

Preparing for Microbicide Access and Use



A Report by the
Access Working Group
of the Microbicide Initiative
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Note: The views expressed in this document do not necessarily reflect the opinions of individual members of the Working Group, nor the policies of their respective agencies or organizations.



This report is a product of the Microbicide Initiative. In late 2000 the Rockefeller Foundation invited an international group of scientists, research organizations, pharmaceutical industry representatives, United Nations organizations, advocacy groups, and donors to come together to find ways to accelerate the development and availability of a safe, effective, and accessible microbicide. “Working Groups” were established to examine five key elements in this process: (1) potential market size and demand for such a product; (2) scientific and technical requirements for accelerating microbicide development; (3) advocacy to encourage additional investment and visibility; (4) priorities to ensure widespread access to a product; and (5) the public health impact.

The reports from the other Working Groups are contained in companion volumes within this series. This document reflects the consensus work of the “Access Working Group,” comprised of six core members. Working with several key consultants, the chairs and members of the group developed a framework for microbicide access that placed the impact on the HIV/AIDS epidemic at the center, and started with the user perspective. The Access Working Group defined its mandate as: *Improving reproductive health and reducing HIV transmission by ensuring that women and girls throughout the world have access to microbicides that are safe, effective, affordable, and easy to use.* To meet this goal, the group identified priorities for action that were reformed and refined through the contributions of key experts in a number of related fields, including: logistics, product introduction, regulatory affairs, financing, social marketing, behavior change, and public-private partnerships. The conclusions and recommendations reflect the understanding and perspectives of the group members, not the official position of any employer or sponsoring agency.

Preparing for Microbicide Access and Use

The rapid spread of HIV highlights the urgent need to expand the range of available prevention methods. Current prevention strategies are not feasible for many women, especially in developing countries. Women urgently need methods to protect themselves from infection with HIV and other STIs that are within their personal control. While no product will address the underlying gender inequalities that constrain women's ability to protect themselves from infection, making such products available could save millions of lives.

Microbicides—topical agents that could be applied vaginally or rectally—offer the possibility of another means for women and men to protect themselves and their sexual partners from infection with HIV and other STIs. Nearly sixty different leads are being explored, and several are poised to enter clinical effectiveness testing. If effective microbicides are to have an impact on the HIV/AIDS epidemic, they must be made accessible to women at highest risk in the poorest regions of the world as soon as possible. Therefore, in addition to accelerating scientific research, it is essential to invest in efforts to ensure rapid access and use.

Systematic and sustained attention to access is especially important because new health technologies rarely become widely available in developing countries until more than a decade after their approval in the U.S. or Europe. Given the urgency of the AIDS epidemic and its devastating impact, especially in developing countries, it is socially, economically, and ethically unacceptable simply to wait for microbicides to “trickle down.” Ensuring that women in developing countries have rapid access to microbicides is a global challenge. It is critical that policy-makers, NGOs, international agencies, and donors begin to tackle this problem today.

In order for a woman or girl to use a microbicide, it must be acceptable to her and she must know how to use it properly. The product must be available in locations that users can easily access at a price they can afford. A woman's ability to access and use microbicides will be facilitated if there is a political and social environment that supports women's use of these products by actively promoting and incorporating them into policies and programs. For all this to be possible, microbicide products will need to be approved by relevant regulatory authorities and promoted as an essential component of a comprehensive HIV prevention package.

While there has been widespread recognition and articulated commitment to the importance of ensuring access to microbicides, little attention has been given to identifying the special initiatives that will be needed to do so. This paper outlines priorities drawing on five main dimensions of access: acceptability and use; a supportive policy and social environment; availability; affordability; and regulatory approval and licensing. Given that the premise of microbicides is to empower women to protect themselves from HIV, and that these products will be user-controlled and will require sustained and correct use, this paper approaches these issues primarily from the user's perspective. Each section contains background information, an overall goal, and several objectives, and sets forth a set of activities and priorities for action. These include a number of specific activities directed toward:

- understanding user preferences and constraints and finding ways to address those—for example, prioritizing for clinical testing those products that best match user needs, as well as choosing formulations, packaging, marketing strategies, and service outlets that maximize acceptability and use;

- creating a supportive policy and social environment by working with communities and policymakers to ensure that the use of microbicides is integrated as one of several legitimate and acceptable ways to prevent the spread of HIV and other STIs;
 - streamlining regulatory, logistics, production, manufacturing, and delivery processes in order to expedite local availability and reduce costs; and
 - ensuring that microbicide development benefits from the global initiatives that are currently transforming the research, development, and distribution of public health goods and commodities to address the market failure to meet the health needs of those most vulnerable to infection and disease.
- Development of a guidance document outlining appropriate, consistent, and expedient regulatory requirements and processes
 - An international working group, representing public- and private-sector interests, tasked to specify the policy, legal, fiscal, and monetary measures necessary to ensure that proven microbicides are accessible
 - Pilot initiatives in three to five countries, particularly those with current or future clinical trials, to establish a framework for ‘microbicides preparedness’
 - Detailed analysis of potential distribution outlets and systems to identify their benefits and shortcomings in relation to getting microbicides to users

There are several activities that can and should be implemented immediately. Of high priority in the next three years, as clinical effectiveness testing and other product development efforts continue, are the following:

- International funding agencies, including the new Global Fund to Fight AIDS, Tuberculosis and Malaria and a number of bilateral and multilateral organizations, make explicit provision for microbicides access in addition to meeting R&D costs
- Rapid establishment of an international entity to accelerate microbicides development that incorporates the promotion of swift and universal access as integral to its mandate and governance

A wide range of actors, nationally and internationally, ultimately bear responsibility for acting on these recommendations: international agencies, governments, funders and investors, politicians, policymakers, health providers, and activists. While this paper sets forth an ambitious agenda, it is one that must begin now if the promise of microbicides—for women’s empowerment in the fight against AIDS—is to be realized.



Introduction

The rapid spread of HIV highlights the urgent need to expand the range of available prevention methods. Current prevention strategies—monogamy, partner reduction, condom use, and treatment of sexually transmitted infections (STIs)—are not feasible for many women, especially in developing countries. For many women in the world, sexual partnerships serve as their only source of economic and social security. Even when women have only one partner, they can be at risk of infection through that partner’s other sexual relationships. Many women simply do not have the power to insist that their husbands or partners use condoms. Female condoms have provided an additional

option, and every effort should be made to ensure that they become more widely available and affordable. Finally, diagnosis and treatment for STIs may not be available, or are stigmatized in many parts of the world; these problems are complicated by the fact that many STIs are asymptomatic in women (Gupta and Weiss 1994; Elias and Heise 1993).

In the global HIV epidemic, more than 90 percent of new infections are spread through unprotected sex, and in the year 2000 more than five million adults were newly infected with HIV. Nearly half of them were women (UNAIDS 2000). Women feature more prominently in this decade

Box 1: Candidate products ready for effectiveness trials

Carraguard™ (Population Council)	Pro2000 (Interneuron, Inc.)	BufferGel™ (ReProtect LLC)
<ul style="list-style-type: none"> • Carrageenan gel; derived from seaweed • Used in food, pharmaceuticals & cosmetics; FDA Generally Recognized as Safe (GRAS) • Inexpensive, widely available, stable • Extensive <i>in vitro</i> and <i>in vivo</i> data • Effective against HIV; HSV-2; gonorrhea <i>in vitro</i> • Multi-site phase 1 completed; safe and acceptable • Phase 2 expanded safety & acceptability study in Thailand and South Africa completed • Phase 3 effectiveness trial due to begin in 2002 in South Africa and Botswana 	<ul style="list-style-type: none"> • Naphthalene sulfonic acid polymer • Active against HIV-1 <i>in vitro</i> • Active against HIV-1 and HSV-2 and non-irritating <i>in vivo</i> • Multi-site phase 1 completed; safe and acceptable • Multi-site, multi-arm phase 2-3 trial to begin 2002 via HIV Prevention Trials Network (HPTN) 	<ul style="list-style-type: none"> • Aqueous gel, pH 3.9; agent Carbopol widely used in pharmaceuticals • Well documented mucosal safety in animals and humans • Maintains natural acidity of vagina (4.2) in presence of semen; acidity kills or immobilizes pathogens; gel also creates a barrier • Multi-site phase 1 completed; safe and acceptable • Multi-site multi-arm phase 2-3 trial to begin 2002 via HIV Prevention Trials Network (HPTN)

of the HIV pandemic than the first in all parts of the world, but close to 90 percent of HIV infections in women now occur in developing countries. Women urgently need methods within their personal control that will protect them from infection with HIV and other STIs.¹ While no product will address the underlying gender inequalities that constrain women's ability to protect themselves from infection, making such a product available could save millions of lives.

