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Evaluation of The Population Council Microbicide Activities

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MICROBICIDE RESEARCH, DEVELOPMENT, AND INTRODUCTION: A PROJECT OF USAID AND THE POPULATION COUNCIL (COOPERATIVE AGREEMENT NO HRN-5972-A-00-3022-00).

An Evaluation in Year Four

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Acronyms

AIDS	Acquired immunodeficiency syndrome
ATSP	AIDS Technical Support Project (of USAID)
CBR	Center for Biological Research (Population Council laboratories)
CDC	U S Centers for Disease Control and Prevention
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
HTLV-1	Human T-cell leukemia virus type I
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)
MuLV	Murine Leukemia Virus
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
PC	Population Council
RTI	Reproductive tract infection
SOP	Standard operating procedures
STD	Sexually transmitted disease
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	United States Agency for International Development
WHAM	Women's Health Advocates for Microbicides
WHO	World Health Organization

Contents

Executive Summary

This report summarizes the major findings of a June-August 1997 evaluation of the microbicides development activities supported by USAID, particularly the work of the Population Council from August 1993 through September 1997 The evaluation team visited the Population Council in New York City, talked with the Thailand coordinator by phone, interviewed officials of USAID and related organizations, contacted individuals involved in the women's advocacy aspects of the project, and reviewed available documents This report summarizes the team's findings with respect to the Population Council project A separate report reviews the current role of USAID in microbicide development and makes recommendations to the Agency regarding future directions

The current project dates from 1992-93 discussions between USAID and the Population Council in which the Council convinced USAID that the Council would be in a good position to contribute to development of vaginal microbicides to prevent HIV infection The rationale for microbicide development is that many women throughout the world are not in a position to insist on the use of condoms and need a method within their own control to protect themselves from HIV and other sexually transmitted diseases The Council was an early champion of the need for a microbicide that is a non-contraceptive as well The organization proposed a five-year research and development activity that could accelerate development of already identified candidate compounds into microbicides ready for human use Sensitive to criticism of previous reproductive health work that had paid inadequate attention to women, consultation with women's health advocates from around the world was proposed as a prominent feature of the project

Recognizing the utility of such a product for the developing world, and concerned about inadequate levels of research, USAID's Office of Health and Nutrition agreed to contribute nearly $200,000 for year one, with complementing support from the Swedish government and the Rockefeller Foundation The Population Council signed a noncompetitive cooperative agreement to continue its microbicide development, prepare for clinical testing, and collaborate with women's health advocates and health ethicists The agreement specified a "substantial involvement" role for USAID, chiefly to provide comments and to

review documents before publication The agreement was renewed a year later for two additional years ($800,000) and finally for the current year ($600,000) Thus USAID provided a total of $1 6 million over four years from its Office of Health and Nutrition, USAID's Office of Population added $180,000 to fund formulation preference studies Funding from other sources (for specific project elements) brought the total to $4 1 million over the four years, with about 44 % of the total coming from USAID

Advocacy

The Population Council has led the international call for development of safe, effective, affordable microbicides to protect women against HIV/AIDS It has played an instrumental and formative role in creating awareness of the need for microbicides and their potential role in HIV/AIDS prevention The Council has been effective in persuading donors, especially the NIH, to support microbicides research

Product Development

The preclinical work of the Population Council, carried out almost entirely at its Center for Biomedical Research (CBR), has demonstrated the capability to evaluate compounds for activity against HIV in primary and continuous cell lines as well as to conduct basic *in vitro* drug activity studies with chlamydia, HTLV-1, *N gonorrhea*, and HSV More than 96 compounds have been tested However, the evaluation team's findings indicated that no standardization or formal screening program has been used or designed The Council's attention seems to have focused more on assay development than on targeted drug discovery Two new products have emerged during the four years

At the time of the evaluation, the team found that pre-clinical compound screening at the CBR for activity against HIV did not include all factors now considered relevant and testable in the process Screening against other STD organisms is inconsistent and limited in scope The effects on, and of, the vaginal environment (e g , pH, opportunistic pathogens, semen) have been inadequately considered The Population Council's useful preclinical animal models address only the sexual transmission of chlamydia and herpes simplex virus The ME-180 model system, a potentially useful auxiliary screening tool, is a significant contribution of the CBR to the microbicide development effort

