for the product.

## **7. Affordability**

Access activities in the area of Affordability strive to ensure that the costs of the dapivirine ring and programs to deliver them are affordable to purchasers, funders, and end-users.

### **7.1 Summary of IPM's actions on Affordability**

IPM has been influencing affordability through acquiring licensing for intellectual property rights early for dapivirine and other microbicide drugs under development. This seeks to ensure that IPM will have flexibility in setting product prices and choosing manufacturers in a way that maximizes affordability. In addition, IPM has sought to influence affordability by prioritizing APIs with lower production costs.

IPM has also been pursuing a strategy of building relationships and partnerships with potential sources of financing for the dapivirine ring. The process of securing adequate financial support for access moves forward in parallel with the process of developing and securing a proven and approved product.

## **7.2 Product Pricing Strategies and Considerations**

### *An overview of pricing options*

In pricing a product, producers take several issues into consideration: covering the marginal cost of production; recouping the manufacturer's capital investments and the costs of distribution (known as the allocated costs); and demonstrating a product's value. In addition, decisions on pricing must consider the value of the product to the consumer and the consumers' ability to pay.

It is important to distinguish between the price paid for the product by the end-user, the price paid for the product by the purchaser (when the purchaser is not the end-user), and the costs of using the product, including non-financial costs to the end-user (such as the costs of traveling to vendors and the costs of related health services).

There are three general categories of product prices—free, subsidized, and commercial—each of which has significant implications. These are summarized in Table 1 below.



**Table 1: An Overview of Pricing Options**

PRICE	COST TO END-USER	TARGET MARKET SEGMENT	DISTRIBUTION CHANNEL	PROGRAM COSTS	FINANCING
1. Free (No-cost)	Access costs*	Women in discordant couples, Low-income women	Public sector, NGOs (not for profit), social marketing	Donor and government funded	Donor and government funding
2. Subsidized price (low cost)	Low-cost or co-pay + access costs	Low-income women, Women in discordant couples	Public sector, NGOs, social marketing, subsidized private sector	Donor and government funded	Donor and government funding Cost-recovery
3. Commercial price (Full cost or full cost plus profit)	Marginal cost + access costs	High-income in developing countries	Public sector/ NGOs; Subsidized private sector	Donor and government funded	Cost-recovery
	Fully allocated costs (w/o profit) + access costs	Developed countries	Subsidized private sector	Non-profit sustainable	
	Fully allocated costs (w/ profit) + access costs	Developed countries	Private sector	For-profit sustainable	For-profit

\* Access costs refer to the costs involved in reaching the distribution point and any social costs of using the product.

### *Pricing strategies for microbicides*

The pricing strategy adopted has important implications for IPM's approach to Financing for Access, since pricing affects the breadth and depth of access achievable in a product roll-out. Financing, in turn, influences the mechanisms and sustainability of production, distribution and marketing of microbicide products. This section addresses pricing options in general, pricing strategies for microbicides in particular, and implications for IPM's choice of approach. IPM has clearly stated that its mission is to create access to microbicide products in areas with great need. Current estimates suggest that a monthly dapivirine ring product produced at relatively small scale for the Phase III program only would cost about \$7.95 per unit to produce (based on production of 100,000 units). The current manufacturing equipment at QPharma could produce 2 to 3 million rings a year.

Negotiations with manufacturers and increased volume will likely drive the cost down considerably from this upper bound.

IPM faces some unique challenges in pricing a microbicide. First, IPM is developing microbicide products primarily with funding from grants. Therefore, unlike commercial pharmaceutical companies, IPM is not seeking to set a price designed to recoup investments in R&D. Second, because microbicides are new products, few comparable models exist. The only existing female-controlled prevention method for HIV, the female condom, is a different type of product. Having no direct competitor products at this time makes it difficult to set a launch price for a new microbicide product.

IPM will need to conduct willingness-to-pay studies among different target consumer groups in order to determine what consumers consider appropriate prices. (It is worth noting, however, that willingness-to-pay studies can be problematic in that what people say they are willing to pay does not always translate into reality, particularly for new products.) After the product launch, IPM and its partners will need to regularly review prices in all markets to determine whether the price charged is achieving its goals of creating value and promoting access to microbicides.

