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**Microbicide Development
Options for USAID**

August, 1997

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**USAID MICROBICIDES DEVELOPMENT. OPTIONS FOR USAID'S
MICROBICIDE DEVELOPMENT STRATEGY**

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Acronyms

| | |
|--------|---|
| AIDS | Acquired immunodeficiency syndrome |
| ATSP | AIDS Technical Support Project (of USAID) |
| CDC | U S Centers for Disease Control and Prevention |
| CEC | Commission of the European Community |
| CICCR | Consortium for Industrial Collaboration in Contraceptive Research (of USAID) |
| CONRAD | Contraceptive Research and Development Project (Eastern Virginia Med School) |
| FDA | U S Food and Drug Administration |
| FHI | Family Health International |
| HIV | Human immunodeficiency virus |
| IAWGVM | Interagency Working Group on Vaginal Microbicides |
| ICCR | International Committee for Contraception Research |
| IND | Investigational New Drug (for FDA) |
| IRB | Institutional review board |
| IWGM | International Working Group on Microbicides |
| MRC | Medical Research Council (U K) |
| NCI | National Cancer Institute (part of NIH) |
| NDA | New Drug Application (for FDA) |
| NIAID | National Institute of Allergy and Infectious Diseases (part of NIH) |
| NICHD | National Institute for Child Health and Human Development (part of NIH) |
| NIH | U S National Institutes of Health |
| N-9 | Nonoxynol-9 |
| STD | Sexually transmitted disease |
| UNAIDS | Joint United Nations Programme on HIV/AIDS |
| USAID | United States Agency for International Development |
| WHO | World Health Organization |

Executive Summary

This report follows an evaluation of USAID's Microbicides Development Project that operated under a cooperative agreement with the Population Council from 1993-1997. It reviews the need for a vaginal microbicide and the Agency's current role in the pursuit of that product, lays out options that seem promising at this point, and makes recommendations for the Agency over the next few years. It argues that the original justification for microbicides research is still valid and that USAID should seize the opportunity to help to stem the AIDS pandemic by supporting the microbicide development effort.

The AIDS pandemic continues to spread. By the year 2000, the number of persons infected with HIV worldwide may approach 40 million, almost half of them women. Women with HIV, 90% of whom will be living in the developing world and are therefore of concern to USAID, will not only be victims themselves. They will leave children without mothers and run the risk of infecting their newborn children with the virus. Abstinence and condoms, the options by which women can protect themselves, are often not acceptable to their husbands and partners. And for a poor woman in the developing world who desires children — an imperative in many cultures — there is at present no method by which she can protect herself against infection by HIV and the other sexually transmitted diseases that increase her susceptibility to infection. Although these women are in urgent need of a microbicide that does not prevent pregnancy, even one that is also contraceptive would be of great value. Protecting the health, indeed the lives, of these women and their families is a public health priority central to USAID's mission.

USAID support has been a major contributor in the search for vaginal microbicides. The concept of a vaginal microbicide that could be used by a woman herself, without the cooperation or consent of her sexual partner, to protect herself from the possibility of acquiring HIV and other STDs emerged when women's health advocates and reproductive health scientists recognized the potential of compounds tested during spermicide research that showed microbicidal activity. The Agency has supported, and continues to support, laboratory work to identify and test promising compounds. Its cooperative agreement with the Population Council specified continuing consultation with

women's health advocates, an important advance over the usual practice of involving the intended beneficiaries only after the product has been developed

In mid-1997, the need for a microbicide is greater than ever, a microbicide product still appears feasible, and increased interest in microbicides is evident. But public awareness remains almost nonexistent, political commitment is limited, the current momentum is grossly inadequate in the face of the pandemic, and efforts by a single organization are clearly inadequate to the size and urgency of the task. New energy is needed, as well as a 'fast-track' approach to product development that coordinates the complementary activities of numerous organizations, USAID among them. This report attempts to identify the most promising role for USAID in the next five to ten years and suggests actions the Agency can employ to establish a dynamic collaboration with other organizations in pursuit of an effective and accessible microbicide for the women of the world and their families.

USAID experience demonstrates that a shortcut to microbicide development cannot be identified with any assurance. USAID support for a single organization, even one with vast resources and an impressive track record in contraceptive development, has foundered at the product identification stage. Vaginal physiology is still poorly understood by the scientific community, and there are many blind alleys in the drug discovery process. Promising compounds have been disappointing when tested for safety, stability, and efficacy against HIV and other STDs. A systematic process has not emerged for testing the myriad of possibilities and selecting only the most promising for further development. Current microbicide development efforts are characterized by limited commitment, lack of direction, fragmented biomedical research, limited understanding of the preferences of individuals who would use a microbicide, and excessive caution to protect potential patent rights. With rare exception, the pharmaceutical industry, discouraged by potential liability issues, regulatory hurdles, and little likelihood of profitability, has not joined the search.

In 1997 there is only one compound, nonoxynol-9 (N-9), that is ready for widespread promotion if a safe and effective formulation can be demonstrated. Two other detergent-type compounds are at nearly the same stage — octoxynol-9 and benzalkonium chloride. Behind these compounds, the next candidates appear to be years away from demonstrating their effectiveness. N-9 has long been used as a spermicide, but its microbicidal efficacy has not been consistently demonstrated in human studies. That is not easy to demonstrate since a candidate microbicide cannot ethically be used in human studies without strongly recommending concomitant use of condoms, N-9 has to demonstrate its efficacy

in addition to the condom. Two important tests are ongoing, one organized by NIAID's HIVNET project, the other by UNAIDS, but the study protocols differ and neither is likely to have sufficient statistical power to confirm the efficacy of N-9. It is uncertain that meta-analysis of their combined findings can be convincing. The evaluation team agrees with the experts who consider resolution of the question of N-9 to be the highest priority at this time.

USAID's Microbicides Development Project has been unable to marshal sufficient resources and technical expertise to accelerate product development. At the same time, the list of other organizations that have entered the field is growing. A partial list of organizations now working in the field includes

- ◆ USAID-funded groups (Population Council, CONRAD, FHI)
- ◆ the National Institutes of Health agencies (NIAID, NICHD, NCI)
- ◆ the Centers for Disease Control and Prevention (CDC)
- ◆ the Medical Research Council (MRC) of Great Britain and, more recently, South Africa
- ◆ UNAIDS

An International Working Group on Microbicides serves as an information clearinghouse connecting these groups, but there is room for greater technical collaboration and political advocacy. From the international perspective, USAID is not seen as a strong player in pharmaceutical research and development. The Agency's greatest strengths are perceived to be its focus on the needs of developing countries, its existing infrastructure for introducing and coordinating activities in many countries, and its ability to support implementation and operations.

The evaluation team recommends that USAID consider the following actions to accelerate the search for microbicides:

- ▶ contributing to finding and implementing a strategy to increase public support and awareness [including finding a better name, like 'VD-blocker'],
- ▶ consolidating the disparate USAID interests and efforts,
- ▶ guaranteeing a market for an effective microbicide,
- ▶ identifying and supporting a strategy for technical coordination,
- ▶ preparing for international clinical testing,
- ▶ supporting resolution of the N-9 question,
- ▶ involving advocacy groups, including women's groups, internationally and in local communities,
- ▶ involving developing country officials to accelerate 'buy-in' and local appropriateness,
- ▶ recruiting pharmaceutical industry support and collaboration.

I. Background: Need For a Microbicide and USAID Involvement

The end of the current AIDS Technical Support Project marks the first opportunity since 1990 for USAID to review and plan strategically to meet the current and future needs for HIV prevention throughout the world. Following on an evaluation, summarized in a separate report, of the 1993-97 cooperative agreement between the Population Council and G/PHN/HIV-AIDS¹, this document reviews USAID's current goals and priorities regarding the development of microbicides for HIV prevention, identifies agencies with which USAID could collaborate, notes the Agency's comparative advantages in this process, and makes recommendations accordingly.

The CDC estimates that 22 million people are now infected with HIV worldwide. Seven thousand new infections occur daily, primarily via heterosexual transmission, and about half of all AIDS victims are now women. Of the 30-40 million persons who will be infected by the year 2000, about 70% will be in Sub-Saharan Africa, 20% in Asia. As increasing numbers of people become infected with HIV, the number of persons who can spread AIDS soars, and the risk to every sexually active individual of HIV

Women, particularly young women, represent the most vulnerable and fastest growing HIV-infected population in the world. Recent studies conducted in 17 sites around the world by the International Center for Research on Women concluded that women need methods to prevent HIV which can be used without partner knowledge, consent, or involvement.

Evaluation Scope of Work

¹ Global Bureau, Office of Health and Nutrition, HIV/AIDS Division

infection continues to rise. Infected women run the added risk of infecting their offspring. Many do not even discover that they are HIV positive until their child is sick.

The human immunodeficiency virus seems to transmit somewhat more efficiently to women than to men during heterosexual intercourse, and the risk to any given woman is affected by a number of known factors. Behavioral and demographic factors include the proportion of sexually active people, the male/female ratio in the population, rates of partner change, the size and rate of contact with the HIV "core group," sex practices, male circumcision, and menses. It is known that HIV-1, responsible for most cases today, is transmitted more efficiently and causes more severe disease than HIV-2, found primarily in West Africa, but the distribution, virulence, and interrelationships of HIV subtypes are incompletely understood. Since intercurrent infection with another STD increases the likelihood that sexual relations with an HIV-positive person will result in HIV transmission, the control and prevention of other STDs is an added imperative.

The major prevention strategies available today are behavior change (including safe sex, abstinence, limited partners, and condom use) and decrease in the susceptibility of the exposed person (through STD prevention and treatment, for example). Abstinence may not be an option, as for example when conception is desired. Male condoms are effective, but women cannot always negotiate their use. The female condom represents an important advance because women control its use, it can be inserted prior to intercourse, and some couples claim to prefer it to the male condom. Nevertheless, it has serious limitations: it cannot be used without partner knowledge and consent, it is relatively expensive, it is not widely available and accepted, and it cannot be used when conception is desired. Safe sex is simply not compatible with pregnancy at this time. Women need an alternative way to protect themselves from HIV and other STDs.

In the absence of a vaccine, one of the most promising methods by which women could protect themselves from HIV and other STDs that increase their vulnerability to AIDS would be an intravaginal product that a woman could use without partner knowledge or consent. Such products, seriously sought only since the late 1980s, have been dubbed *microbicides*, a term that is neither particularly descriptive nor accurate.² It is in the urgent search for such products that USAID's efforts in microbicide development should be viewed

² Microbicide is a generic term for a substance or agent that kills microbes. In this case, only products that can be used vaginally, and perhaps rectally, are intended, and killing the microbe is not required: prevention of transmission is what is sought.

Recent studies reinforce the need for woman-controlled methods. Although the majority of new HIV infections occur in women with only one sexual partner — their husband — gender inequality and the practice of men visiting sex workers have increased the risks to wives because male condom use, the mainstay of AIDS prevention, is rare in stable relationships. In addition, some women have additional sexual partners in exchange for money, goods, or favors needed for the survival of themselves or their children. Seventeen studies on women and AIDS funded by USAID

through the International Center for Research on Women found that 'economic gain and sexual coercion underlie many young

Underlying gender power inequities severely limit the ability of many women to protect themselves from HIV infection, especially in the absence of a prevention technology they can use, when necessary, without their partner's consent. The development of new prevention methods controllable by women would fill an important gap in the global response to the AIDS pandemic

C Elias, 1993

women's sexual experiences," limiting possibilities for condom negotiation. Women may not be protected even if a condom is used: breakage occurs, and African soldiers in focus groups have admitted deliberately puncturing condoms before use.

Sexual coercion of women is widespread, and women in abusive relationships are less likely to use male condoms and more afraid to ask their partners to do so. Women who attempt to convince their partners to use a condom, with unspoken suggestions of mistrust and infidelity, are at increased risk of abuse. Even a woman's refusal to engage in sex may increase her risk of acquiring HIV later if that is perceived to encourage the man to seek other partners. Women clearly need a method they can use without the man's knowledge or consent.

Microbicide research may be said to have grown out of spermicide research, but the potential utility of products that destroy, block, or inactivate pathogens was not fully appreciated until the late 1980s. In 1993, while AIDS research was focused primarily on treatment and secondarily on finding a vaccine, USAID's Microbicide Development Strategy emerged in recognition of a new consensus that microbicides are both promising and feasible. This was largely due to the efforts of the Population Council, especially in the United States, and its allied women's health advocates. The WHO, an organization that typically reacts with big meetings when issues are hot, acknowledged this situation by convening a widely attended consultation on microbicides at the end of 1993. Now, in 1997, when a vaccine still seems a distant hope and the pandemic continues, products to reduce vaginal transmission of HIV and other STDs are even more critically

needed. Scientists remain convinced that a microbicide is feasible. The argument advanced to USAID in 1993 for microbicide development are even more urgent today.

1.1 THE PROCESS OF NEW PRODUCT DEVELOPMENT

There are numerous steps in the development and ultimate distribution of a product such as a microbicide. USAID clearly expects to play a role in its introduction and distribution in developing countries, and it could potentially contribute to any or all of the product development steps as it has in the past for contraceptives. The case for the microbicides is arguably not the same, however, because pregnancy was not the death warrant that AIDS has become in the developing world. There is greater urgency when people are acquiring HIV and dying of AIDS as product development lags. It is important to be clear about the product development process if USAID is to play an appropriate role.

Development of a biologic product such as a microbicide proceeds through a series of steps, some of which can overlap if, as in this case, the need is particularly urgent. First, building on basic research, is the identification of potentially effective compounds and their screening for stability and efficacy under a range of conditions that may be found in nature. Those that

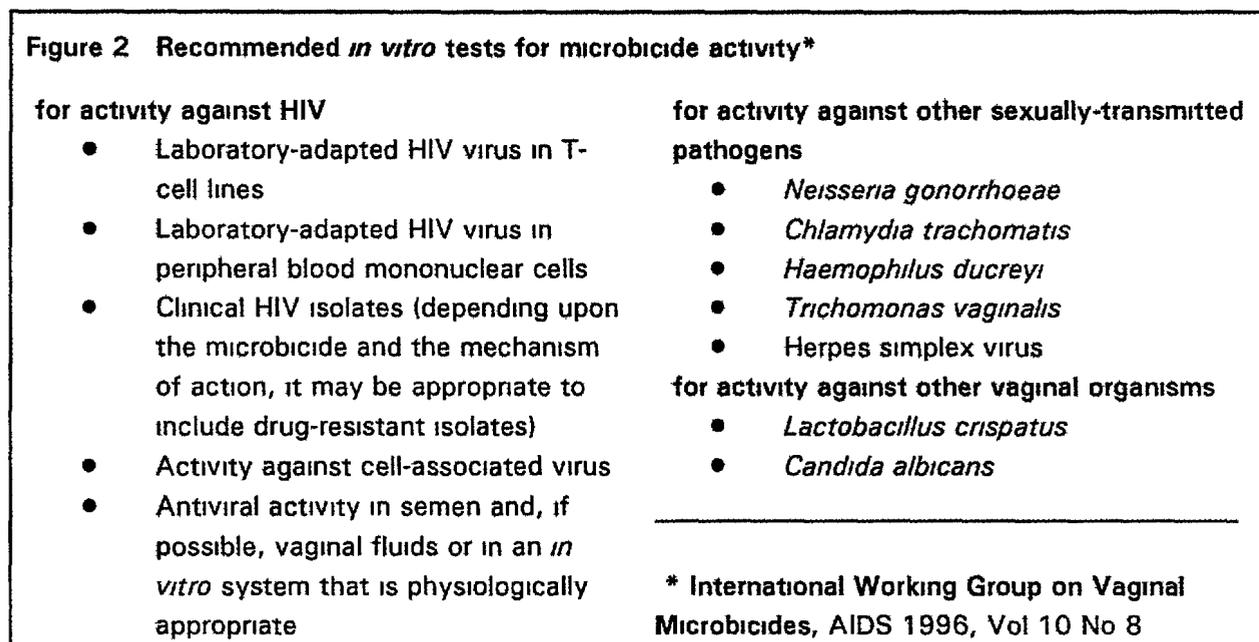
are still promising must then be tested in formulations that might be acceptable to different populations. *In vitro* tests are followed by toxicity tests in animals.