Microbicides—topical agents that could be applied vaginally or rectally—offer the possibility for another means for women and men to protect themselves and their sexual partners from infection with HIV and other STIs.² Some sixty different leads are being explored, and several are poised to enter clinical effectiveness testing. The products furthest along in the product development pipeline are gels that are being tested for effectiveness against a range of STIs, including HIV, when applied prior to vaginal intercourse (box 1). Both contraceptive and non-contraceptive products are being developed, the latter offering the possibility for women to prevent disease while allowing conception. (For many women and men, the need or desire to bear children is a major deterrent to condom use). With sufficient resources, it is likely that additional products with different features and profiles will continue to be developed. Ultimately, a constellation of products with a range of qualities, formulation, packaging, and indications will enhance the ability to meet the different needs and preferences of a wide range of users.

Microbicide research has been ongoing for more than a decade, with product research and development conducted exclusively by academic scientists, small companies, and nonprofit organizations supported largely by funds from

the public sector and private foundations. Progress in this field of work has been hampered by a relative lack of visibility and severely limited resources. Large pharmaceutical companies have been reluctant to invest in research and development of microbicides due to scientific uncertainty and concerns about market size and profit potential. However, momentum, recognition, and investment in this area are all growing, and incentives for encouraging investments in research and development are being explored (annex A). The range of scientific approaches and the number of promising product leads is increasing, and several potential products are now ready for large-scale human effectiveness testing. Acceptability and market research studies have underscored the urgent need for woman-controlled methods, and have indicated that women in both developed and developing countries have a high level of interest in these products (Hill et al. 2000; Darroch and Frost 1999).

If microbicides are to have an impact on the HIV/AIDS epidemic, they must be made accessible to girls and women at highest risk in the poorest regions of the world as soon as possible. To date, the majority of financial and intellectual investment in microbicides has been appropriately focused on establishing scientific proof of concept—that a topical microbicide can indeed work to block HIV and other STI pathogens. However, in addition to scientific research, it is essential to invest in efforts to accelerate access and use. These efforts must move forward as parallel and complementary. While there has been widespread recognition and articulated commitment to the importance of ensuring access to microbicides, little attention has been given to identifying the special initiatives that will be needed to do so.

¹ Throughout this paper, the concepts of “within women’s personal control” and “woman-controlled” are used. There is debate about whether microbicides, like the female condom, will more likely be “woman-initiated” than “woman controlled.” In reality this will depend on whether a given product can be used without a partner’s knowledge, which in turn will be determined by the product’s characteristics and the dynamics of the relationship.

² The Working Group recognizes that microbicides are also urgently needed to prevent HIV and STI transmission through anal intercourse among heterosexual couples and men who have sex with men. However, given the urgent need for a woman-controlled method and the fact that effectiveness testing is moving forward for vaginal microbicides, this paper focuses on vaginal microbicides for use in heterosexual partnerships.

Systematic and sustained attention to access is especially important because experience demonstrates that new health technologies rarely become widely available in developing countries until more than a decade after their approval in the U.S. or Europe (box 2). Given the urgency of the AIDS epidemic and its devastating impact, especially in developing countries, it is socially, economically, and ethically unacceptable to simply wait for microbicides to “trickle down.” This is especially true given that the vast majority of investment in microbicides has come from the public sector, and that most large-scale clinical effectiveness testing will need to take place in developing-country sites.³ Finally, in the last several years the vocal activism and political pressure exerted by people directly affected by AIDS has created a strong moral imperative for immediate access to drugs and technologies.

Box 2: The “trickling down” of Hepatitis B vaccine

The Hepatitis B vaccine was first licensed in the U.S. at the end of 1981. It then took almost ten years before the World Health Organization (WHO) recommended adding it to routine childhood immunizations. In 1999, eighteen years after it was first licensed, the global coverage of infants had reached only 35 to 40 percent, and there was almost no use in the lowest-income countries with a documented problem of severe Hepatitis B disease. Through the efforts of the Global Alliance for Vaccines and Immunization (GAVI) and others, this situation is finally beginning to change.

Ensuring that women in developing countries have rapid access to microbicides is a global challenge. It is critical that policymakers, NGOs, international agencies, and donors begin to tackle this problem immediately. A range of initiatives can and must be undertaken now, even as clinical testing and other product development efforts continue. These include: continuing efforts to

engage policymakers; developing innovative financing mechanisms and securing donor commitment to keep prices low; establishing clear regulatory guidance; ensuring high-quality, efficient, and cost-effective manufacturing and distribution; and conducting research to inform product positioning⁴ and introduction. A number of these challenges are similar to those of other drugs and technologies. It is useful, therefore, for microbicide development efforts to learn from similar work to ensure access to new public health technologies and existing products.

However, microbicides also have characteristics that present special challenges. They are both a “drug” and a consumer product. Because they are a new and as yet unproven product category, they are difficult to describe; and investment, testing, marketing, and approval will also be complicated. Microbicides are likely to be partially effective, and as such will remain a complementary option to the physical barrier of condoms. Even a partially effective product could have a major impact on HIV transmission for individuals and communities, especially where condom use is low (Watts and Vickerman 2000). Weighing the risks and benefits of different prevention methods will be a complicated and critical task for policymakers, providers, and individual users. Like condoms, microbicides will need to be produced, distributed, and used over a long period of time, so continuous supply must be efficient and guaranteed. In contrast to vaccines, microbicides’ benefit is dependent on repeated use initiated by the user rather than occasional contacts with the health system. Finally, in challenging traditions of power, autonomy, and sexuality, microbicides raise complex social and political issues related to the unequal balance of power between men and women that limits women’s access to a range of products and services.

³ Phase 3 effectiveness testing for vaginal microbicides requires populations of women at substantial risk of HIV transmission through vaginal intercourse, without confounding intravenous drug use; most of these populations are in developing countries. Scientists calculate that annual incidence rates of 4 to 5 percent will require enrolling 4,000-6,000 women in a trial. Some phase 1 and 2 safety trials are being conducted in sites in Europe and North America.

⁴ Product “positioning” refers to the manner in which a product’s benefits and attributes are communicated to potential users and communities.

It is these gender-related constraints that make it critical to address access to microbicides from a user's perspective. In order for a woman or girl to use a microbicide, she must perceive herself at risk, the product must be acceptable to her, and she must know how to use it properly. The products must be available in locations that users can easily access at a price they can afford. A woman's ability to access and use microbicides will be facilitated if there is a political and social environment that supports women's use of these products by actively promoting and incorporating them into policies and programs. For all this to be possible, microbicide products will need to be approved by relevant regulatory authorities and promoted as an essential component of a comprehensive HIV prevention package.

This paper outlines priorities to ensure access to microbicides drawing on five main dimensions of access: acceptability and use; a supportive policy and social environment; availability; affordability; and regulatory approval and licensing. Each section contains background information, an overall goal, several objectives, and sets forth a set of activities and priorities for action. A wide range of actors, nationally and internationally, ultimately bear responsibility for acting on these recommendations: international agencies, governments, funders and investors, politicians, policymakers, health providers, and activists. While this paper sets forth an ambitious agenda, it is one that must begin now if the promise of microbicides—for women's empowerment in the fight against AIDS—is to be realized.

Acceptability and Appropriate Use

Goal

Women want to use microbicides, and know how to use them properly

Objectives

1. Products are developed that meet user needs and are easy to use
2. Users are well informed and can decide if microbicides are appropriate for them
3. People who want to use microbicides know how to use them correctly

Background

Microbicides will be products that people will need to use consistently and correctly over a long period of time. Appeal and ease of use will be critical factors in determining the effectiveness of microbicides in everyday life. For a product to be used consistently, a woman must perceive herself to be at risk and understand the benefits of using the product, the elements of correct use, and its potential side effects. The user will also have to weigh these attributes against those offered by other products. Meeting all these goals for the microbicide products under development presents considerable challenges.