Table 1 focuses on four key issues: Price, Cost to End-User, Market Segment, and Financing. The price charged for a product and the cost charged to the end-user influence which market segment is financially able to access microbicides. The size and characteristics of the market segment, in turn, determine which kinds of financing are most appropriate. Two additional considerations are also included in the table: the distribution channel that best fits with a particular pricing scheme; and the program costs that the pricing scheme will require. Engaging the for-profit private sector in microbicide distribution will require building in economic incentives for the private sector to become involved with microbicides. If the private sector will not provide significant distribution support, the public sector must be involved and developed to channel microbicides to end-users. Either approach will also require financing for marketing and supply chain management, additional costs that IPM will include in its plans for Financing for Access.

### **7.3 Cost Considerations**

Identifying and calculating the costs involved in producing, distributing, and delivering a dapivirine ring will be critical to IPM's efforts to mobilize financial resources from stakeholders.

Cost estimates for the access program of a microbicide will consider the following categories of costs:

- Access management (in particular, operating costs for a core team or consortium to oversee and orchestrate the various pieces of the access architecture including the partnerships)
- Manufacturing and Supply
- Distribution
- Quality management
- National regulatory approval and subsequent management of registration (updating summary of product characteristics (SmPC), reporting to regulators, sublicensing, etc.)
- Launch activities and ongoing implementation programming
- Post Sales Services (medical communication, information and training)
- National pharmacovigilance
- Maintenance and analysis of global safety database
- Post-approval research commitments and additional Phase IIB/IV research

Many of these cost categories may be primarily the responsibility of partners rather than IPM, depending on the partnership model selected. The selection of the partnership model, therefore, will determine how the costs are distributed and which items will need financing by IPM and which items will need financing by or through partners.

As IPM achieves a dapivirine ring product that is ready for market launch, IPM and its partners will need to develop cost estimates for each of these categories. The costs will also be negotiable as manufacturers and service providers compete for business and consider market size and potential economies of scale.

#### **7.4 Financing for Access Options**

Once the dapivirine ring is nearing the end of a successful Phase III trial, additional measures will be needed to assure adequate financing for Access. This section presents options IPM could pursue, including options for seeking either core funding or for targeted solicitations of funds from donors with an interest in particular types of activities or specific countries.

Sustaining donors' interest in HIV/AIDS will require concerted advocacy in the coming years, as other issues including donor fatigue could result in shifting focus. The introduction of new products for prevention, such as tenofovir gel and the dapivirine ring, could play a critical role in re-focusing the global aid community on HIV prevention.

There are seven categories of potential sources of financing for the dapivirine ring:

1. Donor financing (bilateral agencies and private philanthropies)
2. Multilateral financing

3. Government financing (from developing countries)
4. End-user financing
5. Manufacturer financing
6. NGO financing
7. Innovative financing

## **7.5 Action Plan for Affordability**

IPM's action plan for Financing for Access explains next steps and potential challenges.

Action 1: IPM will continue to reach out and engage existing and potential new partners, gaining an in-depth understanding of their funding priorities and procedures to determine whether they might be willing and able to provide financing for access.

Action 2: IPM will complete its decision-making processes on a product launch strategy, pricing structure and partnership architecture in order to estimate costs of different activities, project accurate budget requirements and tailor proposals to donors' capacity.

Action 3: Gather data during Phase III manufacture and explore opportunities to simplify and optimize the process. Prepare a detailed plan with stakeholders to drive down the cost of goods post Phase III.

## **8. Appropriate Use**

### **8.1 Activities to ensure appropriate use**

Activities related to Appropriate Use ensure that dapivirine rings are used properly as part of personal and programmatic strategies to achieve the desired health outcome: preventing HIV transmission. Appropriate use can be encouraged through medical education targeted to providers and awareness campaigns for end-users. Awareness campaigns targeted to end-users overlap with demand generation activities that seek to influence demand and uptake (see Section 6, Acceptability). Specific activities can include marketing; social marketing; information, education and communications (IEC) campaigns; and behavior change communications (BCC). Another strategy to ensure appropriate use is the design of packaging and instructions in appropriate languages and with culturally sensitive visual aids. Work in these areas will begin before launch.

### **8.2 Action Plan for Appropriate Use**

IPM's action plan for appropriate use activities explains next steps and potential challenges.

Action 1: As IPM forms its access partnership, it will seek partners with competencies in medical education, awareness campaigns, and secondary packaging. Medical education and awareness campaigns will need to be focused on a variety of audiences including healthcare professionals (doctors, nurses, community health workers and pharmacists) and consumers.