Only products that look successful in these preclinical tests can then go on for human clinical testing for safety, side effects, and efficacy. Since the results of these studies will be needed for eventual FDA approval of a product, early review of study protocols by the FDA can expedite the process. Collaboration with a potential manufacturer should also begin early in the process. Behavioral studies of acceptability, desirability, and likely patterns of use should begin early enough to inform formulations research, but tests in humans are necessarily limited until a suitable product has been identified.

Figure 1 Steps in Product Development

- 1 Identify promising compounds
 - 2 Screen *in vitro* for effectiveness, stability
 - 3 Assess varying needs and preferences
 - 4 Develop formulation(s) for topical use
 - 5 Test for toxicity and safety
 - 6 Begin FDA approval process
 - 7 Secure industry support for development
 - 8 Test in humans for safety ('Phase I')
 - 9 Expanded human safety tests ('Phase II')
 - 10 Test in humans for efficacy ('Phase III')
 - 11 Do market research on use/acceptability
-

In 1996 the International Working Group on Microbicides (IWGM) formalized its recommendations for microbicide identification and testing (Figure 2) In the case of a product as urgently needed as a microbicide, the FDA is eager to collaborate early in the preclinical stages of the product development process to streamline the approval process, much as it has done for the new protease inhibitors that are now included in AIDS treatment The FDA's suggested considerations for the non-clinical pharmacology/toxicology development of topical drugs to prevent STD transmission are attached as Appendix D



Once a product has been demonstrated to be effective in laboratory assays and safe in animal studies, it is ready for testing in humans These are the Phase I, II, and III tests that must be completed to the satisfaction of the FDA before a product can be approved for use

Phase I and II trials assess safety, pharmacokinetics, stability under human physiologic conditions, and tolerability Since a new product's efficacy in preventing HIV transmission has not yet been confirmed, these trials involve persons at minimal risk of exposure to HIV Such studies are important for assessing different formulations, including any product to be used as a placebo because that product could have its own effects The use of already established research sites for Phase I and Phase II studies can save time and take advantage of experienced research teams

Phase III is the critical next step. It is here that the microbicide product must demonstrate its efficacy in reducing, ideally preventing, the transmission of HIV and other STD organisms. Major concerns at this point include informed consent, provision of information and means by which the subjects can protect themselves (usually, in microbicides research, through concomitant use of condoms), and other ethical issues. Various institutional review boards must approve any such testing. In order to carry out a study of manageable size, and under conditions as nearly approximating those of the intended beneficiaries as possible, it is often useful to do these at international sites. Where AIDS prevalence in the community is relatively high, for example, a smaller sample size is sufficient to demonstrate product efficacy with any statistical power, saving both time and resources. Such sites, with careful baseline data, official cooperation, trained staff, and adequate logistics and communications support, will be extremely important. Estimates of the time needed to establish such a site range upwards from six months. Early preparation and baseline behavioral studies at Phase III trial sites will obviously be helpful in speeding the microbicide development process.

USAID experience has demonstrated the utility of behavioral studies in conjunction with the introduction of many new technologies such as contraceptives, child survival interventions, and agribusiness practices. Such studies will be of critical importance to microbicides. Early studies of user preferences, for example, can prevent later delays in product development that can occur if the product must be modified after it has already completed safety and efficacy testing. Desirable characteristics can be determined early, as can behaviors that might affect product efficacy. In the case of a microbicide, the preference in parts of Africa for a dry vagina, and the use of drying agents before sexual intercourse, have important implications for a microbicide and its dispersal within the vagina. Different populations may well require different formulations. Surveys of products that are already in use, together with their costs and distribution, may predict willingness to purchase and use a microbicide product. Some of these studies can be carried out while the biomedical research and testing program is in process. Ultimately, which formulations are possible will be dictated by the characteristics of the effective product.

The process of new product development, culminating in the promotion and distribution activities familiar to USAID, is complex, and new products typically require some ten years to progress through the many steps. With careful coordination of the various US Government agencies concerned with HIV and STDs, this can be reduced, as demonstrated by the development of protease inhibitors. FDA approval, while not required internationally, is important because

US agencies, including USAID when the time comes for introduction and distribution, will only be able to purchase drugs approved by the FDA International coordination of microbicide development is facilitated by the International Working Group on Microbicides (p 26) There remains a critical lack of leadership and greater collaboration, however, particularly among the US agencies that have been funding most of the microbicide development activities to date

1 2 HISTORY OF USAID INTEREST IN MICROBICIDE DEVELOPMENT

A leader in HIV/AIDS prevention and control programs internationally, USAID has a major interest in microbicide development Its projects have been at the forefront of efforts to create awareness

of microbicides and to support research to find the product needed USAID recognizes the key role of women in social well-being and how they are handicapped by inferior opportunities, power, and status When the Population Council's microbicides project was designed, an important feature for USAID was the incorporation of the views of women's health advocates and the women who would ultimately use the products to help guide the microbicides development process

This innovative approach, described below, resulted in women's concerns being addressed much earlier than ever before in pharmaceutical development

A number of longstanding USAID concerns converge to justify its funding of microbicide

Strategic Objective 4 *Increased use of improved, effective, and sustainable responses to reduce HIV transmission and to mitigate the impact of the HIV/AIDS pandemic*

USAID, G/PHN/HN/HIV-AIDS Division, 1997

Fig 3 Reasons for USAID Interest in Microbicides

- AIDS is a leading, increasing cause of death of productive-age persons throughout the world, a threat to all development efforts
 - USAID has a special concern for the women and children increasingly at risk in developing countries
 - USAID is a leading US Government agency dealing with health worldwide
 - Since most research to date has been US-based, USAID is well placed to provide international liaison
 - USAID has the capability to facilitate the introduction and distribution of a microbicide product
 - USAID has access to much of the technical and cross-cultural expertise needed in the overall effort
-

development. One is the welfare of women and children. Another is the development of local capacity to respond to the preventable health problems causing the greatest morbidity, mortality, and risk of spread. A third is the introduction of appropriate technology that can be accessed and used by individuals at community level throughout the developing world. Finally, there is the promotion and strengthening of economic productivity, undermined with disastrous consequences by AIDS. The international development mandate of USAID (Figure 3) gives it a perspective that differs from those of the other agencies involved in microbicides development.

At the World Economic Forum held in Davos, Switzerland earlier this year, it was estimated that, by the year 2005, the economic effects of AIDS will depress the international economy by the equivalent of 4% of the US gross domestic product (Voelker 1997). Most of this impact would clearly be in the developing countries. Since AIDS strikes people in their prime productive years, it reduces labor productivity at the same time that it places added demands on already overburdened social and health infrastructures. It draws scarce resources from some of the world's weakest economic systems. Controlling AIDS will reduce these economic losses and allow governments to spend their limited funds more productively.

As a major international distributor of spermicides, USAID must ensure that the spermicides it distributes for contraception cannot aggravate HIV transmission. Although the large quantities of spermicides purchased by USAID and distributed in developing countries are safe for contraception, their impact on HIV transmission is not so clear. One recent prospective, randomized control study (Kreiss et al.) suggested that spermicides can *increase* HIV transmission. The ancient dictum of the health worker — *first, do no harm* — requires USAID to determine that its spermicides are not unintentionally contributing to the AIDS pandemic.

AIDS has devastating effects on families, removing their economic foundations when productive adults fall ill, and leaving their children orphaned. In high HIV prevalence areas, some villages have lost almost all their productive adult members. The threat to child survival in these areas demands more than the standard package of vaccination, nutrition, and early attention to the common

diseases of childhood A Matlab study in Bangladesh showed that after a mother dies, the risk of death for her children under age 10 triples³

1 3 USAID EXPERIENCE IN MICROBICIDE DEVELOPMENT

Much of the early interest in the potential for microbicides grew out of USAID-supported spermicide research and the enthusiasm of women's health advocates At present the Agency provides funding for microbicide development activities of the Population Council, the Contraceptive Research and Development Program (CONRAD), Family Health International, and WHO's Human Reproduction Programme

1 3 1 The Population Council Cooperative Agreement, 1993-97

In 1992-93 when the Population Council sought support for microbicide development from USAID, it could boast of a strong track record in developing reproductive health products with USAID support (most prominently, the Copper T and Norplant) It also had expertise and organizational interest in microbicides, laboratory capability to test candidate compounds for efficacy against HIV and certain other STDs, access to developed clinical research sites for Phase I and Phase II testing, and a new commitment to working with women's health advocates

In 1993, following preliminary discussions with USAID, the Population Council submitted to USAID's AIDS Technical Support Project (ATSP) a five-year workplan to accelerate microbicide development through a coordinated, multi-donor program of research, development, and product introduction The cooperative agreement that emerged supported continued research in microbicide development, including compound screening, preclinical testing, and development of an IND application for at least one promising compound The scope of work proposed by the Population Council became the working document for the Project Substantive involvement of women's advocates in the process was a prominent feature from the beginning

During the four years that USAID funded the project, the Agency provided 44% of the \$4.1 million which the Population Council spent on microbicides research Other donors include the Mellon Foundation (\$400,000 during 1995-97, an additional \$200,000 committed for 1997-98), the National Institutes of Health

³ Stong, Michael A. 1992. The Health of Adults in the Developing World: the View from Bangladesh. *World Transition Review* 2(2): 215-24

(about \$250,000 annually since 1993, projected to continue at this level until 2002), the Australian Agency for International Development (U S \$11,000 toward the formulation preference study in Thailand) and the Robert H Ebert Program on Critical Issues in Reproductive Health and Population (\$31,000 to support formulation preference studies in Mexico, Thailand, and Minnesota, USA)

Review of the Population Council biomedical program by the USAID evaluation team found relatively modest accomplishments. Several screening and testing assays were developed. A number of products were screened for activity *in vitro* against HIV, herpes simplex virus, *C trachomatis*, and *N gonorrhoea*. One product was developed through the Phase I testing stage before being abandoned because it appeared to *increase* the risks of chlamydial infection rather than prevent it. A product preference study comparing three N-9 preparations among low-risk women in five sites of four countries⁴ demonstrated varied preferences from site to site, with a film preparation being generally the best liked, a suppository the least. To understand the perspective of male partners, men's focus groups in northern Thailand addressed attitudes toward microbicides and their behavior during their wife's peripartum period. Focus groups in Mexico considered how married men react to the concept of microbicides. In Thailand the Council's team is actively developing sites for Phase II and III studies in collaboration with CDC and Thai health officials.

However, the initial leads did not work out as hoped, an appropriate microbicide has not yet been identified, and a systematic approach to finding such a compound has not been defined. The Population Council's preclinical work seems to be stuck at the product identification and laboratory modeling stage, with little movement toward product development within the organization or collaboration with other organizations that have such capability. Preclinical testing by the Population Council laboratories has been inconsistent and incomplete. Without a promising product to test, the limited clinical testing to date is of uncertain relevance, and the northern Thailand site being developed for Phase III trials may not prove useable. Throughout all of this, USAID has not played an active role.

Since the current project shows little momentum in the presence of the AIDS pandemic, the evaluation team recommended that USAID not renew its cooperative agreement with the Population Council. Rather, it recommends that USAID seek a 'fast-track' approach in collaboration with other agencies.

⁴ Abidjan, Bangkok, Harare, Khon Kaen (Thailand), and New York City

1 3 2 Office of Population support for microbicide development

USAID's Office of Population created the Contraceptive Research and Development Program (CONRAD) in 1986 to develop new and improved methods of fertility regulation that could be used in developing countries. The program has concentrated on moving promising contraceptive products through the product development process from the early stages through clinical research, placing highest priority on progressing through Phase I and Phase II testing. When NIAID was looking for an opportunity to advance research on heterosexual transmission of HIV in the early 1990s, the CONRAD scope was expanded to study mechanisms of heterosexual HIV transmission, to screen for agents with microbicidal as well as contraceptive activity, and to carry out behavioral and epidemiologic research related to HIV and other STDs. NIAID provided supplementary funding totaling over \$7 million to date. About one third of the program's financial support goes to intramural research for basic laboratory work, preclinical studies, and Phases I and II testing at Eastern Virginia Medical School. The other two-thirds funds extramural activities at a variety of locations. A 1995 evaluation of CONRAD counted 11 intramural and 110 extramural projects. CONRAD has been managed in close proximity to the Office of Population headquarters, permitting continuous monitoring and guidance, and agency collaboration appears to be excellent. Input from women's health advocates has been limited, however.

Early microbicides interest grew partly out of CONRAD's spermicide development efforts. By the time it entered its second five-year cooperative agreement, a clear mandate to pursue microbicide development had been added. The original focus on contraceptives had been expanded to include research on the mechanisms of HIV and STD transmission as well as the potential for contraceptive products to reduce disease transmission. More than five hundred compounds have now been screened for microbicide potential by the CONRAD and its grantees, and the Project continues to fund microbicides research at a number of extramural sites.