There is a growing body of knowledge and literature about microbicide acceptability and use, based on data from early-phase clinical trials and studies designed specifically to examine acceptability (for example, Coggins et al. 2000; Elias and Coggins 2001; Bentley et al. 2000; Hammett et al. 2000; Hart et al. 1999). Although the main focus of this research has been user preferences for specific product characteristics, some of it has also explored issues related to vaginal practices, partner relations, willingness to pay, and so forth. In general, women express

enormous interest in microbicides, underscoring the urgent need for woman-controlled methods of HIV prevention. Consistently, the most important characteristics are safety and effectiveness, and “excessive” messiness is deemed to be a deterrent to use. Preferences for other product characteristics vary, and seem to be determined by individual circumstances and desires rather than overarching factors like culture or age. The primary concerns are about long-term side effects, especially on fertility. While many women like the idea of a product that could be used without a partner’s knowledge, most say they would want to involve their partner in the decision or would tell him for fear of repercussions if he found out (box 3).

There has been widespread concern among researchers and policymakers that microbicides would not be acceptable in areas with a norm of “dry sex”, where various cleaning and drying agents are used to make the vagina dry or tight (box 4). This practice is generally associated with the expectation and pleasure of male partners. Studies suggest that even in areas where dry sex is considered to be the norm, it is practiced in highly variable ways. Despite these concerns, microbicide acceptability with actual use in these areas has varied, and indeed many women find the extra lubrication adds to sexual pleasure. It remains uncertain whether women will be able to use lubricating agents when male partners expect “dry sex,” because vaginal wetness can be perceived as a sign of infidelity or infection. However, the research findings do underscore the importance of conducting research to test assumptions about what is or is not acceptable, and continuing to gather information on user perspectives based on actual product use in clinical trials and supplementary studies.

Box 3: Microbicide acceptability

Growing evidence from acceptability studies and clinical trials in diverse settings (Belgium, Brazil, India, South Africa, Thailand, Uganda, U.S., U.K., and Zimbabwe):

- Women in a variety of settings express a high level of interest in a microbicide
- Individual women within and among cultures express different preferences for product formulation and other characteristics
- Safety and effectiveness are regarded as most important; excessive “messiness” is a deterrent
- Primary concerns among women and men are about long-term side effects, especially on fertility
- It is important to consider cultural norms of lubrication during sex, and with actual product use
- For some women and men, the contraceptive effect of condoms is a major deterrent to their use; developing both contraceptive and non-contraceptive microbicides is important
- Effect on sexual pleasure is an important consideration, with significant implications for product positioning, promotion, and marketing

Men’s views and experiences are likely to have a powerful influence on microbicide use, so it is important to consider their preferences, and ways to address concerns they may have (Coggins et al. 2000; van de Wijgert et al. 1999; Pool et al. 2000; Ramjee et al. 2001). In general, men are supportive of efforts to develop microbicides, although few acknowledge a need for “their” women to use such products, and many express concern about women using products without permission from their male partners. An early premise of microbicides was that they would be able to be used “covertly,” or without a partner’s knowledge. The lubricating properties of the gel products currently in development make it less certain whether true

“covert use” would be possible, although microbicide use would require less direct involvement and cooperation from men than using condoms. It is important to continue to explore ways to present information and products to men in a way that makes clear their own responsibility for helping to ensure the health of their partners and families. The views and concerns of a range of other people, such as healthcare providers, peers, and influential older women, are also important, as they may strongly influence a woman’s decision to try a product and continue to use it.

Information collected in clinical trials, studies of hypothetical products, and small acceptability studies have clear limitations in terms of their

Box 4: Intravaginal practices and “dry sex”

- Refers to a range of practices (wiping; inserting herbal and other preparations) to cleanse, dry, or tighten vagina
- Variety of practices reported in eleven sub-Saharan countries; variability among individual women, ethnic groups, and communities
- Practiced to remove vaginal secretions, and contract and “warm” vagina
- Vaginal secretions and wetness often associated with infidelity, lack of cleanliness, infection
- Main reason cited is to provide sexual satisfaction for husband to maintain his fidelity; also used to promote cleanliness, fertility, good health, and to enhance male sexual arousal
- Concern that drying practices may increase transmission of HIV and other STIs by: drying out and irritating vaginal mucosa; disturbing normal vaginal flora; or interfering with the acceptability and efficacy of barrier methods

applicability to “real life” situations after product introduction. It is therefore important to continue to collect information in ongoing clinical studies and other settings to explore use dynamics, partner reactions, and so forth, and to carefully monitor and adapt product introduction efforts.

Introduction and product positioning

Microbicides have a number of characteristics that will make introducing them to individual women challenging. As previously mentioned, the products are likely to be only partially effective, and the characteristics and trade-offs among all available prevention methods must be made clear. Strategies need to be developed to convey complex concepts like partial effectiveness, risk reduction, and a hierarchy of method choices to women and to providers. Given the urgent need for additional prevention methods, especially ones that women can control, it will be critically important to foster realistic expectations, and to avoid “overselling” the product—or misleading women or policymakers into thinking that it confers more protection than it does. This is both a practical and ethical challenge.

To meet the needs and demands of a wide range of users, the microbicide market will have to be segmented, and different products, applicators, packaging, and so on will need to be developed. Following initial product introduction, successive generations of products—or new versions of existing products—may be introduced to meet the needs of different market segments. In many markets, condoms are branded and promoted to different segments of the population for contraception or disease prevention by drawing on varied images of responsibility or sexual prowess. Branding and market segmentation must be carefully planned and implemented to increase the pool of users, and to ensure that these efforts do not result in existing users simply switching

from one prevention method or product to another.

There are a number of important lessons to be drawn from existing user-controlled technologies for pregnancy and disease prevention. Experience with many technologies, notably the female condom, makes clear that product introduction must be accompanied by information and support services to help women, men, and providers answer questions and gain comfort and confidence with the new product. Social marketing and community-based distribution systems can and should be used to convey important educational messages, and to distribute the product if appropriate in that setting (see *Availability*, page 18). Considerable investment must be made in developing clear educational messages and resources; advertising and promotional materials; training for field workers; and exploring strategies for developing partner and peer support. Finally, microbicides must be positioned and introduced in a way that minimizes stigma by society in general and within relationships (see *Creating a Supportive Environment*, page 14).

Proposed Activities

Objective 1: Products are developed that meet user needs and are easy to use

1. Explore which product characteristics are most likely to support or undermine a user’s willingness and ability to use a microbicide, and the cultural and individual preferences that influence this
2. Continue dialogues with product developers to ensure that users’ preferences and needs are taken into account in the product development process
3. Ensure that acceptability and user-perspective issues are explored as part of clinical trials, especially during phase 3 effectiveness studies

Objective 2: Users are well informed and can decide if microbicides are appropriate for them

1. Conduct research on how best to communicate key concepts like partial effectiveness and hierarchy of protection to potential users and their partners
2. Support the development and testing of models of education, training, and promotional materials for users and their partners, health care providers, and potential distribution outlets

Objective 3: People who want to use microbicides know how to use them correctly

1. Develop and assess materials for education and counseling on the use of microbicides, and ways to approach partners
2. Develop and test packaging materials and instructions to ensure that they are informative and understandable to potential users
3. Design and establish systems to monitor microbicide introduction, distribution programs, and product use—and to adapt promotion, education, and counseling efforts accordingly



Creating a Supportive Environment

Goal

Policy makers, health professionals, non-governmental organizations, researchers and communities actively support microbicide development, their incorporation into HIV/STI prevention and reproductive health programs, and their use by women

Objectives

1. A social and policy environment exists that actively supports microbicide use
2. Microbicides are adopted by policymakers at international and national levels as an important component of comprehensive HIV/STI prevention and reproductive health programs
3. Health care providers, family planning providers, and other potential distributors are supportive of microbicides, and have the necessary skills and expertise to support users
4. International agencies strongly advocate and support microbicide research and introduction, and serve as a resource for national policymakers and programs

Background

Adopting and incorporating microbicides into HIV/STI prevention and reproductive health programs will require a concerted effort by national governments, NGOs, CBOs, the private sector, faith-based groups, donors, international agencies, the World Bank and the Regional Banks, and the UN system. All of these different entities have a role to play in creating an environment where microbicides are available, affordable, and widely used.

If women and couples are to feel comfortable using microbicides, an environment must be created where it is socially and culturally acceptable to use them. Building such strategic support is particularly important for products and services that deal with women's reproductive health and sexuality; without this support, it is likely that women's choice and control will be limited. Even the ready availability of affordable products will have little impact on the epidemic if women and girls cannot or do not use them.