Action 2: Once partnerships are in place, partners will agree on roles and responsibilities, timeframe for work, working agreements, and contracts.

## **9. Staffing Implications for Dapivirine Ring Access Activities**

The purpose of section is to provide insight into the human resource requirements (FTE) needed to fulfill those activities over the next 6-8 years. The Access Plan was the primary material used to develop these human resource requirements. The following assumptions have been made:

- IPM will want to remain as lean of an organization as possible
- IPM will continue to utilize consultants for specific projects where the required skill sets are not internally available
- As IPM is currently developing its manufacturing strategy, manufacturing-related human resource requirements have not been considered as part of the scope of this exercise.

The Access Working Group is the current structure within IPM that manages activities related to Access. Ideally, this group would have representation from External Relations, Planning and Operations, Global Health Policy, Manufacturing and Regulatory Affairs<sup>1</sup> and would meet monthly to discuss topics and manage projects related to access. This group will continue to manage access related topics. Over the coming years, IPM will assess where the Access Working Group should reside in the organization as it becomes more of an active operational group and less of a “think tank”. One possibility is to set up a new division within IPM focused on access, similar to what the TB Alliance has done with its Market Access division. This division was formalized in 2008 with the mandate of navigating the complex access landscape by reconciling logistical, patient-specific, and resource-related dynamics to shape a comprehensive access plan that meets the goals of Affordability, Adoption and Availability.

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<sup>1</sup> Currently, Regulatory and Manufacturing do not participate in the Access Working Group but are expected to join over time

### **9.1. 2010-2011 Time Period**

#### **Access Project Manager**

The Access Project Manager will manage and coordinate all issues related to access within IPM including the following:

- Access Working Group
- Access partnering approach agreed within the Access Working Group under the leadership of senior management
- Monitoring of trends in key launch countries (such as South Africa and Kenya) as preparation for accessing potential partners
- Coordination of consultant assignments
- Internal and external communications
- Maintenance of access timelines, process maps and strategy
- Review of country studies conducted by the consultants

It is anticipated that this position will be one-quarter to one-half of a full-time equivalent (FTE) in the first 12-18 months, gradually increasing to a full FTE role by the end of 2012. In 2010 and 2011, access activities related to manufacturing of Dapivirine ring and awareness and advocacy for microbicides will take center stage. At the beginning of 2012, the development of a financing mechanism to fund access to Dapivirine ring will commence in earnest. This position will have a specific role in managing and coordinating these activities. The ideal candidate for the position will have experience in both public health and project management, strong interpersonal communication skills, attention to detail and previous experience managing projects in the public health arena.

#### **Potential Consultants**

Potential consultants during this same time period could include:

- MPH with expertise in the developing world (2010-2011)
  - Continue communication activities in initial launch countries to educate and raise awareness around microbicides in coordination with the respective IPM staff
  - Continue advocacy work with donors to prepare for next stage financing work in coordination with the respective IPM staff
  - Fully develop country studies/evaluations to inform partnering strategy
  - Assist Access Project Manager in creating effective partnerships and coordinating them across the variety of involved organizations
- Manufacturing Support with expertise in successful scaling product launch
  - Support selection of primary and secondary manufacturing
  - Identify low-cost, high volume producers
- Paralegal Support with expertise in contract preparation and review

- Assist with the development of partnership contracts
- Assist team with due diligence activities

### **9.2. 2012-2015 Time Period**

Beginning in approximately 2012, it will be important for the Access Working Group to transition to a more formal cross-partner Access Project Team. IPM will have a dedicated Access Project Leader responsible for leading all access related activities within the organization. This role could be one that evolves from the Access Project Manager role, or a unique position. Demonstrated project leadership in a joint venture setting would be ideal.

#### **Access Project Leader (2012-2018)**

- Lead all access related activities within IPM including, the Access Working Group
- Develop and implement the Dapivirine partnering strategy
- Supervise access-related consultants

#### **Potential Consultants**

##### **MPH with expertise in the developing world (2012-2015)**

- Continue communication activities in initial launch countries to educate and raise awareness around microbicides
- Continue advocacy work with donors to prepare for next stage financing work
- Fully develop country studies/evaluations to inform partnering strategy
- Assist Access Project Manager in creating effective partnerships and coordinating them across involved organizations

##### **Public Health Financing Specialist (2012-2015)**

In 2012, financing activities for Dapivirine ring will need to be scaled. A consultant with a background in health economics or public health with a Masters in Business Administration would be well positioned to take on this work. IPM could hire this person as an internal FTE or could identify a consultant with extensive experience in this area.