In 1995, the CONRAD program, with support from the Rockefeller Foundation and the Andrew W. Mellon Foundation, created CICCR, the Consortium for Industrial Collaboration in Contraceptive Research. This project was designed to stimulate contraceptive research and development on the part of the pharmaceutical industry which had decreased from twelve multinational firms active in such research in the 1960s to only four today. The project provides grants to not-for-profit research institutions to work in collaboration with industry. Three priority research areas have been identified — male methods of contraception, *vaginal methods that prevent both pregnancy and STD*

transmission, and monthly contraception regimens Three of the first seven projects that have been selected for funding are for microbicide preparations (one new N-9 formulation and two new chemical compounds)

A related project is the Program for the Topical Prevention of Conception and Disease (TOPCAD) which funds more than twenty scientists from ten institutions in the United States and Brazil who are collaborating on projects including compound discovery and testing, preclinical development, clinical trials, and consumer preferences TOPCAD receives no input from women's health advocates

1 3 3 Special efforts to involve women in all phases of the process

An international conference organized in 1994 by the Population Council and the International Women's Health Coalition resulted in the creation of WHAM (Women's Health Advocates for Microbicides), a loose organization of international women's advocates which provided liaison with the women's health community for the Population Council's microbicides development efforts Information concerning microbicide development was provided periodically to these women, and they advised on issues relating to clinical and behavioral research

Women's groups in the South have long dis-trusted those who develop contraceptives, including the Population Council, identified, in the view of these groups, with a "Neo-Malthusian concern with overpopulation in developing countries" ⁵ Not only feminists

Contraceptive methods are usually tested on poor women of the Third World, who are particularly vulnerable given their limited access to resources and information

Barroso, 1995

accused researchers with ignoring user perspectives As the Institute of Medicine (IOM) noted in 1990, "There is a pervasive sense among women that not enough attention is paid to the desires and needs of current and future users" ⁶ In 1996 an IOM study called again for "an agenda centering on methods more directly under women's control" ⁷

⁵ Barroso, 1995

⁶ Mastroianni, 1990

⁷ Harrison, 1996

Collaboration between the Population Council and WHAM focused new attention on the needs of women in the AIDS epidemic. An IOM study on ethical and legal issues concerning the involvement of women in clinical trials⁸ observed "Studies that involved women much more often considered them as vectors of their babies or their mates' infections than as victims in their own right. Not until 1994 did the NIH undertake a major project to map the disease's course and signs in women." Inclusion of women in clinical trials was only mandated by federal legislation in 1993. Until 1994 women were largely ignored in critical clinical trials related to HIV.

The Population Council's goal to establish a consultative process with women's groups regarding product formulation, the ethics of clinical trial design, and product introduction was innovative, important, and worthwhile. Given the history of distrust and acrimony between women's health groups and those who have developed reproductive health technologies, the collaboration between the Population Council and WHAM marked a significant change.

1.4 USAID INTEREST, COMMITMENT, AND CAPACITY IN 1997

USAID interest in the development of vaginal microbicides is reflected in the Agency's *Strategic Objective 4* and the six Intermediate Results that would contribute to the realization of that objective (Figure 4). Although microbicides are not specifically mentioned, they are one of the *barrier methods and prevention services* alluded to, and their acceptance and use would be one of the changes in sexual behavior envisioned to reduce HIV transmission.

⁸ Benderley, 1997

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|---|
| <p>Figure 4 Selected Elements of USAID Results Framework</p> |
| <p><i>USAID Results and Indicators Relating to Microbicide Development</i></p> |
| <p><u>Strategic Objective 4</u> Increased use of improved, effective, and sustainable responses to reduce HIV transmission and to mitigate the impact of the HIV/AIDS pandemic</p> <p><i>Indicator S O 4 2 2 % increase in reported barrier method use with regular sexual partner</i></p> <p><i>Indicator S O 4 2 2 % increase in reported barrier method use with non-regular sex partners</i></p> <p><i>Indicator S O 4 3 1 Percentage decrease in reported STI prevalence, men</i></p> <p><i>Indicator S O 4 3 2 Percentage decrease in reported STI prevalence, women</i></p> |
| <p><u>Intermediate Result 4.1</u> Increased quality, availability, and demand for information and services to change sexual risk behaviors and cultural norms in order to reduce transmission of HIV</p> <p>Result 4 1 2 Develop, improve, promote, and support cost-effective strategies (in both public and private sectors) to increase the quality, demand for, and access to, male and female barrier methods for the prevention of HIV transmission</p> <p><i>Indicator I R 4 1 1 Percentage increase of target population that know how to prevent STI/HIV</i> [NOTE This should include knowledge of microbicides]</p> |
| <p><u>Intermediate Result 4.2</u> Enhanced quality, availability, and demand for STI prevention and management services</p> <p>Result 4 2 2 Support research to identify, test, and apply improved techniques and approaches to prevent and manage STI</p> <p>[NOTE There are no indicators for this IR that relate to prevention strategies]</p> |

USAID Results and Indicators Relating to Microbicide Development

Intermediate Result 4.3 Improved knowledge about, and capacity to address, the key policy, cultural, financial, and other contextual constraints to preventing and mitigating the impacts of HIV/AIDS

Result 4 3 1 Enhance the knowledge and awareness among policy-makers of the social, economic, cultural, and health impact of HIV/AIDS, and of the potential strategies to address them

Result 4 3 2 Reduce key information and service barriers for vulnerable populations (especially women and youth)

Result 4 3 5 Support global, regional, and national policy initiatives to allocate adequate resources, and develop more cost-effective responses to HIV/AIDS

Indicator 4 3 5 Increased operationalization of the prevention to care continuum

Intermediate Result 4 4 Strengthened and expanded private sector organizations' responses in delivering HIV/AIDS information and services

Result 4 4 2 Mobilize key US and host country commercial organizations to advocate and support HIV/AIDS prevention and care policies and programs

Result 4 4 4 Design, test, evaluate, and disseminate to global and field-level partners, community-led approaches to designing and implementing effective responses to HIV/AIDS

Result 4 4 5 Support and develop effective international, regional, and national NGO networks and coalitions to respond to the pandemic

[NOTE There are no indicators for this IR that relate directly to microbicides]

USAID Results and Indicators Relating to Microbicide Development

Intermediate Result 4.5 Improved availability of, and capacity to generate and use, data to monitor and evaluate HIV/AIDS/STI prevalence, trends, and program impacts

Result 4.5.1 Establish and/or strengthen surveillance and evaluation systems

Result 4.5.2 Develop, validate, and disseminate improved tools and models to determine HIV/AIDS/STI levels, trends, intervention costs, and program impact

Indicator IR 4.5.1 Number of selected countries with operational STI/HIV surveillance systems

Indicator IR 4.5.4 Proportion of intervention models whose effectiveness (program impact) has been established

Intermediate Result 4.6 Provide quality and timely assistance to partners (regional bureaus, missions, other donors, etc) to ensure effective implementation of HIV/AIDS programs

Result 4.6.1 Provide high quality and timely technical and management assistance to field programs for (1) program design and evaluation, (2) sharing of lessons learned in other activities, countries and regions, and (3) keeping abreast of important developments in HIV/AIDS

Result 4.6.3 Establish mechanisms to ensure that field implementation and research agenda inform one another

Indicator IR 4.6.3 Increased coordination and collaboration to improve programming and implementation of STI/HIV/AIDS programming among all partners (CAs, donors, governments, NGOs, etc) on the country level

As a signatory of the Programme of Action approved at the 1994 International Conference on Population and Development (the "Cairo Conference"), the USA supports the principle of involving women and women's health advocates in all stages of research

1 4 1 Program Commitments of USAID

Vaginal microbicide development is entirely consistent with the current focus of the HIV/AIDS Division — prevention of sexual transmission of HIV

Access to barrier methods will now go beyond just male condoms and include female condoms in selected settings and vaginal microbicides as they become available

— HIV/AIDS Program, USAID, June 1997

According to a June 1997 summary of USAID's

program, "Biomedical research will continue to assist with microbicide and STD diagnostics development, with expansion of the research agenda to include key areas of vaccine development to ensure that products under development are suitable for the developing world. Social science research will be expanded to provide better understanding of the socio-economic determinants of vulnerability"

Wider collaboration is planned. "New interventions that will be added to the Global Bureau portfolio include a broad set of activities to further engage communities, NGOs, PVOs (both local and U S -based) and the commercial sector to participate in HIV/AIDS activities." When the question of which should be priority activities was raised in a May 1997 meeting of the AIDS Technical Support Project (ATSP), 'female-controlled barrier methods and women' received six of seven possible votes.

Current Global Bureau HIV/AIDS procurements divide responsibilities into three Results Packages. *Results Package 1*, for global leadership, research, and development, will assist G/PHN to

- 1 identify 'cutting edge' issues,
- 2 suggest refinements for existing programs and activities,
- 3 propose innovative approaches that could be tested through operations research,
- 4 undertake operations research, and,
- 5 recommend demonstrated best practices for important technical and operational questions

Under this RP, the Population Council, which has just been awarded this cooperative agreement, will

- 1 conduct social science research and policy analysis,
- 2 conduct targeted qualitative and operations research activities,
- 3 translate social science qualitative and quantitative research into themes and images to be used in multi-channel communications, counseling, and training activities,

- 4 develop and use qualitative tools for monitoring and evaluation,
- 5 participate in, and lead, HIV/AIDS professional meetings and seminars to gather and/or disseminate the state-of-the-art in these areas,
- 6 prepare practical guidelines for use by field-program implementors,
- 7 develop and test technical training materials and courses, and,
- 8 host internships and study tours

Results Package 2, on field implementation, will be more mission demand driven and support prevention interventions including behavior change and those relating to sexually transmitted diseases. *Results Package 3*, also on field implementation, will be a cooperative agreement to support social marketing of selected products. Additional support will be provided to UNAIDS as one of that organization's co-sponsors. USAID itself will be responsible for design, monitoring and evaluation, and the summation and dissemination of lessons learned.

The Office of Population activities relating to microbicide development include continuing support for CONRAD and CICC (see above).

1.4.2 USAID Technical, Administrative, and Funding Capacity

The evaluation team concluded that a lack of technical guidance from USAID was a serious weakness of the Population Council microbicides project. Due primarily to the vague wording and absence of clear specifications in the cooperative agreement document, it also reflects USAID's limited number of technical staff, their need to backstop several projects, and frequent staff turnover that seem to be facts of life at USAID. Even more important, it reflects the difficulty of providing technical guidance in drug discovery and product development in an area as poorly understood as vaginal physiology and pathology. The evaluation team does not believe that USAID can ensure such technical guidance from within its own ranks; it must look outside for that expertise.

The Office of Population appears to have greater specialized expertise to guide the contraceptive development work it supports. Their scientific focus is narrower than that of the Office of Health and Nutrition, however, and it is unclear that they would be able to provide the level of expertise needed to guide microbicides development. What is clear is that their systems to monitor contraceptive technology development are superior to the hands-off approach taken with the Population Council cooperative agreement. The evaluation team believes that the two USAID Offices could devise a joint monitoring and guidance structure for microbicides development for collaboration with other organizations that have the requisite technical expertise.

USAID capability increases as the process moves from preclinical product development to clinical testing and implementation. Product testing, particularly in international settings, is an area where USAID is well-placed, and several USAID collaborators have experience in this area. USAID has the ability to oversee the large-scale clinical trials and demonstration studies needed to ensure that a microbicide product is appropriate for use in developing countries. Later, its contractors can ensure that microbicides are introduced rapidly to the groups at risk.

USAID has extensive experience in social science research involving issues of women and reproductive health. The 17-country study already referred to is just one example. USAID has or could find the expertise to carry out social science and operational research studies that can inform the development of appropriate formulations of microbicides and that are a necessary precursor to microbicide promotion and distribution. It is important that this be done in almost every country, both to understand the specific interests of the local people, and to permit local officials and other leaders to 'buy in' to the promotion of the new product. USAID has experience in such approaches as well as contacts with the local organizations and personnel who can carry out the studies needed.

USAID resources that could help to ensure that women's interests are fully considered throughout the process of product development and introduction include the Women in Development (WID) Office, which has staff with social science research expertise and familiarity with reproductive health issues, the gender working group within the Office of Health and Nutrition's HIV/AIDS Division, and USAID-funded projects such as the Women's Studies Project of FHI, the International Center for Research on Women (ICRW), and the Centre for Development and Population Activities (CEDPA).

Potential funding on microbicide development by USAID's HIV/AIDS Division — estimated to be in the neighborhood of \$600,000 per year — represents only about one tenth of the very modest current funding for microbicides. It is part of a reproductive health research package that includes the development of affordable tools for quick and easy STD diagnosis to facilitate STD treatment and reduce the heightened risk of acquiring HIV when another STD is present.

II. OTHER ORGANIZATIONS AND THE POTENTIAL FOR COLLABORATION

In addition to USAID and the organizations it funds, other US Government agencies interested in microbicides development include NIAID, NICHD, NCI, the FDA, and the CDC. A number of universities are interested, and several small companies — the 'garage-tech' sector — are also eager to develop an effective product. International interest is mounting. What is largely missing is the participation of the large pharmaceutical companies whose expertise and resources accelerate product development when they deem it to be profitable and feasible.

The evaluation team learned of complementary activities of a number of organizations, summarized below. It is clear, however, that scientific interest in microbicides is growing, and organizations that may make significant contributions may have been missed. What follows is thus not comprehensive, nor could a comprehensive summary of interested researchers easily be compiled at this time. Expanding interest in microbicides underscores the team's conviction that the process should be open to new participants.

2.1 OTHER US GOVERNMENT AGENCIES

Several NIH agencies are currently interested in microbicides, as is CDC, the FDA, and the Office of HIV/AIDS Policy within the Department of Health and Human Services. The level of interest is modest, with only about one percent of AIDS-targeted funding going to microbicide development.

NIAID At least two divisions of the National Institute of Allergy and Infectious Diseases are working on microbicides. These are the Division of Acquired Immunodeficiency Syndrome (DAIDS) and the Division of Microbiology and Infectious Diseases (DMID). They constitute the core of NIAID's internal Topical Microbicides Working Group which coordinates research in basic, applied, and clinical/behavioral science related to the development and evaluation of topical microbicides. The group also provides information exchange and assists investigators and sponsors who are interested in research and development and/or evaluation of products. NIAID's *Topical Microbicides Program Update 1997* describes the breadth of research being sponsored by the Agency.

NIAID sponsors the HIV Network for Prevention Trials (HIVNET), for which Family Health International (FHI) developed nine sites worldwide for Phase III testing of an AIDS vaccine. In the absence of a vaccine, those sites could readily be used for advanced clinical testing of a candidate microbicide.

NICHD The National Institute for Child Health and Human Development has been interested in microbicides as an extension of its interest in spermicides and other contraceptive products. Recently, NICHD funded the important N-9 study coordinated by FHI in Cameroon, a large Phase III trial of an N-9 film formulation that produced indeterminate results.

FIC Within the NIH, the Fogarty International Center occupies an international advocacy and coordinating position. A 1996 External Advisory Panel recommended that its principal functions include the promotion and facilitation of NIH international activities, support for international research that complements the agency's mission, and leadership to identify emerging global health concerns and possible NIH responses.

NCI The National Cancer Institute has an active screening program that screens new products for activity against HIV. This focus emerged when early anti-HIV drugs such as AZT were discovered in the search for anti-cancer agents. The NCI developed a systematic screening program that now includes efficacy against HIV and other viral STDs as well as the effect on normal lactobacilli. Testing for anti-bacterial efficacy is generally contracted out by NCI. Ten thousand compounds were being screened yearly for anti-HIV effectiveness until the discovery of the protease inhibitors pre-empted microbicide development and funding for screening was reduced this year to include only voluntary submissions (by drug companies, for example). The Agency retains the capability to carry out massive screening if it were charged to do so.