The importance of widespread support prior to launching a new service or product is highlighted by the successes and failures associated with the introduction of other new reproductive health products and programs. Relevant lessons can also be drawn from a range of consumer and health goods. For microbicides, these experiences demonstrate the importance of building broad community support and action targeted at:

- Identifying key constituencies that can facilitate or deter introduction
- Ensuring that service providers, community leaders, and policymakers are well informed, and that their concerns have been addressed prior to product launch
- Building the capacities and skills of service providers and program managers to engage them in promoting microbicides and providing accurate, nonjudgmental information and advice
- Developing culturally appropriate educational and advocacy materials targeted at different population groups
- Building on positive norms and behaviors

Product positioning and motivation to use

In order to create a supportive environment, it is important to consider carefully how a product is positioned.⁵ Positioning and marketing will powerfully influence people's perceptions of microbicides, and how widely they are adopted. Microbicides could potentially be introduced as an HIV preventive, a contraceptive, a product to promote reproductive or vaginal health, or a product to enhance sexual pleasure. The introduction and marketing strategy will be critical in setting a social norm for acceptance and use. If initial promotion efforts are aimed at "high-risk" individuals, such as commercial sex workers, microbicides could be stigmatized and rejected by other groups. The first phase of introduction needs to be handled with particular care to maximize the potential for long-term success. Once confidence and experience with the product have been demonstrated, a broader introduction strategy can be devised and implemented. The timing and structure of such a phased strategy will need to be weighed against the backdrop of urgent need for products. One challenge will be determining whether to market the product specifically to women, men, or both, and how openly and publicly to promote a product that some women may want to use without a partner's explicit knowledge.

Previous experience also highlights the importance of product positioning in determining the perceptions of communities and leaders. For example, in Zimbabwe, local women's organizations were concerned about the female "condom" becoming associated with infidelity, prostitution, and other stigmatized behaviors that hampered widespread use of the male condom. Therefore they recommended that it be introduced as a "contraceptive sheath," even though for many women the main motivation to use it was to prevent disease. In Senegal, female condoms were incorporated into a broader empowerment

program for women, and were accepted in those communities that saw the wider benefits of the program.

National support

The positive engagement of national policymakers and key influential individuals is crucial. Decision makers at the national level will ultimately weigh the benefits and costs of microbicides alongside those of other strategies and commodities, and determine whether these products are approved, purchased, and introduced. These actors need to be well informed about microbicides and aware of their potential role in preventing HIV/STI and reducing HIV transmission. Every effort must be made to address their concerns and identify areas where further information is needed to help them evaluate the benefits of microbicides. Among the topics of concern to policymakers are:

- The public health benefits of a microbicide with different levels of effectiveness
- The potential demand for a microbicide and the financial implications of meeting this demand
- The implications of targeting particular population groups
- The potential effects of microbicides on condom use (potential condom substitution)

Before microbicides are introduced into a country, policymakers will need to develop a framework for their introduction, promotion, and delivery. They will also need to determine a level of government involvement in purchase, promotion, and distribution. The sooner these discussions begin, and the more informed policymakers are, the better prepared they will be for making decisions about the adoption of microbicides, once an effective product is identified. Shaping policy attitudes and discourse at the national

⁵ See "product positioning," footnote 4 (p. 8). This concept should not be confused with the actual reason or motivation to use a product. This contraceptive positioning may not be the actual "reason" women use female condoms, as many women may already be using a more effective hormonal method of contraceptive. The positioning allows for both partners in the relationship to consider the issues and motivation for use without accusations or stigmatization.

level is critically important, but it is not sufficient. To ensure access to microbicides, policy interest must be translated into real systems and structures that support product introduction, promotion, delivery, and use (see also *Availability*, page 18, and *Regulatory Approval and Licensing*, page 28).

International agencies

At an international level, funding and policy agencies need to accord greater priority and visibility to microbicides. International policy and health leaders must take an active role in making microbicides a familiar and viable element of the international policy discourse on AIDS. This means ensuring that microbicides are always featured among the current and future strategies in the fight against AIDS: condoms, behavior change, vaccines, and treatment. It also means allocating dramatically increased financial and human resources to microbicide development, testing, and access. Leadership and commitment from the UN agencies in providing technical support and guidance to developing-country governments in the areas of reproductive health and HIV/AIDS prevention is particularly crucial to creating a supportive environment. Finally, additional financial resources, scientific endorsement, and visible leadership can help underscore the importance and credibility of microbicides.

Proposed Activities

Objective 1: A social and policy environment exists that actively supports microbicide use

1. Develop public education and outreach strategies to ensure understanding of the potential benefits and limitations of microbicides
2. Explore women's and men's perspectives, and identify ways to build on existing beliefs, attitudes, and practices to support microbicide use
3. Explore the implications of different approaches to positioning, introducing, and

promoting microbicides for use in different population groups so as to maximize acceptability and reduce stigma associated with the product

Objective 2: Microbicides are adopted by policymakers at international and national levels as an important component of comprehensive HIV/STI prevention and reproductive health programs

1. Identify the best ways to present and promote microbicides as part of a comprehensive approach to HIV/STI prevention—to policymakers, health care professionals, health promoters, and community leaders
2. Identify and address concerns of policymakers, health care professionals, and community leaders about microbicide research and introduction
3. Continue and expand analytical studies to inform decisions on the potential benefits and costs of a microbicide, including:
 - the potential impact and public health benefits of microbicides with different levels of effectiveness and coverage in different settings; and
 - the cost-effectiveness/cost benefit of incorporating microbicides into HIV/STI prevention programs.
4. Develop model national policy frameworks for microbicide introduction, promotion, financing, and delivery through health systems and as over-the-counter (OTC) products

Objective 3: Health care providers, family planning providers, and other potential distributors are supportive of microbicides and have the necessary skills and expertise to support users

1. Analyze the knowledge and concerns of health care providers, family planning providers, and other potential distributors

2. Develop skills, expertise, and leadership within countries and communities for incorporating microbicides into HIV/STI prevention and reproductive health programs

Objective 4: International agencies proactively support and advocate for microbicide research and introduction, and serve as a resource for national policymakers and programs

1. Advocate for international and bilateral agencies to include microbicides in their HIV/STI prevention and reproductive health

portfolios, and to develop a set of clear policy guidelines on the introduction of microbicides

2. Initiate introduction trials and effectiveness evaluations as soon as phase 3 trials are completed, even in advance of formal regulatory approval

Availability

Goal

Microbicides are readily and reliably available in outlets convenient to women and girls who need them most, especially in developing countries

Objectives

1. Microbicides are available in the range of outlets convenient to different potential users
2. Efficient, effective, and reliable distribution systems are in place within countries
3. A reliable supply of microbicides is in place globally and nationally

Background

For a microbicide to be used, it needs to be readily and reliably available in a convenient and easily accessible location, in good condition, and priced so that consumers can afford it (box 5). This is a goal that has yet to be realized for a number of important health products. Ensuring that microbicides, once approved, are widely available throughout the world is an enormous and complex undertaking. It requires deliberate

planning and sustained commitment at all levels—local to international, public to private. It also requires investment of time and resources in: estimating demand for microbicides with different characteristics; developing manufacturing and packaging capabilities to meet global demand and facilitate local availability; strengthening national procurement, delivery, and distribution systems; and identifying and building outlets convenient to different user groups. These issues must be incorporated into negotiations with developers, producers, and donors. The microbicide field can build on a number of ongoing efforts to strengthen the provision of public health commodities in developing countries.⁶

Distribution outlets

There are a number of different distribution outlets that could be used to ensure that microbicides are widely available within countries (box 6). The feasibility of some of these outlets will depend on the type of marketing approval given by the relevant regulatory authority (see also *Regulatory Approval and Licensing*, page 28). Ideally, from an access perspective, microbicides will be approved as OTC products and can be distributed through a broad range of outlets. Depending on their mode of action, some microbicides may be approved as prescription-only.⁷ Other products may begin as prescription-only and then move to OTC status once there is sufficient experience of use. Strategies for distributing microbicides therefore need to consider scenarios for both OTC and prescription-only products.

Box 5: The Six Rights of an effective commodity program

- The Right Product
- in the Right Quantity
- in the Right Condition
- in the Right Place
- at the Right Time
- for the Right Cost

(Source: Deliver Project)

⁶ Examples of these initiatives include: UNFPA's Reproductive Health Commodity Security Strategy; and the Deliver Project, a collaborative effort of JSI, PATH, and the Wallace Global Fund supported by USAID.