The successful consultant will have a Masters in Health Economics or Masters in Public Health with a Masters in Business Administration. This individual will possess proven experience in developing strategic financial partnerships, allowing access to products in the developing world setting and experience in understanding, developing and negotiating large tenders with a variety of providers and purchasers. Over the course of 2012-2015 they will be responsible for:

- Conducting willingness-to-pay studies in launch countries
- Designing pricing options for IPM
- Developing a pricing strategy that is agreed in the cross-partner Access Partnership Project Team

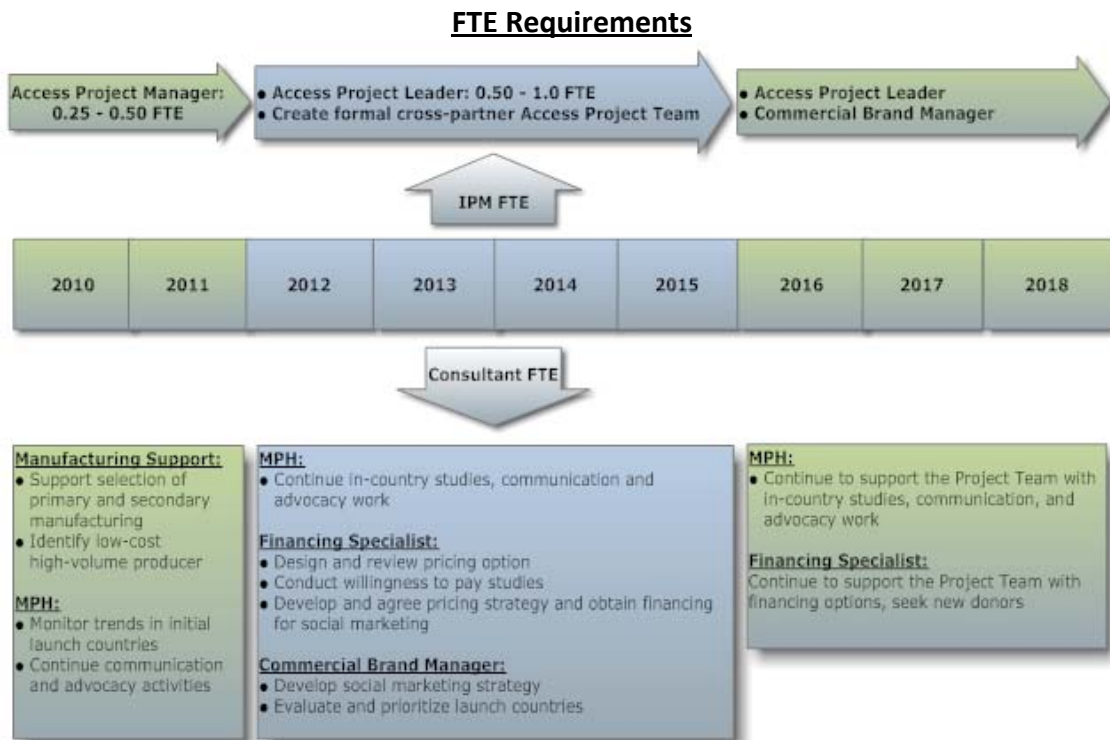
**Developing World Commercial Marketing Specialist (2014-2015)**

IPM is considering bringing on a consultant with commercial experience to support the overall project team structure in 2014. This role should be approximately a .25 to .33 FTE during this time frame. Depending on the overall partnering strategy, this commercial consultant could be internalized to IPM as a FTE around 2015 (at the time Phase III results become available and IPM is preparing the post-NDA dossier). Specific activities that this specialist would be responsible for include:

- Developing a draft package insert
- Developing a social marketing strategy, also informed by IPM’s previous market assessments
- Assisting with market forecasts and branding exercises

**9.3. 2016-2018 Time Period**

In 2016, the Developing World Commercial Marketing Specialist role could become a FTE within IPM. All other consultants can remain as in the 2012-2015 time period.