FDA The Food and Drug Administration has a continuing interest in the development of microbicides, and has made available on its Website suggested topics for consideration as part of the development/approval process (Appendix D) The FDA's antiviral group and, more recently, the reproductive medicine section are using 'pre-IND' coordination to facilitate the process of product development Several products have already progressed through the entire process with FDA assistance Product sponsors are encouraged to come forward as soon as they believe they have identified a viable product, and the FDA team will work closely with them to get something approved or to prove that it will not work The FDA is ready to provide such assistance for microbicides development

HHS The Office of HIV/AIDS Policy of the Department of Health and Human Services has identified the coordination of efforts to identify and implement effective HIV prevention strategies as one of its principal areas of activity

2 2 INTERNATIONAL ORGANIZATIONS

Outside the United States there are relatively few bilateral or multinational donors supporting microbicide development In addition to the organizations described below, the following organizations have expressed interest in the past and may fund microbicide activity

- the Wellcome Trust, which has agreed to fund field trials of microbicides, non-contraceptive if possible, at a reproductive health center in Natal, South Africa
- the Rockefeller Foundation, which supported the Population Council work on microbicides and assists CICCR, TOPCAD, and South to South
- France's Agence nationale de recherche sur le SIDA
- SIDA (Sweden)
- the French Ministry of Health
- the Belgian Government
- the South African Medical Research Council
- South to South, an organization of scientific and developmental organizations from within the developing countries which has supported the study of at least one microbicidal candidate, a formulation of an extract from the neem tree

2 2 1 Medical Research Council, United Kingdom

The MRC, with additional support from the UK's Department for International Development (formerly ODA), has about £4 million (about \$8 million) of microbicide research funding as part of its microbicide development plan. This includes preclinical screening and animal models as well as clinical evaluations, behavioral studies of product acceptability, and surveys of industrial interest in microbicides. Larger clinical studies in the planning stage include a Phase III intervention trial.

The MRC microbicide research program includes support for basic virology, immunology, epidemiology, sociology, and human seminology as well as support for the MRC team in Uganda and the MRC clinical trials center. In addition to this substantial investment, marginal spending specifically for microbicide development is currently about £1.3 million annually and expected to increase.

To date the MRC has strengthened research capacity within the UK and produced four serious candidates from which to select for Phase III evaluation within one to two years:

- 1 dextrin sulphate
- 2 a combination of dextrin sulphate and N-9
- 3 Pro2000, a product developed by Procept with input from NIH and CONRAD
- 4 a combination of Pro2000 and N-9

MRC is now exploring where — probably in several developing countries — the products might be tested for efficacy, and it is seeking collaboration with other funding and technical agencies to accomplish this. Phase III trials could start as soon as 1998.

2 2 2 Commission of the European Community (CEC)

The CEC funded a consultative meeting in Antwerp in 1995 and subsequently commissioned a study of market size for microbicides in Europe and developing countries. A major objective was to assess whether future sales would be sufficient to make a microbicide profitable and thus render public sector funding for its development unnecessary. Results from this study are expected in late 1997 or early 1998. MRC studies indicate that major investment from the private sector will not be forthcoming until a Phase III trial is successful, after which major interest can be expected. That will not remove the need for continuing public sector involvement, however, particularly to address issues such as low

profitability in the developing world (where the greatest need is), liability and indemnity, and protection of international patent rights

2 2 3 Joint United Nations Programme on HIV/AIDS (UNAIDS)

UNAIDS is funding a Phase II/III evaluation of an N-9 gel in Thailand, South Africa, the Côte d'Ivoire, and Benin. In 1997-98, \$1.3 million was obligated to this study, and another \$2.1 million is expected for 1998-99. This UNAIDS activity is supported by the UNAIDS core budget and also benefits from earmarked contributions from the governments of Belgium and Germany.

The UNAIDS study has now completed Phase II evaluations, and Phase III is starting. UNAIDS is seeking collaboration through cooperative agreements from FHI and NIAID to evaluate at least one N-9 containing gel before the end of the century.

In addition to its development work, UNAIDS provides the secretariat for the International Working Group on Microbicides.

2 2 4 World Bank

The World Bank provides programmatic (undesigned) support to UNAIDS and could support other microbicides programs in the future. It considers that it has neither the technical expertise nor the time to make technical judgments itself in managing a project. The Bank does supply large quantities of N-9 spermicides to some of its projects.

2 3 PHARMACEUTICAL INDUSTRY

Pharmaceutical industry interest in microbicide development is of particular concern because of a lack of expertise elsewhere in the formulation and development of vaginal products. Research and development by a major pharmaceutical company that has scores of scientists, state-of-the-art laboratories, and vast resources could accelerate microbicide from the current "business as usual" pace. Few major companies are actively engaged in such research. Perhaps the major exception is Johnson & Johnson's Advanced Care Products (ACP). Most of the other interested firms, as illustrated by what the evaluation team learned from the Population Council in New York, are small and eager, but with limited resources. The factors limiting pharmaceutical industry participation in microbicides development appear to be the uncertain profitability of developing

country markets, regulatory hurdles, and potential liability issues when dealing with a disease as lethal as AIDS

The CONRAD program's CICCR project, mentioned earlier, is an innovative and promising approach to stimulating pharmaceutical industry interest through the development of public-private partnerships. Acceleration of the normal FDA approval process, illustrated most recently by protease inhibitor development, could also stimulate industry interest, as could assurances of donor willingness to purchase or subsidize microbicides for developing countries. Marketing surveys have been initiated by CICCR (with ACP), and the Alan Guttmacher Institute is funding related product preferences research. Although the current US market for spermicides is only about \$42 million yearly, estimates place the potential global market for a microbicidal spermicide at many times that amount. Such surveys will provide information relating to markets and profits for microbicides. Additional studies may be needed.

2.4 ADVOCACY GROUPS

Given the size and continuing spread of the AIDS pandemic, microbicides awareness is surprisingly limited, even among health professionals. This is reflected in the fact that less than one percent of current AIDS funding supports microbicide development. Perhaps the term 'microbicide,' traditionally used for any agent that kills microbes, is part of the problem. It is neither descriptive, accurate, nor catchy. Another problem may be a failure to 'cross-over' from the relatively specialized reproductive health / contraceptive field to the standard health services, infectious diseases, and primary health care. Whatever the reasons for the low profile of microbicides, there is much room for it to move higher on the list of research and development priorities.

If awareness of microbicides in the US is disappointing, it is dismal in most of the developing world where its introduction would have the greatest impact. Only in the area of international women's health advocacy has substantial progress been made, largely through the initiative of WHAM. Of all the biomedical organizations actively pursuing microbicides, only South Africa's MRC and the South to South organization are not located in North America or Europe. The UNAIDS program is the only clear evidence of interest on the part of multinational organizations. It is not yet clear whether WHO's HRP will take any interest.

A high-level meeting of the heads of the agencies interested in microbicides development is being organized for later this year by Dr Mahmoud Fathalla of the Rockefeller Foundation. It is not known yet to what extent the meeting will deal with issues of awareness and commitment in addition to coordination and funding, but such a high-profile meeting may prove helpful in building the critical mass of interest and commitment that is now lacking.

III. CURRENT NEEDS IN MICROBICIDE DEVELOPMENT

Internationally, microbicide development has been characterized today as suffering from the following weaknesses

- ▶ A certain lack of coordination between the public sector agencies working on microbicides persists in spite of real collaboration through the IWGM
- ▶ The public sector agencies lack product development focus, tending to be more interested in broader, academically interesting projects
- ▶ There is limited awareness of microbicides outside of the reproductive health and women's health advocacy communities
- ▶ There is a lack of private sector input

European colleagues have noted that the effort there suffers also from limited absorptive capacity (except in the UK and Belgium) for research and development on microbicides, lack of evidence that the microbicides approach will be

Figure 4 Qualities Desired in a Microbicide

- prevents HIV transmission
 - safe for at least daily use
 - prevents transmission of other STDs
- (at least does not increase it)
- does not disturb normal vaginal or cervical ecology
 - usable without partner's knowledge
 - inexpensive
 - stable for long periods at ambient temperatures
 - compatible with douching
 - compatible with drying agents (ideally)
 - can be used rectally (ideally)
 - not contraceptive (ideally)
 - pleasurable (ideally)
-

successful, and lack of incentives to develop product development capacity because of the uncertainty of continued funding. However, there are signs that the CEC and other European donors are becoming sensitized to the problem, which may presage major European support in years to come.

Before returning to the question of wider collaboration to address these concerns, it is useful to consider where we are and what needs to be done in the various steps of the microbicides development process.

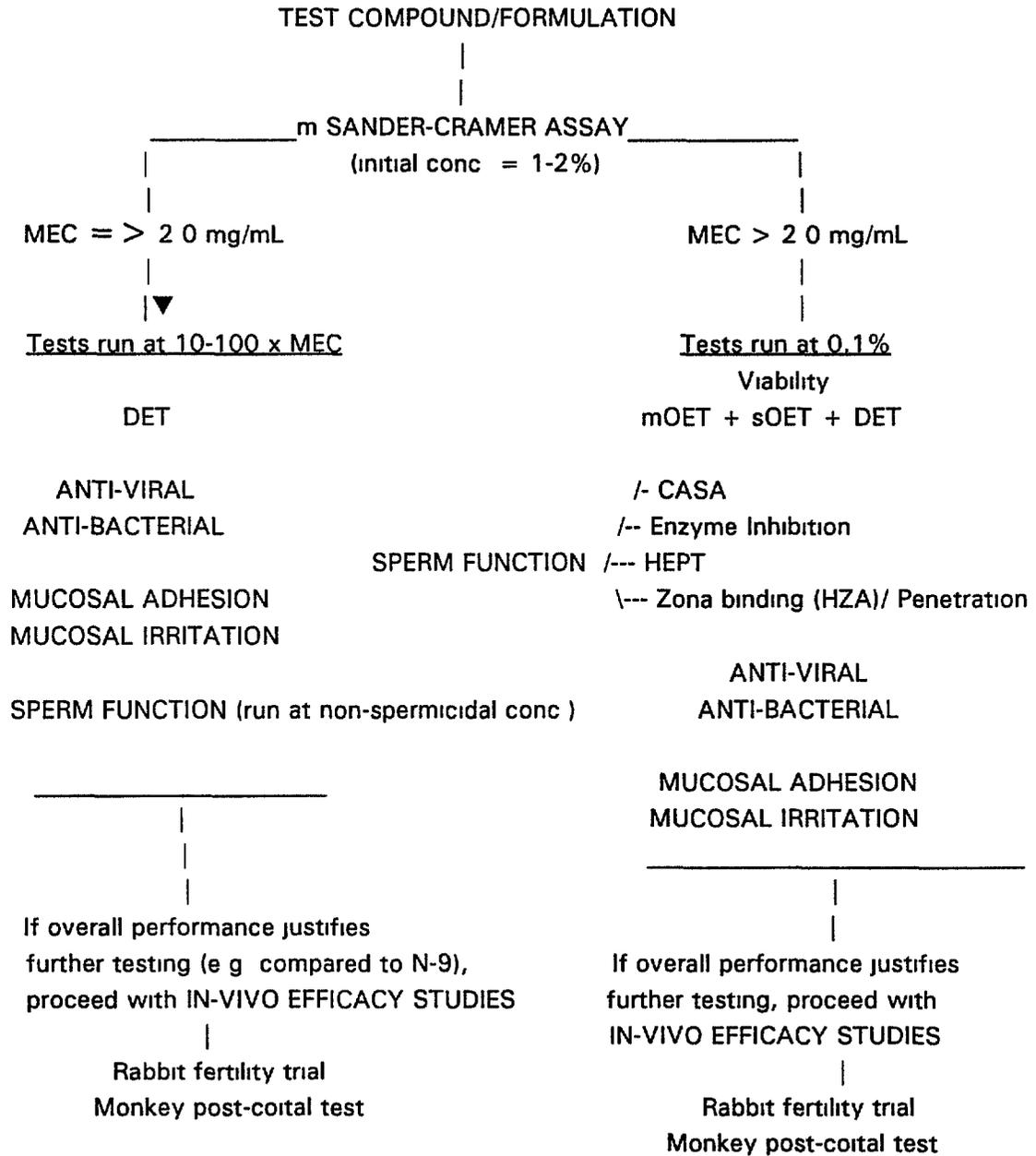
3.1 NEEDED BIOMEDICAL RESEARCH

A first need is obviously for an effective, safe, and affordable microbicide. Until that is realized, we need rapid and systematic methods to identify promising compounds, test and formulate them properly, and begin clinical testing.

An urgent priority is a clear outline of the product development process that would permit monitoring of progress and ensure that all essential steps are covered. An algorithm or decision

Figure 5 *Example of a preclinical screening algorithm*

Chemical Vaginal Contraceptives Tentative preclinical screening algorithm



Abbreviations

m modified MEC minimum effective concentration DET double-end test
 sOET simultaneous one-end test mOET modified one-end test
 CASA computer-assisted computer analysis HZA hemizona assay
 HEPT hamster-egg penetration test

tree would help to clarify the process steps expected. The algorithm should state which tests are essential, what results are acceptable and which would be so unacceptable that the compound under consideration should be reconsidered or abandoned. Agreement on that algorithm, with input from FDA to ensure their collaboration, is an important next step. Figure 5 is an example, from the field of contraceptive development, of the type of algorithm that would be useful. In management terms, this would constitute a sort of PERT chart with decision points clearly marked.

There is at present only one product ready for advanced clinical trials — nonoxynol-9. The product is considered safe, on the basis of considerable experience, but its effectiveness in interrupting HIV transmission is unclear. Previous studies have yielded equivocal results, and the studies now underway are too small to answer the critical questions with adequate statistical power. It is as yet unclear whether meta-analysis will be able to combine their findings in a meaningful way. If N-9 can be formulated into an effective microbicide — a question which is very much open — months, perhaps years, could be gained in the race for a microbicide. Many experts believe this is the most urgent current research need in microbicides. The evaluation team concurs and considers supporting such a study one option for USAID at this time.

Anticipating the need to test other potential microbicides, additional Phase III testing capacity around the world need to be identified. Early preparation will save time in the long run, and maximal involvement of local scientists will contribute to quality testing and pave the way for eventual acceptance and use. Current preparations in Thailand are commendable, but additional sites will surely be needed. The HIVNET sites would be appropriate if they could be made available.

3 2 NEEDED BEHAVIORAL RESEARCH

USAID experience in the promotion and distribution of reproductive health products, whether through existing channels or through new social marketing approaches, has demonstrated the importance of local behavioral research. Typical behavioral questions that will have to be addressed in many different sites and with varying populations include when the microbicide would be used, what are current practices of vaginal toilet and the use of other vaginal products that might affect its use, how can people be persuaded not to abandon male condom use if a microbicide is available, how can microbicide use be introduced into

stable relationships without causing fear and mistrust, and how can microbicides be made accessible to women at an affordable price and without embarrassment

The behavioral research need not be large-scale, formal research. Much can be learned from focus groups and “participant observation” that can often identify trends before a major study could do so. What is important is to come to understand how a variety of different individuals and groups view the subject of concern — microbicide promotion and use.