⁷ Several developers are exploring topical application of PMPA, Nevirapine, and other anti-retroviral therapies as microbicides. These products, still in the early stages of development, would be likely to remain as prescription-only due to concerns about resistance.

A number of specific product characteristics, such as biostability, storage requirements, and shelf life, need to be considered in assessing the feasibility of different distribution outlets. User concerns, including ease of storage within a home, frequency of use, need for secrecy, and so forth, must also be taken into account. It is likely that a range of educational, counseling, and support efforts will be needed to ensure that microbicides are introduced and used appropriately.

Given the urgency of the HIV epidemic, regulatory authorities, program planners, and policymakers must balance these many considerations against the acute need for a microbicide in many parts of the world, and must be bold and innovative in assessing and developing potential service delivery and product distribution strategies. The launch plan, and therefore the choice of outlets, should carefully consider the implications of targeting certain population groups, and balance the potential public health impact against the possible problems caused by stigmatization. For a completely new product category like microbicides, it may be advisable to establish an initial base of clients who can successfully use the products, and then devise a further outreach strategy from there.

Health care clinics, pharmacies, and various health programs (such as HIV/AIDS, family planning, STI, and primary health care) will clearly be important routes for distributing both prescription-only and OTC products, especially in the early stages of their introduction. Distribution through these routes allows for education, counseling, and support for potential users, and provides the added assurance to users that the product is sanctioned by the health system. Products can also be provided free to people who cannot afford to purchase them. Social marketing,⁸ network marketing, franchising, and distribution through the commercial sector are

Box 6: Potential distribution outlets

- government health and family planning clinics
- NGO and religious health and family planning clinics
- private health clinics
- workplace clinics
- pharmacies
- community-based distributors
- village health workers
- local shops, beauty parlors, taxi stands, markets, convenience stores, cinemas, etc.
- organizations targeting particular populations
 - youth groups
 - women's organizations
 - sex workers

other important avenues. These approaches have successfully increased the availability and affordability of other preventive health technologies such as condoms, contraceptives, and bed nets for malaria prevention. Such approaches offer great potential for making microbicides widely accessible.

Several acceptability studies have explored where women and men would like to obtain microbicides, and the answers vary (see *Acceptability and Use*, page 10). Some people would prefer to get the products through the formal health system. Reasons for this preference include: the added assurance that a doctor or provider “approves” or “recommends” the product; the opportunity for information, counseling, answers to questions, and other services; privacy; and the possibility that the product could be free (or, in the U.S., covered by insurance). Others are more concerned with convenience and would like the products to be available more widely. Given that this research explored hypothetical products,

⁸ Social marketing involves the distribution of needed products to lower-income persons by marketing through the existing local commercial and nongovernmental organization (NGO) infrastructures at a price they can afford, and by promoting healthy behavior. A key ingredient of successful social marketing is effective communications to encourage the adoption of appropriate health practices (including proper use of the products). This is done by brand-specific advertising as well as by generic educational campaigns, using a mix of strategies and channels—including mass media and interpersonal communications—to reach the target audience. The retail price of the product can be lower than the manufacturing cost, and therefore donor subsidies are a vital element of the social marketing process.

there are clearly limits to this kind of information for developing a distribution strategy. More work needs to be done to understand where different categories of users would like to obtain microbicides and how this links to distribution networks, storage requirements, frequency of use, and social acceptability. Acceptability and clinical studies should continue to explore these issues, and actual programs will need to assess and modify these strategies based on experience.

Procurement and distribution systems

The availability of a product in local outlets depends on strong local and national distribution systems. Ensuring that there is a reliable distribution system is essential if microbicides are to fulfill their potential. A strong distribution system can increase the impact of a program by providing a consistent, reliable supply of high-quality products; increasing cost-effectiveness and accountability by reducing loss and waste; and minimizing the risk of diversion or unregulated use.

There is considerable variation within countries and between countries in the structure of the distribution networks handling health care products and other products that women and girls use. Identifying the most appropriate distribution system, or systems, will depend upon the range of outlets being serviced, and will have to be tailored for each setting and user group. Building on existing systems for essential drugs and contraceptive commodities is one possibility; other avenues that should be explored include distribution for consumer goods like cosmetics, soft drinks, soap, and fuel oil. Assessing the feasibility, strengths, and weaknesses of existing distribution systems can determine how they should be modified or strengthened to handle microbicides efficiently. This will require

considerable lead time and should be initiated well in advance of product approval.

The success of a distribution system depends on its ability to move products efficiently and effectively. This in turn requires an adequate and reliable supply of quality product. It is crucial to strengthen national procurement mechanisms, and clarify how existing international procurement systems can be used for microbicides. In settings where the need for microbicides is greatest, microbicides are likely to be initially a subsidized product provided by donors and the public sector. These procurement systems are intended to allow countries and donors to secure reduced prices through pooling orders and bulk purchase. However, their effectiveness can be hampered by lack of coordination and uncertainty among donors, national programs, and suppliers about what commodities are needed in a given setting—and what entity will purchase and supply them. Recognizing these problems, a number of efforts are currently underway to strengthen the provision of public health commodities in developing countries. The microbicides field should engage in this process, and explore concrete ways that existing procurement and distribution systems can be strengthened to include microbicides.

With new products, especially completely new product categories, uncertainties in estimating demand are considerable. This is particularly true for a product like a microbicide that does not yet exist, and where few people have experience with even a related product.⁹ Despite these problems, such estimates are vital, as they inform a range of critical decisions: investment, production capacity, distribution systems, and introduction strategies.¹⁰ Forecasting and modeling techniques can be used, and estimates should

⁹ To date, two studies have investigated the potential demand for a microbicide. One study was conducted in the U.S. (Darroch and Frost 1999), and the other in twelve European and developing countries (Hill et al. 2000). Both found a high level of interest among women in both developed and developing countries in using a microbicide. However, given that expressed interest in a hypothetical product tends to overestimate what is commercially achievable, more targeted research will be necessary as products move through the pipeline.

¹⁰ There are numerous challenges in accurately estimating demand, including: (1) actual product demand is quite distinct from the need for a product; (2) there is generally little correlation between expressed interest in a product and actual demand for it; (3) it is difficult to build, and to sustain, demand for a brand new product; and (4) there are few reasonable proxies for microbicides.

continually be adapted based on new information. The risks of inadequate attention to estimating production and supply could have disastrous consequences—on one hand, there could be insufficient supply of a product that finds a market and generates significant demand, or product (and resources) could be wasted due to oversupply. Given the uncertainties of estimating demand for a product—and the high stakes—it is important to establish reliable and flexible distribution and manufacturing systems that can shift and adapt to demand.

Meeting the global demand for microbicides will require substantial investments in manufacturing and packaging capacity, and these investments must be made early if products are to be made available quickly. Collating information on potential manufacturers, and refining estimates of initial demand and demand projections, are important for making investment decisions. Depending upon the active ingredient(s) and the product design, some of this capacity may be met by existing manufacturing plants that produce pharmaceutical or consumer products. Locating facilities in key developing countries could have several benefits: reducing costs of production, shipping, and imports; eliminating some steps in the logistics process; technology transfer; and providing opportunities for investment and employment. Local production also has a number of potential drawbacks, which should be weighed carefully.

Plant design, development, and ensuring that the plant meets international standards of Good Manufacturing Practices all take time. For products with a high profit potential, investment decisions are often made, and building started, while the product is still being tested. With microbicides, the market size and uncertainties in regulatory processes may hamper early investment without financial assistance from the public sector, either directly or as tax credits. However, the public health benefits of this investment could be substantial by reducing the time between a product's approval and its availability.