**Table 1: Definitions of Dapivirine Ring Access Activities**

Microbicide Access Activities	Description
<b><i>Ongoing Product Development &amp; Support:</i></b>	
<i>Pharmacovigilance</i>	Activities relating to the detection, assessment, understanding and prevention of adverse effects.
<i>Phase IIIB/IV</i>	<p><i>Phase IIIB:</i> Studies conducted just before or during regulatory filing and can assist in gaining market approval, provide evidence to support product claims, develop data on the use of a drug or device in an expanded population of patients, and further define the safety profile of a product by demonstrating safety in larger and more diverse populations.</p> <p><i>Phase IV:</i> Studies conducted after the dapivirine ring has been marketed to gather information on the product's effect in various populations and any side effects associated with long-term use. Phase IV studies can include randomized controlled clinical trials or observational cohort studies.</p>
<i>Product use guidelines</i>	Documents created and endorsed at the national, regional or global level describing the optimal use of a product or class of products through normative agencies such as WHO.
<b><i>Architecture: The network of organizations at the global, national, and local levels that will support, connect, and implement all access activities for the dapivirine ring.</i></b>	
<i>Management of partnership (global)</i>	Activities at the global level related to the management of the network of organizations involved in dapivirine ring access activities. These activities include monitoring, evaluation, and operations research of the global partnership. They also involve securing ongoing financing from groups including donors, international financing institutions, and developing country governments.
<i>Implementation strategy (national)</i>	The decision to introduce the dapivirine ring into a specific country and the design of a specific implementation strategy.
<b><i>Availability: Sufficient high-quality production and supply of the dapivirine ring, and reliable channels for distribution, to meet user demand.</i></b>	
<i>Registration and Market authorization holder function</i>	The listing and licensing of the dapivirine ring with the relevant national regulatory authority in order to ensure that it meets public standards of safety, quality, and effectiveness.

<b>Microbicide Access Activities</b>	<b>Description</b>
<i>Pricing</i>	Pricing is determined by partners close to the time of launch and depends on i) cost of goods, ii) operating expenses, and iii) the manufacturer's margin. Procurement organizations (e.g. the Clinton Foundation) will then negotiate from that initial price.
<i>Manufacturing &amp; Sales</i>	The processing of raw materials into the finished dapivirine ring product, and the selling of these products to public or private purchasers.
<i>Demand forecasting</i>	The assessment of how much of the dapivirine ring product is likely to be purchased and used, and at what price.
<i>Procurement</i>	The purchasing of dapivirine rings from either private or public suppliers, in order to ensure availability. Decisions about procurement are influenced by the unit cost of the product, the quantities required, the quality of available goods, the potential for bulk purchase or minimal cost plus mark-up arrangements, the budget constraints and tendering procedures of institutional or government purchasing agencies, the availability of adequate data with which to forecast either demand or supply, and the accessibility of transparent information on suppliers, prices, and products.
<i>Distribution &amp; Storage</i>	Part of the supply chain; the path by which dapivirine rings are (1) ordered and dispatched from the manufacturer and/or supplier, (2) received, cleared, and inspected at port by public or private procurement agencies, and (3) transported, inventoried, and stored by private- or public-sector entities to the point at which they are available for delivery to the end-user.
<i>Prescribing &amp; Delivery</i>	The point in the supply chain at which the dapivirine ring is physically transferred to its intended end-user by private or public channels, including pharmacies, hospitals, health clinics, and shops.

<b><i>Acceptability: The dapivirine ring and how it is provided need to be satisfactory to end-users and to gatekeepers who control and facilitate availability.</i></b>	
<i>Global advocacy</i>	Advocacy for microbicides (as a mode) of HIV/AIDS prevention) and microbicide rings (as a specific delivery platform) amongst global actors including international technical agencies and other technical experts.
<i>Global policy</i>	Creation of policy related to microbicides within international technical agencies such as WHO, UNICEF, UNAIDS, or UNFPA.
<i>Advocacy &amp; awareness campaigns for policymakers and providers (national)</i>	Advocacy and awareness campaigns for microbicides (as a mode of HIV/AIDS prevention) and microbicide rings (as a specific delivery platform) targeted to national policymakers and providers. The purposes of the campaigns for policymakers are to gain political commitment and adopt relevant guidelines. The purposes of the campaigns for providers are to ensure product uptake and appropriate prescribing.
<i>National policy</i>	Creation of policy at the national level; usually involves the adoption of relevant protocols.
<i>Demand generation and awareness campaigns for end-users (national)</i>	Demand generation activities targeted to end-users to ensure demand and uptake of dapivirine rings. These activities overlap with awareness campaigns for end-users to influence appropriate use (see Appropriate Use section). These activities include marketing; social marketing; information, education and communications (IEC) campaigns; behavior change communications (BCC); and branding of the dapivirine ring. A brand is a name, sign, symbol, or slogan used to identify and distinguish a specific product such as a microbicide.
<b><i>Affordability: The costs of the dapivirine ring and programs to deliver them must be affordable to purchasers, financiers, and end-users.</i></b>	
<i>International financing</i>	Provision of financing by donors (developed country governments and private foundations) and international financing institutions (such as the GFATM) to purchase the dapivirine rings and/or pay for delivery programs.
<i>Government financing</i>	Provision of financing by developing country governments to purchase dapivirine rings (through government procurement processes and using funds from national budgets) and to distribute the products through government and non-