A partial list of groups and individuals whose knowledge, attitudes, and behavior should be considered includes

- the intended users, grouped by ethnicity, class, age, education, occupation, marital and family status, and place of residence,
- husbands/partners of users,
- medical professionals, especially women,
- NGOs, other promoting organizations,
- marketers and other distributors,
- women’s leaders,
- community leaders

These are not the classical epidemiologic categories, but rather those that make sense in each local context.

3 3 NEEDED COLLABORATION

No one organization has the expertise and other resources to develop a microbicide as rapidly as possible. Experience with the 1993-97 Population Council project demonstrated the weakness of that approach. Managed competition between a number of organizations, each striving to find the answer before others do, is more likely to result in an appropriate product, or products, in the shortest period of time. Since the CDC estimates that 7000 persons per day are now being infected with HIV worldwide, the duplication of effort that may occur would surely be over weighed by the lives saved if a microbicide can be made available soon. Microbicide development needs effective collaboration to develop a product as rapidly as possible, including appropriate testing and introduction that acknowledges user and community perspectives.

“Managed” competition means that guidance and coordination will be provided to ensure that each organization’s efforts should not only be up-to-date, objective-oriented, realistic, sensible, and efficient, but also pulling together in the right direction at the right speed to achieve the common objective. Expertise in pharmaceutical product development is key to this process, as is maintaining the

confidence of the committees, scientists, and clinicians concerned. To ensure that the multiple efforts of such collaboration are coordinated and mutually reinforcing, a central coordinating point must exist. The International Working Group on Microbicides (IWGM) provides some coordination at present, but it lacks authority and stature. Stronger coordination could be provided by a Technical Advisory Committee (TAG) and a centrally placed individual — a 'microbicides czar' if you will. The functions of this central direction, ideally having a high political profile, would be to coordinate the work of major research efforts, to advocate for funding and other support, and to disseminate new findings.

As USAID has learned during the development of numerous contraceptive products, collaboration with pharmaceutical companies is a critical element in the product development process. Product formulation for topical vaginal use is a relatively new area for public sector agencies in which the drug companies have most of the existing expertise. Collaboration with those companies, perhaps using the model of the CONRAD Program's CICC, will be important to accelerate the microbicide development process.

3.3.1 The International Working Group on Microbicides (IWGM)

International collaboration on microbicides development is currently coordinated primarily by the IWGM, for which the UNAIDS representative serves as coordinator. Among the organization's objectives are advocacy to place and keep microbicides on the international agenda, information sharing, identification and discussion of research issues and gaps, development of guidelines for testing microbicides,

International Working Group on Microbicides Members 1997

- Centers for Disease Control and Prevention, USA
 - Contraceptive Research and Development Project (CONRAD), USA
 - Family Health International, USA
 - Food and Drug Administration, USA
 - Institute of Tropical Medicine, Belgium
 - Medical Research Council, United Kingdom
 - NIAID (NIH), USA
 - NICHD (NIH), USA
 - Population Council, USA and Thailand
 - Society for Women and AIDS in Africa, Sierra Leone
 - UNAIDS, Switzerland
 - Women's Health Advocates on Microbicides, USA
 - World Health Organization, Switzerland
-

development and coordination of draft protocols and testing, and effective communication and collaboration with the pharmaceutical industry. One IWGM product is a list of suggested *in vitro* tests for activity against HIV, other pathogens, and vaginal organisms (page 5). Another is the formation of a technical working group on colposcopy which will assess the usefulness of colposcopy in identifying vaginal and cervical lesions, develop recommendations concerning the place of colposcopic observations in Phase I protocols for vaginal microbicide testing, design a study comparing colposcopy with naked eye observations, and explore ways to decide what is "significant."

3.4 NEEDED ADVOCACY, POLITICAL WILL, AND COMMITMENT

As noted above, there is surprisingly little awareness in the health community of the potential for microbicides. Women's Health Advocates for Microbicides (WHAM) appears to have created microbicides awareness among many women's health advocates throughout the world, but awareness among other groups remains grossly inadequate to the need. Microbicides have no internationally recognized spokesperson or agency to champion their cause. An internationally recognized figure, someone with stature like former President Jimmy Carter or former Surgeon General C. Everett Koop, who could voice the urgency of the need for microbicides would provide a much needed boost.

Since increased awareness would seem a prerequisite to increased political will and funding, efforts to increase general understanding of the concept of a microbicide and to emphasize its feasibility would be very helpful.

IV. CONSIDERATIONS AND RECOMMENDATIONS FOR USAID

4.1 COMPARATIVE ADVANTAGES OF USAID

Internationally, as a partner in microbicide development, USAID is recognized for its well-established connections between technical experts and agency support, its focus on the needs of the developing countries, and as providing an established framework for implementing and coordinating activities in numerous countries. Its future role in microbicides development should be more as facilitator than participant in pharmaceutical research and development.

Internally, USAID views itself in much the same way, although it would emphasize as well its commitment to the welfare of women and children, a special concern for economic well-being, and a commitment to the principles of democracy and the empowerment of individuals, particularly women. The Office of Population is proud of its experience in contraceptive research and development, but this is an atypical role in the Agency as a whole. Other efforts in research and development, such as the development of a vaccine against malaria, for example, have been notably less successful. Other agencies and organizations may have greater expertise and resources for microbicide discovery and product development. What then are USAID's special strengths?

Advocacy Since any potential microbicide is most greatly needed in the developing countries of the world where 90% of HIV positive individuals will be found by the year 2000, USAID has a key advocacy and leveraging role to play even before the product is ready for testing and distribution. As the largest donor to international HIV/AIDS

prevention programs, the Agency can use its leverage to ensure that products be affordable, at least in the long term, and stable in an environment that may lack refrigeration or rapid access to pharmaceuticals. The product must also be available in formulations that accommodate local sexual practices and preferences, such as the use of lubricants or drying products and frequent douching in some areas.

Field testing USAID has a potential role to play in coordinating field testing in such a way that local scientists and leaders, as well as the perspectives of women and women's health advocates, are involved from the start. Longtime USAID collaborators, FHI among them, are experienced in Phase III testing and the transition to product introduction. Identifying and developing logistics and distribution systems to serve dispersed and varied populations is also an area familiar to USAID. The Agency can play an important international liaison function with other donors, bilateral and multilateral.

Product introduction and sustained availability USAID has invaluable experience in the introduction of health products in developing countries and in developing sustainable systems to ensure wide access, resupply, and sustainability. Training local personnel and creating awareness will be early tasks. Assisting local officials to take 'ownership' of microbicides, with integration into the standard public health package of efforts to prevent STDs and assumption of the supervisor and trouble-shooter roles, is also a function that USAID knows well. Since false rumors can cause a microbicide to fail as surely as lack of efficacy or unacceptable side effects, it is here too that USAID expertise in social and behavioral research will be useful.

Market guarantor As a potential purchaser/distributor of large quantities of a microbicide, USAID must demonstrate a sustained commitment to the development process to prevent it from flagging when problems appear and potential profitability looks dim. Given the importance of attracting pharmaceutical industry collaboration to microbicide product development, at least two recent efforts of USAID could be used to excellent advantage. One is the CICCR Project, already described. The other is a marketing analysis financed by PHN/HIV-AIDS to demonstrate to industry the potential market for STD diagnostic products.

In addition to guaranteeing an early market, USAID experience can guide introduction of health products to local markets, creating long term sustainable markets, and can recruit support from other donors as well as national ministries of health. Because of the economic impact of AIDS on the development process, it should be possible to convince funders of the importance of ensuring affordable access to an effective microbicide.

4 2 ROLES OF OTHER ORGANIZATIONS

Ground-breaking technical research can take place at many levels. All organizations with the potential to develop a microbicide, or to contribute to that development, must be encouraged in their microbicide development efforts. This includes academic and government research institutions, major industry, and the limited scale "garage tech" efforts that are often the most innovative. Microbicide development must be receptive to progress from all sides.

The NIH agencies have a central role to play, as does the FDA, in the guidance and supervision of the preclinical and early clinical aspects of microbicide discovery and development. If the FIC were to take a strong leadership and coordinating position within NIH, important parts of the collaborative role and advocacy for the international perspective could be ensured.

The current activities and interests of non-US microbicide researchers have already been summarized. Since the assistance of local scientists and leaders will become increasingly important as the process advances to the clinical and product dissemination stages, expanding role and the numbers of this small group of interested organizations should be a priority.

The international development banks can play a major role. The World Bank, for example, may be interested in supporting clinical testing as part of its special projects. The other banks can be prepared to play a role as the need for additional resources accelerates.

4 3 COORDINATION AND FOLLOW-UP

Coordination could be achieved in a variety of ways, but it will depend heavily upon political commitment by decision makers who supply the funding. High profile support is needed, first to create awareness of a product, then to maintain interest until the product can be developed and demonstrated to be effective. A blue ribbon committee headed by a respected figure with wide public recognition (discussed above) would be helpful, at least within the United States.

Because no effective microbicide is currently available and increasing numbers of people are dying from AIDS, the biomedical identification and testing of candidate microbicidal compounds should be accelerated as fast as good science will allow. Compound identification and preclinical development would benefit from a clarification

of the criteria to be met (the testing algorithm) and from coordination of the laboratories engaged in the pursuit. For the US Government agencies involved, some sort of technical coordinating board, having the expertise to monitor and guide the process and speaking with a single voice, could speed the process and coordinate the expeditious follow-up of the most promising leads. Although the board would be more appropriately led by other agencies, USAID could contribute to it, particularly when products are ready for international review and testing.

4 4 MAJOR RECOMMENDATIONS

The need for a vaginal microbicide is clear, and it is increasing as the AIDS pandemic spreads. The evaluation team was impressed that all the knowledgeable scientists with whom they spoke seem convinced that such a product is feasible. To encourage USAID to continue to support the development of microbicides, the evaluation team offers the following recommendations. While addressed to USAID, it should be noted that many of the actions suggested cannot be carried out by USAID alone. The recommendations are therefore presented to USAID in the understanding that the Agency would be collaborating with other organizations in the pursuit and eventual introduction of an effective vaginal microbicide.

1 USAID should continue to support the microbicides development process. This support should include funding of selected activities, support for international collaboration through UNAIDS, and participation in interagency efforts to coordinate microbicides development. To the extent possible, USAID should use competitive procurement to encourage new organizations and ideas.

2 USAID should identify institutions with which it can collaborate on microbicide development. It should then reassess its particular role(s) in light of actual and potential collaborators. Technical collaboration with the US Public Health Service agencies (NIH agencies, FDA, CDC, HHS) that are interested in microbicides is a first priority. This collaboration should involve regular meetings, ideally on a monthly basis but not less often than once a quarter. It should develop a regular agenda of issues to address. It should prepare written summaries of the state of microbicide development and advertise opportunities for needed research by any interested organizations using a mechanism such as the "sources sought" method of NIH.

On the basis of the capabilities of the collaborating agencies and their different comparative advantages, USAID should define its own special role. This can be expected to include expanding its current CICCR efforts to promote pharmaceutical

industry collaboration and addressing the questions of price guarantees for the international market for microbicides and issues of potential liability and patent rights

The group, and USAID in particular, should collaborate regularly with international funding agencies to keep microbicide development on their agendas and to promote maximal collaboration and minimal overlap. A special effort should be made to recruit the international development banks to support microbicides development.

3 USAID should organize itself internally in order to pursue microbicide development in a manner that coordinates its various strengths. USAID should establish an intra-USAID working group on microbicides, with representation from HIV-AIDS, the Office of Population, and WID as a minimum. A major function of the working group should be to assure ongoing communication between Health and Nutrition, Population, and any other groups involved in microbicides development or promotion. Another function should be to liaise with outside agencies and organizations in a coordinated fashion, providing a voice to represent USAID on the hill, in international conferences, and with other donors. A third function is to build awareness and invite participation from Missions and other groups within the Agency.

If the role USAID identifies for itself includes continued support for basic and preclinical research, the Agency should identify technical experts who have the necessary range of knowledge and skills and establish mechanisms by which they can provide real monitoring and guidance. It should consider hiring a TAACS or AAAS Fellow with a microbicides background and give him or her specific direction and authorization to coordinate the microbicides portfolio and to carry out USAID's substantial involvement rights and responsibilities.

For activities funded by USAID, competitive procurement should be employed, with the expectations and responsibilities of both USAID and the funded agencies clearly defined. This includes activities to be carried out, steps to be followed, interactions to be developed, and a periodic "formative" review process.

USAID should increase investment in the gender issues working group to ensure consideration of women's health perspectives in microbicides development and all other reproductive health programs. These perspectives can be expected to include, but are not limited to, increasing investment in sexuality education, partner communication strategies, and women's empowerment. The working group should build on the lessons learned from the Population Council/WHAM experience and seek to develop more systematic and transparent processes for priority setting and decision-making regarding health resources and the design, implementation, and evaluation of programs in the field. The following mechanisms should be considered:

- An advisory committee, with at least half of the membership being health advocates not affiliated with contracting or cooperating agencies
- An external priority-setting review and comment process for RFPs/RFAs before they are released for bids
- A clearly articulated process for circulating, reviewing, and receiving comments on strategic plans
- Alternative strategies for incorporating the views and concerns of local constituencies in the design, implementation, and evaluation of programs in the field

USAID should develop mechanisms to ensure early and meaningful consultation with community members and leaders for any USAID-funded effort concerning women and AIDS. The inclusion of community inputs should be mandated in the RFA/RFPs to ensure that this is an integral part of all activities. Women in the community where clinical trials are conducted should be included in the planning of the trial and analysis of the results. A community advisory board is one of several mechanisms to ensure that

- the community has a role in identifying and defining problems and risks,
- the community is included in the dialogue shaping research approaches to the problem,
- the community participates actively with researchers and health care providers in developing responses and setting priorities for intervention strategies (NIEHS 1994)

Wherever confidential information is not involved, diffusion of information, questions and concerns should be disseminated through women's health networks, such as, for example, the Latin American & Caribbean Women's Health Network

4 USAID should work with other organizations to develop a study to answer the question of whether nonoxynol-9 is an effective microbicide. The question of the real utility of N-9 as a microbicide has not been fully resolved. Considering that N-9 is the only product even close to market availability, the questions concerning its formulation should be resolved as soon as possible. If uncertainty persists following meta-analysis of the findings from the two current N-9 studies (of HIVNET and UNAIDS) and previous studies, USAID should identify a way to design and carry out a study that avoids the weaknesses of past studies and has adequate statistical power

Who should manage it and who should fund it should be resolved in consultation with the UNAIDS and the group of collaborating agencies recommended above. Unless another method can be identified, USAID should consider supporting FHI, CONRAD, or the MRC for the express purpose of continuing N-9 research trials

5 USAID should seek opportunities to increase awareness of microbicide development among decision makers in all collaborating agencies that could contribute to the process This outreach should include private as well as public sector organizations, international as well as domestic

USAID should take as its special responsibility the promotion of the concept, and its eventual implementation, in the international health community Other organizations with more recognizable scientific credentials should take responsibility for promoting awareness among the community of scientists involved in basic sciences USAID should build particularly on its contacts with international health leaders and women's health advocates