Proposed Activities

Objective 1: Microbicides are available in the range of outlets convenient to different potential users

1. Assess experience with reproductive health, feminine hygiene, and other consumer products to inform distribution strategies
2. Incorporate into planned and ongoing microbicide studies questions on where and from whom users would like to acquire microbicides, and the factors that influence this
3. Identify opportunities for, and constraints to, integrating microbicides into existing HIV/STI prevention and reproductive health programs
4. Explore the feasibility of, and opportunities for, different outlets and distribution systems for a product approved as
 - an OTC product
 - a prescription-only medicine

Objective 2: Efficient, effective, and reliable distribution systems are in place within countries

1. Assess the capacity of existing distribution systems for storing microbicides and distributing them to proposed outlets; engage experts in logistics early to help overcome barriers
2. Strengthen distribution systems if necessary so that they can handle microbicides reliably and efficiently at low cost
3. Advocate that product stability and shelf life are factored into decisions that determine which products move forward through the pipeline
4. Design monitoring and feedback system to inform revision and refinement of national distribution strategies

Objective 3: Efficient and reliable supply is in place globally and nationally

1. Ensure that there is sufficient and timely investment in manufacturing capacity at the global level to meet projected demand
2. Explore options for manufacturing and/or packaging microbicides, including building on existing manufacturing capacity and developing additional sites in key developing countries
3. Assess and strengthen the capacity and coordination of existing international procurement systems to handle microbicides, and establish new mechanisms as required to help countries secure fair prices and a reliable supply
4. Use modeling and forecasting to generate global and national estimates of public- and private-sector demand and uptake for microbicides
5. Develop strong and flexible manufacturing and distribution systems that can respond quickly to shifts in demand

Goal

Cost is not a barrier to microbicide use

Objectives

1. Microbicides are priced at a level users can afford
2. Product, manufacturing and distribution costs are as low as possible
3. Subsidies/financing mechanisms are in place to ensure a sustainable supply of microbicides
4. Overall revenues make product commercially viable

Background

There is likely to be a significant market of consumers who can pay for microbicides (Darroch and Frost 1999; Hill et al. 2000). This is particularly true for products active against a wide range of STI pathogens in addition to HIV. However, many people who would benefit most from a microbicide will be those least able to afford to purchase it, and so development, production, and distribution need to be subsidized. The lack of proof of concept, and concerns about a profitable market, have deterred private-sector investment in research and development. Currently, virtually all funds for microbicide product development come from the public sector and foundations motivated by public health and equity concerns. This gives added impetus to ensuring that these products reach people who are most vulnerable and at greatest risk, regardless of their location or economic

status. Ensuring that microbicides are affordable begins with investing in product development, and affordability must be considered and addressed at every step of the process—pre-clinical development, clinical testing, licensing, production, introduction, delivery, and use. Ultimately the need for affordability for the poor must also be balanced against the need to cover manufacturing costs and overall commercial viability.

Product affordability must be considered from several perspectives—individual, household, health system, country, and international community. A product’s “affordability” reflects a balance between its cost and the financial resources available for its purchase. As a result, efforts to ensure that microbicides are affordable must focus on both reducing costs and mobilizing resources locally and internationally. Thus, it will require a concerted global effort and attention to intellectual property rights, licensing, manufacture, packaging, distribution, pricing, levels of subsidies, government policies, and a host of other issues.

Reducing costs

The final price of a product reflects: the cost of producing the product, its formulation, and applicators (including investments in research and development, and any royalty payments); the cost of packaging the product¹¹; the other costs and profit margins that producers, importers, wholesalers, and distributors receive; tariffs and duties on imported products; logistics, including shipping and warehousing; marketing

¹¹ For microbicides, the cost of packaging and applicators is likely to make up a significant proportion of the total cost. The “costs” and “benefits” of different options need to be considered from both the user and the provider perspectives. “Savings” on packaging or applicators that make a product less appealing or acceptable are not a good investment.

Box 7: Reducing cost

Actions directed at reducing the cost of the product:

- Low-interest loans for building manufacturing plants
- Tax credits for:
 - building manufacturing plants
 - research and development expenses
 - accepting reduced royalty payments
 - manufacturing or packaging in developing countries
- Tax incentives for firms providing product donations on a substantial basis
- Differential tax treatment of profit earned in different parts of the world

Actions directed at reducing procurement and distribution costs:

- Establishing an international tendering or bulk procurement system
- Eliminating tariffs and duties on microbicides or imported goods for manufacturing or packaging microbicides
- Eliminating national and local taxes on finished product or raw materials
- Building on existing distribution systems and/or partnering with other products
- Price-tiering systems for the poorest markets/populations

costs; and national and local taxes. To reach those at greatest risk in poorer populations, microbicides will need to be subsidized, and funds for HIV/STI prevention are limited. It is therefore essential that the final cost per use is as low as possible for these groups—without jeopardizing safety, quality, or the product’s overall commercial viability. Box 7 outlines some of the different ways that governments, international agencies, nongovernmental organizations, and funding agencies can work to influence the different components of the final product price for the poorest consumer.

Experiences with both patented and non-patented products have shown that price reductions of 90 percent or more can be achieved through bulk purchasing, competitive tenders, and skillful negotiations (box 8). Significant price reductions have been achieved for contraceptives, vaccines, and a number of essential drugs. The success of this level of differential pricing depends on having the right legal, technical, and political environment. For this system to work, politicians, policymakers, and consumers in the OECD countries must accept

sustained price differences (tiered pricing). There must be an effective way to segment markets and maintain clear boundaries. Product differentiation through branding, packaging, and marketing can contribute to effective market segmentation. This is important to prevent the “flow back” of low-priced products to high-income markets, and what is termed “price erosion” in affluent markets.

Market segmentation and differential pricing through branding and subsidization is also a useful strategy within countries. Efforts to promote the distribution of male and female condoms highlight the importance of developing a coherent pricing strategy, and show that this strategy may involve setting sharply different prices for brands directed at different population groups. Some individuals who would benefit from the product will not be able to pay anything for it; some will be able to pay a subsidized price; while others will be able to pay the full market price. Each country will need to assess the size of these different population groups and how best to reach them.

Box 8: Contraceptive prices comparison of UNFPA procurement prices and U.S. market prices

Item	Unit	UNFPA price	US market price ¹²	Percent reduction
Oral contraceptives – generic	cycle	0.175	30.00	99.4
Oral contraceptives – single source (on patent)*	cycle	0.364	34.00	98.9
Male condom	piece	0.025	0.50	95.0
Female condom	piece	0.57	2.80	79.6
Intra-uterine device	piece	0.430	350.00	99.9
Injectable contraceptives	dose	0.675	65.00	99.0
Spermicides	tube	0.060	1.20	95.0
Hormonal contraceptive implants	set	23.00	393.00	94.1

* Example of third-generation oral contraceptive

(Sources: Report of the workshop on differential pricing and financing of essential drugs, WHO and WTO Secretariats, 8-11 April, 2001. Data from a presentation by Mr. C. Saunders of UNFPA; Mitchell Warren, Female Health Company, personal communication, 2001.)

Another approach is to negotiate price guarantees in exchange for public investment in product development or for access to publicly financed clinical trial sites. This is one of the approaches being used by the International AIDS Vaccine Initiative (IAVI) to ensure access to HIV vaccines in developing countries. IAVI's agreements allow private-sector partners to retain development rights and to charge a market price in the industrialized world and in the private market in developing countries. In return, they must make the product available at a reasonable price to the public sector in developing countries (e.g., cost plus no more than 10 percent). If the latter condition is not fulfilled, IAVI retains "march-in rights" and can transfer the technology to another producer. The key to this type of agreement is maintaining an interest in managing the intellectual property generated by the project. This includes ensuring that agreements around intellectual property rights are maintained when companies are sold or change ownership.

This is also an important and appropriate approach to pursue for microbicides, given that the bulk of investment in research, development, and testing currently comes from the public sector and foundations. Doing so will require a significant increase in resources in the microbicide field through an organization that can leverage similar agreements. Recognizing that the burden of microbicide clinical testing is in developing countries, the benefits of these price-reduction strategies should be prioritized for the poorest populations and countries in which clinical trials take place.

Mobilizing resources

Funding for the purchase and delivery of microbicides for the poor in developing countries will come from both internal sources (users, government, and NGOs) and external sources (bilateral agencies, foundations, NGOs, UN system, development banks). It is clear that if microbicides are to be made widely available to women at risk of HIV in developing countries, a

¹² Price also includes packaging, marketing, and distribution costs.

significant level of external support will be required. In reality, “demand” for purchase of microbicides as part of commodity packages will be negotiated among national authorities and staff of international donor agencies. It is therefore important to inform and engage policymakers and staff of donor organizations in advance so they will prioritize microbicides when allocating resources and purchasing commodities.

Funding for international health is in a state of change at the global level with the recent establishment of the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). Agreements to ensure access to microbicides will also be influenced by the activism and negotiations around access to AIDS treatment. The specific working arrangements and scope for the GFATM are currently being developed, but it is likely to be a major player in ensuring access to products directed at preventing or treating HIV/AIDS, malaria, and tuberculosis.