	governmental facilities.
<b><i>Appropriate Use: Dapivirine rings need to be used properly as part of personal and programmatic strategies to achieve the desired health outcome: preventing HIV transmission.</i></b>	
<i>Medical education</i>	Information and awareness specific to the dapivirine ring product targeted to providers.
<i>Awareness campaigns for end-users (national)</i>	Awareness campaigns targeted to end-users to ensure appropriate use of dapivirine rings. These activities overlap with demand generation and awareness campaigns for end-users to influence demand and uptake (see Acceptability section). Activities include marketing; social marketing; information, education and communications (IEC) campaigns; and behavior change communications (BCC).
<i>Packaging (also a part of the manufacturing function)</i>	Packaging and instructions (in correct languages and/or with visual aids) specific to the dapivirine ring product that encourage appropriate use of the product by the provider and end-user.

*Some definitions in this table adapted from Frost and Reich, 2008.*

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## Endnotes

<sup>1</sup> Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010 Sep 3;329(5996):1168-1174.

<sup>2</sup> International Partnership for Microbicides, *Strategic Plan 2011-2015 [Draft]*, March 2011

<sup>3</sup> See, for example: Lilani Kumaranayake, Anna Foss, Andrew Cox, Fern Terris-Prestholt, Peter Vickerman, Charlotte Watts, *Cost and Cost-Effectiveness of Microbicide Introduction in Southern India and Urban South Africa* [Powerpoint presentation], no date; and, Mark Pearson, Lilani Kumaranayake, *Financing Mechanisms for Microbicide R&D and Future Introduction: Final report*, April 2007.

<sup>4</sup> George F. Brown, Vimala Raghavendran, Saul Walker, *Planning for Microbicide Access In Developing Countries: Lessons from the Introduction of Contraceptive Technologies*, July, 2007.

<sup>5</sup> Amy L. Keller, *Access to Medicines in the Developing World: Lessons Learned from Antiretroviral Access Programs*, May 15, 2009.

<sup>6</sup> Bill and Melinda Gates Foundation, Boston Consulting Group, *Access Design Team #4: PDP Support Project* [Powerpoint Presentation], July 23, 2009.

<sup>7</sup> Laura J. Frost, Michael R. Reich, *Access: How Do Good Health Technologies Get to Poor People in Poor Countries?* Cambridge: Harvard Center for Population and Development Studies, distributed by Harvard University Press, 2008.

<sup>8</sup> See, for example: Frost and Reich, 2008; E. Sevene et al., "System and Market Failures: The Unavailability of Magnesium Sulphate for the Treatment of Eclampsia and Pre-Eclampsia in Mozambique and Zimbabwe," *British Medical Journal* 331 (2005): 765-769; S. Sundar, H.W. Murray, "Availability of Miltefosine for the Treatment of Kala-Azar in India," *Bulletin of the World Health Organization* 83 (2005): 394-395.

<sup>9</sup> World Health Organization, *The World Medicines Situation* (Geneva: WHO, 2004), 61.

<sup>10</sup> Frost and Reich, 2008: 205.

<sup>11</sup> By "typical country" we are referring to general characteristics in the majority of countries in sub-Saharan Africa. These characteristics differ by country due to different health systems, financing sources for health programs, mix of public and private actors, etc.

<sup>12</sup> Adapted from: Prashant Yadav, *Countering Drug Resistance in the Developing World: An Assessment of Incentives Across the Value Chain and Recommendations for Policy Interventions. Working Paper 183*, Washington DC: Center for Global Development, 2009.

<sup>13</sup> Amy L. Keller, *Access to Medicines in the Developing World: Lessons Learned from Antiretroviral Access Programs*. May 15, 2009.

<sup>14</sup> Keller, 2009.