At national levels, USAID should promote consultation with women's health advocates and start a database of community groups and women's health advocate groups with whom researchers could consult USAID should leverage resources to support women's health advocacy groups in the South and ensure the participation of women's representatives in technical advisory group meetings

Among methods from which USAID could choose to foster awareness are (a) searching for a better term than microbicide, (b) disseminating a periodic monograph to inform the public health field and politicians, (c) hosting international conferences, (d) creating advisory groups of interested parties such as women's health advocates, and (e) identifying a well known public figure as advocate and spokesperson for microbicide research and development

Transparency, wherever possible, is fundamental in the ultimate success of product use and dissemination Transparency of any USAID-funded effort is the best way to combat past perceptions of USAID as treating women from the South as guinea pigs on which to experiment Whenever there is a controversial product under development involving previously underserved groups, the process of product development and dissemination is advanced by early involvement of the consumers

6 USAID should find a new mechanism by which to provide technical oversight and guidance for preclinical research on microbicides This function can be accomplished under a "Microbicides Czar," a Technical Advisory Group (TAG), or both Other options include innovative arrangements with pharmaceutical firms with expertise in topical vaginal products and collaborative agreements with other agencies that have such expertise One possibility is an umbrella organization that would provide strong management to the process and expedite the research through numerous subcontracts, or alternatively a series of contracts to the various organizations needed to do the research The evaluation team favors a TAG, certainly for USAID and possibly for all US Government agencies working on microbicides, and it suggests that the Agency consider

a microbicides czar who could combine high profile advocacy with access to expertise in pharmaceutical product development

Set up a Technical Advisory Group on Microbicides with participation from FDA, NCI, NIAID, NICHD, CDC, the Center for Population Research, a women's health advocacy specialist, and other USAID-funded projects (CONRAD, FHI, the Population Council)

Liaison with FDA should be a special concern of the TAG so as to come to general agreement on an algorithm for microbicide testing and to expedite testing

This TAG should comment on methodology and affect changes in study design TAG members should review in-country efforts, including the involvement of national and local women's health advocates Women's health advocates and researchers from the South should be represented TAG members could include HIV/AIDS activists, those with direct patient contact, and scientific researchers

7 USAID should prepare to play a more central role in clinical trials and eventual product implementation Because of its local connections with officials and scientists throughout the developing world, USAID is well placed to coordinate much of the Phase III clinical trial activities and to build in local participation Several organizations with long USAID experience (FHI, Population Council, others) should be available to contribute to this task

The site being developed by the Population Council in Chiang Rai is very likely to prove unacceptable Attention should therefore be directed to potential sites in sub-Saharan Africa This includes developing collaborative arrangements with local leaders, scientists, community groups, and women In addition, USAID should plan to fund social science research relating to microbicides and reproductive health

8 USAID should determine whether it can help to ensure a market and profits for the the organization(s) that make(s) and distribute(s) a microbicide By emphasizing its intention to purchase large quantities of microbicides for introduction and distribution, USAID can play an important role in moving the process along, keeping it on track, and removing obstacles USAID should not delegate this role, it has the clout because it is a major funder of microbicide research and is likely to be the major purchaser of the ultimate product

Because of USAID's funding for research and development, it can also insist on public-sector pricing and an affordable product

USAID should seek clarification of product rights and pricing mechanisms. This is especially important with a microbicide because a relatively ineffective compound may have a very limited market in the developed countries.

ANNEXES

***ANNEX A: THE EVALUATION TEAM, ITS ACTIVITIES AND
SCOPE OF WORK***

List of Evaluation Team Members

James Sonnemann, M D , M P H , served as Team Leader. A medical epidemiologist who has practiced medicine in Africa and managed a variety of primary health care and MCH projects for USAID, he brings a field perspective to program planning, behavioral research, epidemiology, and disease control. Most recently, he participated in the design of the Health Sector strategic objective results packages for the Guinea USAID Mission. Thus, he is well versed in USAID's results orientation and current priorities in the health sector.

Jill Gay has written extensively on women's advocacy issues in the health field, and served as a consultant at the Pan American Health Organization on ensuring that STD detection and treatment is integrated into maternal health and family planning services. She has written a background paper on "Women's Access to Quality Health Services" for the World Bank, and has worked with NCIH in co-editing a book on The Health of Women: A Global Perspective.

Sherry Lard, Ph D , is a microbiologist on loan from the Food and Drug Administration. As a staff member of the FDA's Division of Antiviral Drug Products at the Center for Drug Evaluation and Research, Dr. Lard is uniquely qualified to examine the regulatory issues surrounding bringing a new product to the market. Her academic background as a microbiologist brings an understanding of the biomedical issues related to preclinical and clinical trial designs as well.

Gabe Bialy who holds a Ph D in Pharmacology, is on loan from the Center for Population Research at the National Institutes of Health. With his extensive experience in new product development in the population field, he brings expertise in how behavioral research links to new product development, as well as specific knowledge on pharmaceuticals.

Cheryl Walker, M D , is highly knowledgeable about clinical research and has followed the development of microbicides over the past several years. Currently on the faculty of the Medical School at the University of California at Irvine, she brings knowledge as an Obstetrician/Gynecologist in private practice as well.

Jos Perriens, M D , is Chief of the Clinical Research and Product Development Division for the Department of Policy, Strategy, and Research at the Joint United Nations Programme on HIV/AIDS (UNAIDS). He thus brings technical knowledge of the disease, the clinical research issues, and the international perspective. He is knowledgeable about the contributions not only of UNAIDS, but the priorities and activities of other donors as well.

Cynthia Green, Ph D , has done extensive work in research, writing, and editing publications and broadcast materials on population health, nutrition, and drug abuse prevention. With training in sociology and demography, she is also knowledgeable about behavioral research and health sector issues.

USAID Microbicide Program Strategic Evaluation and Development

I Purpose of the Evaluation

This scope of work outlines three Phases for the evaluation and enhancement of USAID's Microbicide Development Strategy. The goal of USAID's Microbicide Development Strategy is to develop, test, introduce, and provide a safe, effective and affordable means which women can use to reduce the risk of sexually transmitted infections, including HIV. USAID has been funding microbicide development activities since 1993. The end of the current AIDS Technical Support Project within the Global Bureau marks the first opportunity since 1990 to review, reflect and strategically plan to meet future needs in HIV prevention globally. An evaluation of existing activities in microbicide development and the enhancement of the current strategy is an essential part of this strategic planning.

Phase I of this evaluation consists of an external and final evaluation of The Population project initiated in September, 1993 and entitled "The Development and Evaluation of Microbicidal Compounds for Intravaginal Use in Preventing the Sexual Transmission of HIV".

The goal of phase I is to assess adequacy of the Population Council's project on Microbicide Research, Development and Introduction project in addressing its primary purposes:

- a. The identification and evaluation of a wide range of vaginal microbicidal products including those that would allow conception while still providing protection against RTIs (reproductive tract infections),
- b. Provision of public sector leadership to ensure that products once developed will be available and affordable to all the world's women, and
- c. The incorporation of a range of women's perspectives in all steps of the technology development process from the laboratory to the pharmacy shelf.

The results of the evaluation of this cooperative agreement will be used in concert with Phase II of USAID's Microbicide Strategy Development. The goal of phase II is three fold:

1. Strategic analysis of current USAID Cooperating Agency (CA) projects in Microbicide Development and CA capacity to expand or enhance their efforts,
2. Strategic analysis of national efforts in microbicide development being funded through other US Government agencies and the private sector, investigation of opportunities to share expertise and partnerships with other national entities,
3. Analysis of international strategies being conducted by other donors and multilateral organizations (e.g. UNAIDS). The purpose of this phase is to

identify overall global strategies in microbicide development and to identify possible partnerships for USAID for the future

The goal of Phase III is to synthesize the analysis and results of Phases I and II, identify gaps and provide recommendations to USAID for its future involvement in microbicide development. The analysis will address areas of USAID's comparative advantage in the introduction and use of microbicides in the developing world. Recommendations will address the role of USAID in the next five to ten years.

II Background and Overview

In early 1993, the Population Council submitted a five-year workplan to USAID for a microbicide research, development, and introduction initiative which was initially envisioned as a cooperatively funded donor effort budgeted at approximately \$8,000,000. At that time minimal research on the effectiveness of existing spermicides agents and novel agents to reduce vaginal transmission of HIV and other RTIs was being conducted. In September 1993, USAID contracted with the Population Council through a cooperative agreement (No. HRN-5972-A-00-3022-00) under the AIDS Technical Support Project (ATSP) to support this microbicide initiative contributing \$199,431 for the first year. During 1994, USAID renewed the contract with the Population Council to continue development of this initiative with an estimated two year award of \$800,000. In 1996, concomitant with the redesign of the ATSP, USAID has increased the ceiling of the cooperative agreement and added an additional \$300,000 to the Population Council's program for the next six months. USAID is now initiating an external evaluation of the progress made by the Population Council, including an analysis of the need for female-controlled prevention technology and the current USAID strategy in microbicide development in the context of related projects sponsored by other donors and partners.

Recommendations for the continued funding and strategic development of the Population Council program and microbicide development as a whole will be addressed.

In the second decade of the HIV/AIDS pandemic, female controlled prevention technology which is effective, safe, and available for use in the developing world remains elusive. Women, particularly young women, represent the most vulnerable and fastest growing HIV-infected population in the world. Recent studies conducted in seventeen sites around the world by the International Center for Research on Women concluded that women need methods to prevent HIV which can be used without partner knowledge, consent, or involvement. In these studies, researchers found that nonconsensual sex, fear of domestic violence or economic abandonment, and difficulties in initiating or sustaining discussions concerning condom use greatly limit the options women might use to prevent infection with HIV or other STDs.

Physical Barriers

Given these findings what options are available for women to protect themselves against reproductive tract infections (RTIs) in the developing world? The effectiveness of physical barriers (diaphragms cervical caps, sponges and the female condom) are currently being evaluated for effectiveness in preventing transmission of RTIs. Thus far, the Reality Female Condom appears to be the first female-initiated barrier method which may be used to prevent RTI (including HIV) transmission. The acceptability of the product has also been analyzed in the developing country context through a USAID (Population Office) funded program.

Non-Prescription Products

Several non-prescription spermicidal products which contain biodegradable ingredients are available in the US and in other countries (i.e., products containing nonoxynol-9, benzalkonium chloride and menfegol). Although in vitro evidence has shown that some biodegradable ingredients, including nonoxynol-9, effectively inactivate HIV, there is no conclusive clinical data addressing protection against HIV infection. Some studies, however, suggest that biodegradable ingredients provide partial protection against cervical infections of gonorrhea and chlamydia. Several controlled clinical trials addressing the efficacy of these products against RTI and HIV infections are underway in the developing world. The NIH has funded Family Health International (FHI) and the Cameroon Ministry of Health to evaluate the effectiveness of a film containing nonoxynol-9. Additionally, UNAIDS has completed an expanded safety study of a reformulated nonoxynol-9 product, Col-1492 which may have bioadhesive characteristics which improve coating of the reproductive tract and enhance duration of action. UNAIDS has recently announced a new multi-center Phase III efficacy trial of Col-1492 in Cote d'Ivoire, South Africa and Thailand, and NIH's HIVNET program is about to initiate an efficacy trial of Col-1492 in Kenya. Finally the recent evaluation of HIV-NET recommended that the program should increase its microbicide development focus.

Novel Microbicidal Compounds

Research to identify novel microbicidal compounds is rapidly expanding. The product development path for new products, however, is long in addition to extensive clinical evaluation, expensive and time-consuming reproductive toxicology studies are required for approval. Consequently it is unlikely that any novel microbicidal product will be ready for introduction or marketing before the end of the decade. This underscores the need to refine current prevention strategies and resolve questions concerning the microbicidal profile of existing spermicides.

New Product Concepts Kill/Inactivate the Virus

There are a number of new products formulated to kill or inactivate HIV and/or other STD pathogens which have shown varying degrees of promise. These include surfactants as well as compounds such as C31G, a mixture of two amphoteric surfactants in development by Biosyn. Like other biodetergents, the product disrupts cell membranes and is both spermicidal and microbicidal. Preliminary clinical studies are underway.

Several investigators are pursuing the development of acid-buffering agents as research indicates that the survival of free and cell-associated HIV may be highly pH dependent. The normal vagina has an acidic pH, and it is postulated that intravaginal agents which keep the vagina acidic in the presence of semen may afford some protection against infection. Phase I clinical evaluations will begin this year.*

In the category of natural products, Dr. Sharon Hillier of the University of Pittsburgh is initiating a clinical study using a twice-a-day vaginal suppository containing *Lactobacillus crispatus*, gonorrhea and bacterial vaginosis will be the principal outcome indicators in this Phase II study. *Lactobacillus* is not a chemical microbicide, but rather relies on maintaining normal vaginal ecology, characterized by a predominance of hydrogen-peroxide producing lactobacilli, to maintain a low vaginal pH, thereby increasing resistance to infection.

A number of natural antimicrobial peptides of the protegrin class as well as magainins, such as squalamine, have shown potential for broad microbicidal activity in vitro. These leads are still in preclinical development. Additionally, Gossypol and Proneem, (plant extracts) are currently under investigation by the South to South Collaboration for Reproductive Health.*

New Product Concepts Inhibitors of Viral Entry

Another group of investigational compounds inhibit viral entry into mucosal cells. Several compound classes have shown promise in vitro but few have progressed to clinical studies. Recently a formulation of n-docosanol was evaluated in macaque monkeys where it was shown to protect 5 out of 6 monkeys after vaginal exposure to SIV. N-docosanol, a 22-carbon straight-chain alcohol, is also being evaluated as a topical therapy for recurrent herpes simplex infections.*

Only the sulfonated polymers have been evaluated for vaginal application in humans. Investigators in London recently completed a vaginal safety study of varying dextrin-2 sulfonate doses in gel formulation as part of the UK Medical Research Council's virucide research program [15]. The Population Council recently completed a

Phase I evaluation of PC 213, another sulphated polymer gel (preliminary data) In both studies, the daily application of gel formulations of sulphated polymers was well tolerated and without significant irritation. Several agencies are currently pursuing this compound class and more clinical studies of sulphated polymers are expected in the near future.

New Product Concepts: Inhibitors of Viral Replication

Vaginal applications of HIV replication inhibitors are also being explored. While all of the compounds listed in Table 3 have been discussed, only two have been evaluated in vivo. Recently a vaginal gel containing PMPA has been shown to have some protective action in the SIV/monkey model [16]. The number of monkeys, however, is small, and more work must be done before potential use in humans is explored.

To date, the only compound of this class which has been evaluated in women is loviride. Janssen Pharmaceuticals conducted a Phase I toxicity trial in Belgium using loviride in a suppository with chlorhexidine (personal communication, Paul Stoffels, July 1996). The product was well-tolerated by the study population in Phase I trials but further clinical trials are on hold pending clarification of the path to market.*

Given the recent advances in the evaluation of possible products, as well as the increased number of potential partners for USAID in future strategic development of microbicides, the overall evaluation of USAID's current funding is appropriate. The purpose of this strategic evaluation of microbicide development efforts is (1) analysis of the gaps in international efforts to develop this much needed prevention technology and (2) identification of USAID's comparative advantage will be in this field for the next five to ten years.