Donors, international agencies, the new Global Fund, and national governments will need to work together to devise funding mechanisms and purchase agreements to ensure that microbicides are accessible and affordable in those areas where they are most needed. Ongoing discussions focused on developing mechanisms for the purchase of existing public health products should be actively encouraged and monitored. If these mechanisms can be shown to work for other products, then the examples could be applied when microbicides are available. For example, a coordinated, donor-funded commodity bank for products, especially new products, could be a major accomplishment. The World Bank is exploring ways that funds from other organizations could be used to transform IDA loans into de facto grants. The Bank is also actively exploring appropriate and constructive ways to engage in pricing and purchasing negotiations early in the development and testing of a given product.

Putting new funding mechanisms in place before a candidate microbicide has been approved will almost certainly accelerate product availability. Demonstrating a credible market should also provide more incentives for commercial research and development, and for investment in production capacity. A credible commitment to develop and purchase microbicides should also help engage national governments in preparing for microbicide introduction.

Proposed Activities

Objective 1: Microbicides are priced at a level users can afford

1. Review current pricing strategies for public health commodities and, in particular, HIV/STI prevention and family planning products
2. Explore strategies for negotiating price guarantees in developing countries in exchange for public funds for research and development and access to publicly funded trial sites
3. Assess what women in different settings are “willing to pay” for a microbicide and how this compares to what they may be able to afford to pay
4. Estimate the likely gap between the final “price” (i.e., price of the commodity plus delivery costs and mark-ups) and the amount users in different settings can afford
5. Analyze the likely short-, medium-, and long-term implications of different pricing strategies on microbicide use

Objective 2: Product, manufacturing, and distribution costs are as low as possible

1. Advocate that cost of product and production is one of the criteria used to select products for testing, especially in publicly funded trial sites

2. Explore options for manufacturing and/or packaging microbicides locally, and whether such approaches are cost-effective
3. Support national actions to reduce product costs for all prevention methods—for example, by removing taxes and tariffs
4. Explore options for keeping distribution and procurement costs as low as possible without jeopardizing supply
5. Establish controls to ensure that subsidized, discounted, or donated products are not re-exported
6. Assess the likely costs and requirements of establishing manufacturing capacity, as well as the potential for technology transfer and developing-country production
3. Estimate the level of financial support that will be required to support the distribution of microbicides in developing countries
4. Identify and monitor potential sources of public- and private-sector funding for subsidizing the purchase and delivery of microbicides
5. Work with international agencies, bilateral donors, and other funders to develop a concrete commitment to fund the distribution of microbicides
6. Work with World Bank and other donors to develop concrete commitment and mechanisms for subsidies
7. Identify criteria for targeting external aid to subsidize microbicides for the poorest countries and populations in greatest need

Objective 3: Subsidies/financing mechanisms are in place to ensure a sustainable supply of microbicides

1. Explore and advocate national and international actions designed to reduce the R&D costs incurred by firms in exchange for reduced prices in developing countries
2. Monitor ongoing discussions on international financing mechanisms for health products, and ensure that microbicides are included in these discussions (e.g., the Global Fund, the EC Accelerated Program, World Bank)

Objective 4: Overall revenues make product commercially viable

1. Support international actions directed at encouraging the OECD countries to accept differential or tiered pricing
2. Estimate the potential demand and market size for microbicides in developed countries
3. Continue ongoing analyses to assess market viability



Regulatory Approval and Licensing

Goal

Microbicides are approved and licensed by relevant authorities rapidly and efficiently

Objectives

1. Relevant regulatory authorities have the information, procedures, and capacity to approve and license microbicides for use
2. Delays arising from differences in regulatory requirements between countries are minimized
3. National and international systems and protocols are in place to assure product quality and to monitor the use of microbicides

Background

Before a microbicide can be marketed for use in a country, it has to be approved by the appropriate regulatory authority. This process can be long and complex, and varies considerably between countries in terms of approach, criteria, standards, and requirements. For microbicides this situation is further complicated: microbicides are a new product category that is not yet well defined; there is no clear regulatory pathway or precedent to follow; and international consensus on safety, effectiveness, and quality assessment is still evolving.

From a global public health perspective, it is important that microbicides are approved and licensed widely as soon as possible, particularly in those countries where HIV infection is spreading rapidly. At the national level, this will require clarifying the regulatory processes and requirements for marketing approval of microbicides with different characteristics and sponsor

claims.¹³ A key consideration for widespread availability and access is whether a product could be approved for OTC use and distribution, or whether it will be restricted to prescription-only. Depending on the specific active compound, it may be that microbicides could and should be approved immediately as OTC products, especially in countries with urgent need. This could encourage involvement by private companies, and would facilitate the use of a wide array of distribution channels (see *Availability*, page 18). Of course, primary consideration would have to be given to protecting public health by establishing product safety and effectiveness before such approval is granted.

While a number of developing countries have approval processes for new health care products, many have only limited regulatory infrastructure or scientific expertise. As a result, approval in many countries can be heavily influenced by the decisions of the United States Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMA). However, regulatory agencies in the developed countries may take a relatively conservative approach to microbicide approval, given the profile of the HIV/AIDS epidemic there. A partially effective microbicide or HIV vaccine that might not be sponsored for licensing or approved in the U.S. or Europe could make a major difference in curbing the spread of HIV in a setting where prevalence and incidence are much higher. Decisions within countries about when to approve a product, and what type of marketing approval to grant, must be based on a detailed analysis of the product's characteristics, weighed against the specific public health needs of the country. Ideally, all countries could have the capacity to review and make decisions based on their own need rather

¹³ The sponsors' claims may include: effectiveness against HIV, effectiveness against other STIs, duration of protection provided, and contraceptive effectiveness. The sponsors' claims drive what data need to be presented to a regulatory authority.

than waiting for, or following, the decisions made by agencies in the U.S., Japan or Europe.¹⁴

However, given shortages of resources and the complexity of strengthening national regulatory infrastructure in all settings where microbicides are needed, building regulatory capacity by country is not practical. The urgent public health and ethical need for microbicides warrants exploring new regulatory paradigms. One approach is to draw together key regulators, scientists, and nongovernmental organizations from a range of countries to decide on appropriate pathways that could be used widely for guidance. Other practical areas for cooperation include: study design for determining safety, efficacy, and quality; and formats for submitting data. Including regulatory authorities from a range of countries in discussions to design and conduct microbicide clinical trials may also reduce the need for trials to be conducted or repeated in multiple countries. WHO and UNAIDS have initiated such discussions related to AIDS vaccines, and a similar meeting is being planned for microbicides in early 2002.

The microbicides field should be strategic in looking for other opportunities and approaches to clarify and streamline regulatory requirements. For example, strengthening national regulatory infrastructure could be prioritized in countries with great need for microbicides, especially those where clinical trials are being conducted. The microbicide field should identify key countries, like South Africa or India, that can develop regulatory guidance on microbicide approval. These countries have good scientific and regulatory capacity, great need for a product, and may be able and willing to approve and register microbicide products in the absence of EMEA or FDA approval. They could potentially provide regional leadership for other countries.

Similar strategies could be adopted for other regulatory responsibilities, such as monitoring

product quality and conducting post-marketing surveillance. In the case of childhood vaccines, WHO plays a role in supporting these activities by developing guidelines and recommendations on production and quality control, and by managing the pre-qualification process for manufacturers selling to UN agencies. It may be appropriate for WHO or another international agency to play a similar role for microbicides.

International agencies and the public sector may also have an important role to play in product licensing and registration. Private companies or sponsors file for marketing approval in a given country and tend to phase their efforts—with initial emphasis on countries with a large potential market and a clear and transparent regulatory process. Because many of the countries where microbicides are needed do not fit this profile, clarifying requirements and strengthening regulatory review mechanisms could make a significant difference in encouraging the private sector. Alternately, the public sector may need to play a direct role, either by supporting companies to file applications for approval in multiple countries where the need is great, or to take on the role of filing directly.

Microbicide developers and advocates should examine other efforts, already ongoing, to encourage international harmonization between regulatory agencies. For example, the International Conference on Harmonization (ICH) brings together the FDA, EMEA and the Japanese Ministry of Health and Welfare with pharmaceutical industry associations to look for opportunities for harmonizing technical requirements in the areas of safety, efficacy, and consistency. For products like microbicides that are being developed primarily in the academic and public sectors, it would be critical to include new actors in this process to represent and address the specific issues related to microbicide development.

¹⁴ In many settings, local approval depends on prior approval of the product in a major market in the U.S. or Europe. This may also have implications for donor purchase, since regulatory approval in the donor country may be required.