*Note: Much of the above overview was taken from Elias CJ, Coggins C, Female-Controlled Methods to Prevent Sexual Transmission of HIV, AIDS, in press -- this paper was derived from the text of the plenary lecture Chris gave at the XI International Conference on AIDS in Vancouver, July 1996 - Please see review for details.

PHASE I

Population Council End of Project Evaluation - Scope of Work

I. Activity to be Evaluated

Project Name The Development and Evaluation of Microbicidal Compounds for Intravaginal Use in Preventing the Sexual Transmission of HIV

Contractor The Population Council

Cooperative Agreement Number HRN-5972-A-00-3022-00

Start Date September 1993

Expected Life of Project (LOP) Cost \$1,000,000

Obligations through 12/95 \$999,431

Expenditures thru 6/96 \$793,156

II. Statement of Work The following list of questions regarding the project are meant to be a guide for the evaluation team. The team is welcome to add questions or areas for further consideration. The progress of the team toward achieving the designated project goals will be determined by its progress in answering the questions set forward at the initiation of the evaluation.

A. STD Laboratory at the Population Council

The development of new microbicidal products which can be controlled by women requires a state-of-the-art laboratory and appropriately trained staff. The evaluation of the laboratory at The Population Council should therefore address the following issues:

1. Is the design of the in vitro screening process appropriate for the development of an intravaginal preparation?
2. How effectively has information from other basic research addressing spermicide analysis and HIV (i.e., vaccine development) been used in developing screening protocols for development of a microbicide in a developing country context?
3. Have the in vitro assays been used effectively to screen compound activity against other STDs?
4. Does the in vivo model measuring activity against Chlamydia and Herpes Simplex virus adequately evaluate formulation effectiveness?
5. How do animal models fit into a strategic development plan?
6. How will animal models be effectively managed within the laboratory for optimal results?

- 7 Is the Council's work on bioengineered anti-microbials or naturally occurring antimicrobial peptides applicable to microbicide development?
- 8 Is the Council's investigation of the role of genital tract secretions on microbicide efficacy useful?
- 9 What significant advances has the Center for Biomedical Research STD laboratory contributed to microbicide development and how are these activities viewed by their peer scientists?
- 10 How are priority areas of research determined?
- 11 How could the research agenda be improved to achieve the overall objectives of the program?

B Formulation at the Pop Council

- 1 Which formulations have been investigated, and was the investigation conducted appropriately?
- 2 Is the Center for Biomedical Research equipped to handle the formulation of products in the future?
- 3 How will findings from the Programs Division behavioral research be used to affect product formulation decisions?
- 4 How effectively are product formulations tested in the STD laboratory?
- 5 How is the decision made to take a product from the laboratory to the clinical stage?
- 6 Is The Population Council the most appropriate institution to perform product formulation research?

C Clinical Research through the Pop Council

- 1 What clinical research has been completed to date?
- 2 How are decisions to advance of a potential microbicide through development made?
- 3 How are decisions to terminate development of a potential microbicide made?
- 4 Are additional Phase I studies planned?
- 5 Will The Council's existing network of clinical sites be adequate for microbicide research? If not, what is needed, and at what cost? Is The Council the most appropriate conduit to identify and utilize clinical sites?
- 6 How are potential sites for larger-scale effectiveness/efficacy trials being identified and evaluated?
- 7 How will current and planned behavioral research affect clinical trial design?
- 8 Is The Population Council willing to perform clinical trials on formulations or compounds not developed within their own laboratory?
- 9 Under what circumstances would The Population Council be willing to test potential microbicides not developed within their own laboratories?

D Consultative Meetings and Collaboration

- 1 How has collaboration with women's health advocates influenced The Council's microbicide development effort?
- 2 Do Women's Health Advocates and the scientists view this effort as useful?
- 3 How could this collaboration be improved?
- 4 What are the major accomplishments forged by Women's Health Advocates and The Population Council?
- 5 Has this collaboration influenced other efforts of The Population Council?
- 6 How has the Council's participation in the Interagency Working Group on Vaginal Microbicides contributed to both The Council's scope of work and to the international microbicide effort?
- 7 What is the relationship between The Population Council and other USAID funded Cooperating Agencies which address microbicide development (CONRAD and FHI)?
- 8 Does the collaboration allow for optimal progress toward the goals of the stated program?

E Coordination and Communication

- 1 Have the Center for Biomedical Research and the Programs Division within The Population Council collaborated effectively?
- 2 Has The Population Council microbicide effort effectively drawn upon expertise within and outside The Population Council to meet its objectives?

III Project Management and Funding

A Management within the Population Council

1 Staff and Facilities

- a Is the program adequately and appropriately staffed to achieve the stated objectives? Are any changes needed to achieve the objectives required?

2 Project Management and Administration

- a Is the management structure of the program appropriate to project goals?
- b How is information concerning potential microbicides made public?

B Documentation and Financial Reporting

- 1 Are required documents and financial information/reports submitted to USAID on time?

● C Funding Levels

1 Which donors have contributed to this multidonor effort and at what level have they continued?

● 2 Which donors are currently funding components of The Council program, for what purpose and at what level?

3 Are current funding levels adequate? What level of funding is needed to achieve the program's purpose using the current design?

● D USAID Management

1 Has USAID provided adequate and efficient technical and managerial oversight?

2 How has USAID been involved in technical management and planning?

● 3 How could USAID's technical and management oversight be improved?

● IV Methods and Procedures Most of the data for the evaluation is expected to be collected through interviews and from existing documents. A list of existing data sources and suggestions for procedures to be followed are listed below

A. Population Staff for interviews

● Christine Burillo, Jr. Research Technician, Center for Biomedical Research

Christiana Coggins, MPH, Staff Associate, Programs Division

● Christopher J. Elias, MD, MPH, Senior Staff Associate, Programs Division, The Population Council, Bangkok, Thailand

● Charlotte Ellertson, MPA, PhD, Program Associate, Programs Division

● Darrell Fortenot, Research Investigator, Center for Biomedical Research

● Barbara Friedland, Administrative Assistant/Secretary, Programs Division

Elof Johansson, MD, Vice President, Center for Biomedical Research (as of 8/1/96)

● Elizabeth McGrory, MPH, Staff Associate, Programs Division

● Veera Mendonca, PhD, Post-doctoral fellow, Center for Biomedical Research

David Phillips, PhD, Senior Scientist, Center for Biomedical Research

Yan Tan, Research Investigator, Center for Biomedical Research

Beverly Winikoff, MD, MPH, Director, Reproductive Health

Vanaja Zacharopoulos, Research Investigator, Center for Biomedical Research

B Articles published, submitted or presented

Christiana Coggins

Faundes A, Elias CJ, Coggins C "Spermicides and Barrier Contraception" *Current Opinion in Obstetrics and Gynecology* 1994, 6 552-558

Christopher J. Elias

Peer-reviewed Articles

Elias CJ, Leonard A "Family Planning and Sexually Transmitted Diseases: The Need to Enhance Contraceptive Choice" *Current Issues in Public Health*, 1995, 1 191-199

Heise LL, Elias CJ "Transforming AIDS Prevention to Meet Women's Needs: A Focus on Developing Countries" *Social Science and Medicine* 1995, 40(7) 931-943

Elias CJ, Heise LL "Challenges for the Development of Female-Controlled Vaginal Microbicides" *AIDS* 1994, 8 1-9

Technical Reports and Working Papers

Elias CJ et al "Recommendations for the development of vaginal microbicides" from *The International Working Group on Vaginal Microbicides* *AIDS* 1996, 10 (8) 1-6

Grant J, Elias CJ (eds) "Partnership for Prevention: A report of a Meeting Between Scientists, Advocates, and Program Planners" *Ebert Program for Critical Issues in Reproductive Health and Population* New York: The Population Council 1994

Elias CJ "Sexual and Reproductive Health: Advocacy for Action" *International*

Roundtable on Women's Health Bellagio, Italy Advocacy for Women's Health, 1994

Elias CJ, Leonard A, Thompson, J "A Puzzle of Will Responding to Reproductive Tract Infections in the Context of Family Planning Programs " *Conference Paper* Africa Operations Research and Technical Assistance Project Nairobi, Kenya, 1993

Elias, CJ, Heise LL "The Development of Microbicides A New Method of HIV Prevention for Women " *Programs Division Working Paper No 6* New York. The Population Council, 1993

Elias, CJ "Enfermedades Transmitidas Sexualmente y la Salud Reproductiva de las Mujeres en Países en Vías de Desarrollo " *Programs Division Working Paper No 27* Mexico City The Population Council, 1993

Book Chapters

Elias CJ, Heise LL, and E Gollub "Female Controlled Prevention Methods of HIV " In *AIDS in the World* The Global AIDS Policy Coalition (forthcoming)

Elias CJ, Heise LL "Challenges for the Development of Female-Controlled Vaginal Microbicides " In *Women's Experiences with HIV/AIDS* Ankrah, EM and Long L (eds), Columbia University Press, 1996 (forthcoming)

Elias, CJ "AIDS An Agenda for Population Policy " In *Beyond the Numbers A Reader on Population, Consumption, and the Environment* Mazur LA (ed) Island Press, 1994

Elias CJ "Critical Issues Concerning the Accessibility of Essential AIDS Related Health Technologies for the Developing World " In *AIDS, Health and Human Rights* Mann J, Dupuy C (eds) Lyon, France Fondation Marcel Merieux, 1993

Elias CJ and LL Heise "Nonoxynol-9 the need for policy in the face of uncertainty " (Letter) *AIDS* 1995 3 311-312

Elias CJ "Reproductive Tract Infections Global Impact and Priorities for Women's Reproductive Health " by Adrienne Germain, et al (eds) (Book review) *Reproductive Health Matters* 1 111, 1993

Elias CJ "Sexual Behavior and Networking Anthropological and Socio-Cultural Studies on the Transmission of HIV " by Tim Dyson (ed) (Book review) *Population and Development Review* 19(1) 204, 1993

Selected Invited Presentations

"Female-Controlled Methods to Prevent Sexual Transmission of HIV," Plenary lecture given at the *XI International Conference on AIDS*, Vancouver, BC, Canada, July, 1996 (to be published in the journal, *AIDS*)

"An Overview of Interventions to Address Reproductive Tract Infections " *Working Group on Reproductive Health* The Population Council, Cairo, April, 1996

"Development of Vaginal Microbicides " Symposium on Women and AIDS *Third International Conference on AIDS in Asia and the Pacific* Chiang Mai, Thailand, September, 1995

"Barrier Prevention Methods of Preventing HIV Infection " Panel Discussion *Third International Conference on AIDS in Asia and the Pacific* Chiang Mai, Thailand, September, 1995

"Challenges for the Development of Vaginal Microbicides " Presenter and Session Co-Chair "Female Controlled Methods of Prevention " *Xth International Conference on AIDS* Yokohama, August, 1994

"Sexual and Reproductive Health Advocacy for Action " *International Roundtable on Women's Health*, Organized by the Commonwealth Medical Association on behalf of *Advocacy for Women's Health*, held at the Rockefeller International Conference Center, Bellagio, Italy February 1994

"STDs and the Reproductive Health of Women " Workshop *INCLIN* *Reproductive Health Working Group*, Chiang Mai, Thailand, January 1994

"Female-controlled Methods of Prevention " Session Chair *IXth International Conference on AIDS* Berlin, June 1993

David Phillips

Pearce-Pratt R, Phillips DM Studies on adherence of lymphocytes to epithelia Implications for sexual transmission of HIV *Biol Reprod* 1993 48 431-445

Tan X, Pearce Pratt R, Phillips DM Productive infection of a cervical epithelial cell line with human immunodeficiency virus implications for sexual transmission *J Virol* 1993 67,6447-6452

Pearce-Pratt R, Malamud D, Phillips DM The role of the cytoskeleton in cell-to-cell transmission of human immunodeficiency virus *J Virol* 1994,68 2898-2905

Phillips DM The role of cell-to-cell transmission in HIV infection *AIDS* 1994,8 719-731

Phillips DM, Tan X, Pearce-Pratt R, Zacharopoulos V Towards developing a vaginal formulation which will prevent infection by human immunodeficiency virus In Gillet J-Y, Bongain A, eds *2nd International Symposium on AIDS and Reproduction* Montpellier, France Sauramps Medical Pub, 1994 229-238

Phillips DM, Zacharopoulos V, Tan X, Pearce-Pratt R Mechanisms of sexual and transplacental transmission of human immunodeficiency virus *Trends in Microbiology* 1994,2 454-458

Phillips DM, Tan X, Pearce-Pratt R, Zacharopoulos V An assay for HIV infection of cultured human cervix-derived cells *J Virol Methods* 1995,52 1-13

Zaretzky FR, Pearce-Pratt R, Phillips DM Sulfated Polyanions Block *Chlamydia trachomatis* Infection of Cervix-Derived Human Epithelia *Infect Immun* 1995,63 3520-3526

Pearce-Pratt R, Phillips DM Sulphated polysaccharides inhibit lymphocyte-to-epithelial transmission of HIV *Biol Reprod* 1996,54 173-182

Phillips DM Intravaginal formulations to prevent HIV infection *Perspectives in Drug Discovery and Design Vol 5* Ed J Fantini and J -M Sabatier pp 213-223 Perotti M-E Tan X, Phillips DM, Polar secretion of HIV from primary monocytes *J Virology* In Press

Tan X, Phillips DM Monocyte-mediated infection of a cervical epithelial cell line with primary isolates of human immunodeficiency virus *Arch virol* In press

Burillo CA, Fontenot JD, Phillips DM Mouse model for sexual transmission of *Chlamydia trachomatis* *Infect Immun* Submitted

Fontenot JD Zacharopoulos V Phillips DM Proline-Rich Tandem Repeats of Anticody CDRs Bind and Neutralize HIV-1 Particles *J Virology* (In Press)

Phillips DM Tan X Early Events in HIV Induced Syncytia Formation *Virology* (Submitted)

D Financial Records

Please refer to the following reports

First Quarter 1996, submitted by J Tuite, Comptroller (6/20/96)

Fourth Quarter 1995, submitted by J Tuite, Comptroller (6/19/96)

Second & Third Quarters of 1995, submitted by J Tuite (1/29/96)

First Quarter of 1995, submitted by J Tuite (1/29/95)

Fourth Quarter 1994, submitted by J Tuite (6/22/95)

Fiscal Report No 4, submitted by J Tuite (2/1/95)

Fiscal Report No 3, submitted by Richard Balzano, Comptroller (11/18/94)

Estimated Fiscal Report No 2, submitted by Richard Balzano, Comptroller
(5/25/94)

Fiscal Report No 1, submitted by Richard Balzano, Comptroller (4/27/94)

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USAID data sources and contacts

- 1 Cooperative agreement
- 2 Yearly PIO/Ts for this Cooperative agreement
- 3 Reports submitted by the Pop Council
- 4 Individuals to contact
 - a Dr Helene Gayle, former chief HIV/AIDS Division, USAID
 - b Dr Ioanna Trilivas, former technical Advisor to Population Council, HNO Office
 - c Dr Jacob Gayle, former chief HIV/AIDS Division, USAID
 - d Mr Victor Barnes, Deputy Director HIV/AIDS Division
 - e Dr Jeanine Buzy former technical advisor to the Population Council, HN Office
 - f Dr Paul Delay chief, HIV/AIDS Division, USAID
 - g Dr Jeff Spieler, Chief, Research Division, Office of Population, USAID
 - h Dr Felice Apter, technical advisor to the Population Council, Population Office
 - i Dr Barbara de Zalduondo, technical advisor, HIV/AIDS Division, USAID

IV. Evaluation Team Composition

The evaluation team should be composed of individuals with the following skills

- 1 Comprehensive knowledge of microbiology virology and animal model testing as well as specific knowledge regarding sexual transmission of HIV and other STDs

- 2 Knowledge of reproductive biology particularly related to fertilization and immunology
- 3 Biomedical research skills and programmatic experience
- 4 Knowledge of preclinical and clinical trial design and development
- 5 Familiarity with new product development process vis-a-vis FDA requirements and industry
- 6 Experience in developing potential clinical trial sites
- 7 Understanding of the role of women's health advocates or experience as an advocate
- 8 Knowledge of the role of behavioral research in product development

PHASE II

The goal of Phase II in the evaluation and enhancement of USAID's Microbicide Development Strategy, are the identification of projects in microbicide development currently supported by USAID partners, partner capacity and plans for the future, and potential partnerships for the enhancement of USAID's current strategy

Phase II consists of three levels of analysis

Level 1 (USAID and partners) Identification of strategies being employed by USAID Cooperating Agencies (other than the Population Council) which are funded by the Population Health and Nutrition Center (including FHI and CONRAD) examination of the capacity of these CAs for future strategic development

Level 2 (National governmental agencies) Analysis of current and planned national strategies and activities of other U S Government Agencies and private sector organizations Examination of these strategies will focus on the ways in which these external strategies can be used to shape USAID's strategy, and identify areas where USAID can work in partnership with these organizations

Level 3 (International organizations) Multilateral organizations including UNAIDS and other donors have developed strategies for microbicide development Their current and future plans will effect the priorities USAID will choose for the future and will help shape potential partnerships between these organizations and USAID

Overall the purpose of the analysis and synthesis of the strategies and activities of other donors multilaterals US Government and USAID Cooperating Agencies is to inform USAID about potential gaps as well as opportunities for partnerships which may enhance USAID's microbicide development strategy over the next five to ten years

I. Scope of Work

A. Level 1 USAID Cooperating Agencies (CA)

- a. What corporate commitments exist within USAID's Cooperating Agencies for microbicide development and introduction?
- b. What strategies are being used by CAs to develop and introduce microbicides in the developing world?
- c. What activities are currently being funded by USAID? To what extent are they funded by other donors?
- d. What is this CA capable of achieving in microbicide development and introduction given adequate funding?
- e. What could this CA achieve with little to no extra funds specifically earmarked for microbicide development and introduction?
- f. What would be financially required to fulfill the stated capability of this CA in microbicide development and introduction?
- g. Is the CA committed to this project?

B. Level 2 National Strategies

- a. What are the currently existing and planned strategies within the NIH and CDC for microbicide development which would be applicable to the developing world?
- b. How much financial support have these agencies allocated to these goals?
- c. What new funding is being allocated to microbicide development which could potentially be available to women in the developing world?
- d. For what time period have these strategies been developed?
- e. When will existing strategies be reviewed?
- f. What major gaps in allocation of resources and expertise have been identified by these groups?
- g. What do these institutions see as USAID's comparative advantage?
- h. How could USAID work in partnership with these institutions efforts?

C Level 3 International Strategies

- a What are the currently existing and planned strategies of bilateral and multilateral donors for microbicide development which are applicable to the developing world?
- b What are the existing resource levels which are allocated to these goals?
- c What new funding has specifically been allocated to develop microbicides appropriate to women in the developing world?
- d What is the time line for these projects?
- e When will existing strategies be reviewed?
- f What do these institutions view as the major gaps in allocation of resources and expertise in achieving the availability of a microbicide?
- g What do these institutions see as USAID's comparative advantage?
- h What could USAID provide in partnership with these institutions efforts?

Method of Analysis Most of the data for the evaluation is expected to be collected through interviews and from existing documents. A list of existing data sources and suggestions for procedures to be followed are listed below

List all reviews and documents which address the state of microbicide development globally

- 1 CONRAD Pop Tech Evaluation 1995
- 2 National Institute of Allergy and Infectious Diseases 1995 Update on Topical Microbicides

Agencies and Individuals to contact

USAID Cooperating Agencies

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PHASE III.

The goal of Phase III is to synthesize the analysis and results of Phases I and II, to identify gaps and to provide recommendations to USAID for future involvement addressing USAID's comparative advantage in relation to their partners in Microbicide Development for introduction and use in the developing world. Recommendations should address the next five to ten years.

April 30, 1997
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ANNEX B

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ANNEX C: DOCUMENTS CONSULTED

ANNEX C

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ANNEX D: FDA CONSIDERATIONS FOR MICROBICIDE DEVELOPMENT

Points to Consider in the Nonclinical Pharmacology/Toxicology Development of Topical
Drugs Intended to Prevent the Transmission of Sexually Transmitted Diseases (STD)
and/or for the Development of Drugs Intended to Act as Vaginal Contraceptives¹

Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II

Division of Antimicrobial Drug Products
and
Division of Antiviral Drug Products
Office of Drug Evaluation IV

¹ This document is an informal communication under 21 CFR 10.90 (b) (9) that represents the best judgement of the Divisions of Reproductive and Urologic Drug Products, the Division of Antimicrobial Drug Products and the Division of Antiviral Drug Products at this time. This document does not necessarily represent the formal position of the Center for Drug Evaluation and Research or the Food and Drug Administration, and it does not bind or otherwise obligate the Center or Agency to the views expressed.

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Introduction

This document discusses several nonclinical pharmacology/toxicology issues that are inherent with the development of topical drugs that are intended to prevent sexually transmitted diseases (STD) or with the development of drugs proposed to act as vaginal contraceptives. It is not meant to replace existing guidance concerning the nonclinical pharmacology/toxicology safety data required to support the submission of Investigational New Drug (IND) applications. Rather, it offers insight into some aspects of these classes of drugs that make them unique from systemically administered drugs, namely, the topical sites of their administration and action and the prophylactic nature of the indications. The publication of this document is a joint effort of three independent review divisions in the Center for Drug Evaluation and Research of the FDA, and represents their best harmonized view of the issues at this time. However, all the recommendations contained herein may be subject to modification and sponsors are encouraged to discuss the content of their nonclinical submissions with the review division appropriate to each individual application.

Toxicology Studies

To support the safety of the individual phases of clinical development, studies in at least two animal species (one being a non-rodent) should be used to assess acute, subchronic and chronic toxicity at the proposed site of exposure. Potential sites of exposure to topical microbicides for the prevention of STDs include vaginal, cervical, penile, oral and rectal mucosal areas. For the purpose of this document, contraceptives are considered to expose vaginal and penile tissue. All toxicology studies should use at least three dose levels of the drug and an appropriate control, with the high dose showing frank toxicity (it is understood that there may be limits to the ability to achieve a toxic dose), and the low dose showing little or no toxicity. With the exception of the varying concentrations of the active product, the drug to be applied should be in its final formulation and the study duration should be equal to, or longer than, the proposed duration of treatment in the clinical trial. However, if in an early trial, the duration of treatment is for less than two weeks, a nonclinical study duration of two weeks should generally be used. All nonclinical studies carried out to assess safety of a drug should be performed according to Good Laboratory Practices as outlined in 21 CFR 312.63. Sponsors should consult with the FDA reviewing pharmacologists concerning approaches and protocols regarding these issues.

Because the topical microbicides are intended for intermittent use during periods in which the individual will be at risk of contracting a STD and contraceptives are intended for intermittent use over long periods of reproductive competence, they are, for regulatory purposes, considered to be chronically administered drugs. Thus, in the later stages of clinical development, six month studies in a rodent and one year toxicity studies in a non-rodent will be necessary to support phase 2/3 human trials. Carcinogenicity studies in rats and mice should be performed during the late stages of the drug development program.

Pharmacokinetic/Toxicokinetic Studies

During the conduct of subchronic and chronic toxicity studies, concurrent pharmacokinetic/toxicokinetic analyses should be performed to evaluate the drug's ADME (absorption, disposition, metabolism and excretion) profile and to determine if the drug is systemically absorbed. Appropriate analytical methodology should be established as early as possible to provide for precise, consistent and reliable pharmacokinetic data. Major pharmacokinetic endpoints such as maximum plasma concentration, time to maximum plasma concentration, area under the concentration time curve, volume of distribution, bioavailability and clearance should be determined. To better assess margins of safety, the animal pharmacokinetic data should be compared with data in humans. For instance, a drug might be absorbed in humans and the vaginal route of delivery in animals cannot achieve much higher systemic drug levels than those seen in humans. In that case, a one to three-month toxicology study in one species, with parenteral or oral administration of the drug, may be requested to produce sufficiently high blood levels to identify all potential toxicities. If the drug is absorbed, histopathology should be carried out on the full spectrum of organs and tissues.

Irritation

The likelihood of drug-induced irritation (adverse reactions such as inflammatory responses) to drug exposed tissues should be evaluated in animals at both the macroscopic and microscopic levels. Vaginal irritation tests should be carried out in rabbits with daily applications for ten days. If rabbits are adequately tested by the vaginal route for adverse effects in toxicology studies, no separate vaginal irritation study is required.

If the drug is found to be irritating to mucosal tissues and the sponsor decides to pursue further development, additional pharmacokinetics should be carried out to compare the extent of penetration of the drug across the inflamed tissue with that occurring in intact tissue. These data will help to determine whether the absorption kinetics of the drug is facilitated when the mucosa is compromised.

Hypersensitivity and Photosensitivity

If appropriate, the potential to produce hypersensitivity and photosensitivity of the drug should be evaluated. Examples of animal models and protocols for tests related to these toxicities can be found in references such as Marzulli and Maibach's "Dermatotoxicology" or Burleson, Dean and Munson's "Methods in Immunotoxicology."

Genotoxicity

A standard battery of tests should be carried out to evaluate all new molecular entities for the potential to induce genotoxic effects. A drug should be evaluated for potential genetic toxicity prior to the submission of the IND. The standard battery consists of the three following tests:

- 1) A gene mutation test in bacteria,
- 2) An in vitro mouse lymphoma tk assay or a mammalian cell in vitro cytogenetic test for chromosomal aberrations,
- 3) An in vivo test for chromosomal damage to rodent bone marrow cells or a mouse micronucleus test

If the three tests chosen indicate that the drug is devoid of genetic toxicity, no additional studies need to be carried out. If one or more of the battery is positive, the sponsor will be expected to carry out additional genotoxicity tests in consultation with the appropriate review division. For detailed information regarding genotoxicity, sponsors should refer to the document entitled "Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals." Copies of the Guideline are available from the CDER Consumer Affairs Branch, HFD-210, Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD 20857.

Reproductive Toxicology

Reproductive toxicology studies should be carried out to explore the possible effects of the drug on fertility and reproductive performance. Additional studies should be performed to examine whether the drug is teratogenic or has an effect on perinatal/postnatal development. Studies designed to assess the teratogenic potential should be carried out in two species, usually in rats and rabbits. It is expected that reproductive toxicology studies will be completed prior to Phase 2/3 trials. For detailed information regarding reproductive toxicology, sponsors should refer to the document entitled, "Guideline for Industry, Detection of Toxicity to Reproduction for Medicinal Products." Copies of the Guideline are available from the CDER Consumer Affairs Branch, HFD-210, Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD 20857.

Carcinogenicity

Carcinogenicity information is usually obtained during the final phase of the clinical development program. For a vaginal contraceptive, carcinogenicity tests in rats and mice should be submitted with the NDA. For a microbicide, carcinogenicity studies are also required, but the expected date of completion of the studies in relation to the filing of the NDA may vary. The drug should be administered for two years and the doses used should be chosen according to the principles outlined in the document entitled, "Guideline for Industry Dose Selection for Carcinogenicity Studies of Pharmaceuticals." Copies of the Guideline are available from the CDER Consumer Affairs Branch, HFD-210, Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD 20857. Sponsors should consult with the appropriate reviewing division for the current position and strategic approaches to these issues. Currently it is recommended that sponsors request that the Executive Committee of the Carcinogenicity Assessment Committee of the Center for Drug Evaluation and Research review the protocols for the carcinogenicity studies.

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Already Marketed Drugs

On 2/3/95, a notice of proposed rulemaking from the Food and Drug Administration entitled, "Vaginal Contraceptive Drug Products for Over-the-Counter Human Use" appeared in the Federal Register (Vol 60, No 23, pp, 6892-6903). The proposed rule stated that manufacturers of over-the-counter (OTC) vaginal contraceptive drug products would be required to obtain approved applications for marketing of the products. The agency took this action because the effectiveness of these products is dependent upon the final formulation. Therefore, each product must be tested in appropriate clinical trials under actual conditions of use. The proposed rulemaking does not affect the current marketing status of OTC vaginal contraceptives. However, on the effective date of a final regulation, an OTC vaginal contraceptive drug product that is not the subject of an approved application would be regarded as a new drug and be subjected to regulatory action regardless of its status prior to the publishing of the final regulation.

The agency has determined that nonoxynol 9 and octoxynol 9 would be appropriate ingredients for an approved application and has concluded that although nonoxynol 9 and octoxynol 9 kill sperm in vitro and in vivo, the spermicidal activity and resulting effectiveness of these contraceptive active ingredients cannot be considered separately from a product's vehicle. These active ingredients lose some of their effectiveness in humans when the spermicide in final formulation is diluted by various amounts of genital secretions during coitus. Thus, clinical studies are necessary to establish effectiveness of the spermicide's final formulation when used in humans. However, applications for currently marketed OTC products containing these ingredients require no additional nonclinical data, but, instead, may refer to (1) the recommendations of the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products that appeared in an advanced notice of proposed rulemaking in the Federal Register (12/12/1980, Vol 45, No 241, pp 82014-82049), entitled, "Vaginal Contraceptive Drug Products for Over-the-Counter Human Use, Establishment of a Monograph, Proposed Rulemaking," and (2) the history of use of approved drug products containing nonoxynol 9

The quest to identify safe and effective products for the prevention of HIV and other STDs is a high priority public health concern. Sponsors are strongly encouraged to evaluate OTC contraceptive products towards this use. However it should be recognized that studies designed to assess the safety and effectiveness of a formulated drug to prevent pregnancy and to prevent the transmission of an STD may be different. Manufacturers wishing to develop a formulation towards one or the other are encouraged to enter into a dialog with the appropriate reviewing divisions concerning the content of their applications.

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