It is critically important that these efforts at collaboration and streamlining do not result in the requirements of the jurisdiction with the most exacting review process becoming the norm. The purpose of harmonization should be to accelerate availability of safe and effective products where they are needed most, not to hinder it.

Proposed activities

Objective 1: Relevant regulatory authorities have the information, procedures, and capacity to approve microbicides for local use

1. Establish appropriate, consistent, and expedient regulatory requirements and processes for approving microbicides
2. Strengthen capacities for reviewing and approving products, based on local risk/benefit decisions
3. Develop a country matrix for all key markets and countries in need that outlines existing regulatory processes
4. Clarify regulatory requirements for contraceptive claims for microbicides

Objective 2: Delays arising from differences in regulatory requirements between countries are minimized

1. Encourage dialogue and information-sharing among regulatory authorities to speed regulatory processes
2. Ensure that the FDA and EMEA are prepared for rapid turnaround to facilitate global access

3. Monitor and collate evolving national, regional, or international procedures and requirements for approving microbicides
4. Accelerate efforts to develop international guidelines on regulatory requirements
5. Identify and work with regulatory authorities in key countries that can provide leadership in establishing guidelines
6. Explore opportunities to establish regional systems to help countries accelerate the approval of microbicides, and monitor quality and use

Objective 3: National and international systems and protocols are in place to assure product quality and monitor the use of microbicides

1. Explore the role that WHO and other international institutions can play in developing guidelines and recommendations on production and quality control
2. Strengthen national regulatory agencies and their enforcement capacities and ensure that effective surveillance systems are in place to:
 - a. monitor product quality;
 - b. monitor the use of microbicides and the consequences of misuse; and
 - c. respond to the distribution of unproven or ineffective microbicides.
3. Ensure that appropriate authorities have the capacity to monitor compliance with manufacturing protocols in countries where microbicides are produced

More than two decades of research on women's economic and social status worldwide has established that women, as compared to men, have less access to key productive resources such as education, land, employment, or credit (UNIFEM 2000). Data from around the world show that this unequal access creates an imbalance of power in heterosexual gender relations that greatly constrains women's ability to negotiate with their male partners for protection against HIV and other STIs. The fear of abandonment, economic destitution, and violence has prevented many women from insisting on condom use or fidelity in sexual partnerships. Poverty and economic dependency have also forced many women to sell sex for economic gain or survival (Gupta and Weiss 1994; Gupta 2000).

Ultimately, containing the HIV/AIDS epidemic will require an improvement in women's economic and social status. While no product can equalize the power balance between women and men, woman-controlled methods to protect against infection could greatly reduce the number of HIV and other STI infections, and save millions of lives. Microbicides offer this possibility.

Increased investments in scientific research are essential to make microbicides a reality. However, simultaneous and parallel investments must be made to ensure that once proven to be effective, they are accessible to vulnerable women in the poorest regions of the world. There are concrete ways in which the scientific agenda for the development of microbicides can be infused with, and informed by, priorities to ensure access.

This paper recommends steps that, if implemented, could facilitate women's access to microbicides. These include a number of specific activities directed towards:

- understanding user preferences and constraints and finding ways to address those—for example, by prioritizing for clinical testing those products that best match user needs, and choosing formulations, packaging, marketing strategies, and service outlets that maximize acceptability and use;
- creating a supportive policy and social environment by working with communities and policymakers to ensure that the use of microbicides is integrated as one of several legitimate and acceptable ways to prevent the spread of HIV and other STIs;
- streamlining regulatory, logistics, production, manufacturing, and delivery processes in order to expedite local availability and reduce costs; and
- ensuring that microbicide development benefits from the many global initiatives and international financing mechanisms that are currently transforming the research, development, and distribution of public health goods and commodities in order to address the market failure to meet the health needs of those most vulnerable to infection and disease.

While some of these recommended activities have to wait for the development of a clinically effective product, planning can start now, and there are several activities that can and should be implemented immediately. Of high priority in

the next three years, as clinical-effectiveness testing and other product-development efforts continue, are the following:

- International funding agencies, including the new Global Fund to Fight AIDS, Tuberculosis and Malaria, and bilateral and multilateral organizations, make explicit provision for microbicides access in addition to meeting R&D costs
- Rapid establishment of an international entity to accelerate microbicides development that incorporates promoting swift and universal access as integral to its mandate and governance
- Development of a guidance document outlining appropriate, consistent, and expedient regulatory requirements and processes
- An international working group, representing public- and private-sector interests, tasked to specify the policy, legal, fiscal, and monetary measures necessary to ensure that proven microbicides are accessible
- Pilot initiatives in three to five countries, particularly those with current or future clinical trials, to establish a framework for ‘microbicides preparedness’
- Detailed analysis of potential distribution outlets and systems to identify their benefits and shortcomings in relation to getting microbicides to users

It is inefficient, even unethical, to repeat the mistakes of the past that have forced individuals in the developing world to wait years, sometimes decades, to gain access to much-needed drugs or vaccines. The ongoing global activist movement to guarantee people living with HIV/AIDS in the developing world access to AIDS treatments serves as a vivid reminder of the urgent need for the research and development of new products to be guided as much by accessibility priorities as by scientific imperatives. By selecting accessibility to the end user as the only criteria for claiming success, the field of microbicide development could serve as an example to be emulated by future technology development efforts. The objective, after all, is not just to develop new technologies and products that are effective, but rather to ensure that their use contains the spread of the HIV/AIDS epidemic and saves lives.

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Encouraging Industry Engagement in Product Development for Public Health Goals

The historical—and ill-defined—division of responsibilities between “public” and “private” sectors in research and development (R&D) for drugs, vaccines, and other health products sometimes requires additional interventions to ensure the desired outcomes for public health. Government agencies (such as U.S. National Institutes of Health, U.K. Medical Research Council, and intergovernmental agencies like WHO) and other “public interest” funders (such as foundations) typically fund research that leads to the understanding of diseases and concepts for interventions.

The skills and resources for moving potential products through the development and regulatory phases, including manufacturing and quality-control process development, are mainly found in the commercial industry. Whether industry will engage these skills and resources to develop a particular product for public health purposes depends on the balance of a range of factors. These include but are not limited to:

- the scientific base for product design and anticipated probability of success;
- the difficulty and expense of further development;
- relevant expertise within the companies;
- the potential for profitable markets; and
- opportunity costs, i.e., other products that could be developed by applying these resources.

For products that are not commercially attractive (as in cases where the major perceived need is in poorer populations), the likelihood of industry’s engagement can be increased (but not guaranteed or compelled!) by a variety of

interventions by the public sector, or by “public interest” funders of R&D. For convenience, these interventions can be grouped into “push” and “pull” mechanisms.

Push interventions lower the costs or risk for industry of product development or improvement, or remove or reduce disincentives or barriers to their involvement. Examples of push interventions include those that:

- (i) Lower costs and risks of research and development
 - Basic research funding (from government or philanthropy)
 - Grants for product development
 - R&D tax credits to companies
 - R&D expense “write-offs”
 - Tax credits to investors
 - Establishment of R&D capacities in endemic situations, e.g., phase 3 trial sites
 - Protocol assistance, as per U.S. Orphan Drug Act
 - Support for R&D to identify new indications for existing entities:
 - financial
 - through mass screening facilities
 - consortia (public; private; or public/private):
 - “horizontal” – discovery
 - “vertical” – development/manufacturing
- (ii) Remove barriers in the development “pipeline”
 - Regulatory harmonization
 - Expediting regulatory/licensing processes

- Lowering regulatory fees for specified product categories
- Simplification (not lowering) of standards
- Protocol assistance
- Setting ethical guidelines for conduct of research involving human subjects, and/or international collaboration

“**Pull**” interventions establish incentives for industry involvement in product development or improvement that typically operate post-licensure, by ensuring markets or other economic rewards. Examples include:

- Improved delivery of existing drugs and vaccines
- Identification of public health priorities for new projects
- Product specifications/contingent recommendations for use
- Recommendations for use (earlier)
- Market assessments

- Patent extension
- Patent “exchange” (extension on another product)
- Market exclusivity
- Prizes (for first to meet specified product characteristics)
- Market “assurances”
 - purchase funds (for existing and/or future products):
 - contingent loans and credits
 - minimum price guarantee “cost-plus” formulas
 - requisition to buy
- Legislation on product liability litigation

Consideration is underway, in a number of venues of legislation similar to orphan (rare disease) drug laws, to address products needed for prevention or treatment of important diseases occurring predominantly in poorer countries.



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