The evaluation team found it difficult to evaluate the formulation process due to the limited number of formulations and a lack of specifics in the information

provided It is not clear that the Council has the expertise to advance the field for formulation research for vaginal products The capacity of the CBR to take a product beyond the identification stage to the formulation and testing stages appears to be minimal While the Population Council has worked on novel formulations in the past, no evidence was presented in the microbicide context Consequently, it is not clear that the Population Council has a competitive edge in the formulations area The CBR has brought one compound, a lambda carrageenan, to Phase I clinical testing Other potential products, such as antimicrobial peptides and mucibodies, are in initial stages of development

The evaluation team could not detect a systematic process within the Population Council for decision-making regarding preclinical compound selection, screening, formulation, or testing At this level, the evaluation team was not presented with clear evidence of collaboration with other organizations Preclinical testing decisions are in the hands of the Microbicides Priorities Committee Decisions may reflect other funding mandates and the interests and expertise of the limited laboratory staff more than the needs of microbicide identification and development The USAID managers of this project have not been included in the decision-making process, including meetings of the Microbicide Priorities Committee

One Population Council microbicide, an iota carrageenan, reached Phase I clinical testing The compound was abandoned, by decision of the Microbicide Priorities Committee, when it failed to prevent, and possibly promoted, chlamydial infection in an animal model The evaluation team would have liked to have seen the results with this compound in a Macaque monkey model team

Two studies of the Population Council's International Programs Division--the formulation preferences study and the survey of men's attitudes in Mexico--explored behavioral issues in microbicde development The results of the formulation preferences study has however no immediate consequences for the formulation of PC213, but might inform decision making in later formulation later on, and may be applicable to gender issues pertaining to women's reproductive health

Clinical activity has been limited by the lack of products (other than N-9) to test This constraint also limits the usefulness of the Council's current efforts to develop Phase II/III testing sites in Thailand and South Africa While the methods used to identify and prepare sites for clinical testing appear generally appropraite in focus and coordination with local groups, the evaluation team is concerned that the evolving epidemiology of HIV and prevention efforts in

Thailand may preclude its use as a site for clinical trials of microbicides Potential sites in sub-Saharan Africa may be more suitable for such a study

Collaboration with Women's Groups

The Population Council is to be commended for having made a genuine, continuing effort to involve women in the process of microbicide development Women's Health Advocates for Microbicides (WHAM) was founded in 1994 as a result of a conference organized by the Population Council and the International Women's Health Coalition WHAM had its troubles as an organization — no secretariat, uncertain representativeness, biomedical technical information that was difficult for some members to understand, members with a long-standing antagonism to reproductive health technologies, and no clear connections with any organization other than the Population Council — but it did succeed in promoting an awareness of the potential of microbicides within the women's health community internationally, and it demonstrated that such working collaboration is possible Although WHAM elected to disband as an organization following the April 1997 microbicides conference, its members are poised to continue to advocate for microbicide development The experience yielded many lessons on involving prospective clients, communities, and women's health advocates in product development

Involvement of USAID

The cooperative agreement had few stipulations, outside of broad general categories, as to how the funds were to be spent USAID was unable to deliver "substantial involvement" and consequently, the project was managed like a grant The Population Council was left to follow its own scope of work, with minor yearly modifications and with no real oversight, either technical or contractual

Involvement with Other Organizations

Except for participation in the International Working Group on Microbicides, the Population Council has collaborated surprisingly little with other researchers It has contacts with several pharmaceutical manufacturing companies, but for microbicides, no active industrial involvement was reported

Conclusions and Recommendations

USAID was convinced in 1993 that the Population Council had a competitive edge in the development of vaginal microbicides The need was real, as it remains

four years later, especially in light of the expanding AIDS pandemic and the continued discouraging results in the development of a vaccine against HIV At the time of the evaluation, one product had received an IND, and an IND was being prepared for a second product Given the Council's confidence that it can carry out the whole process itself, from product identification through preclinical and clinical testing to introduction in the community and an organizational reluctance to collaborate that goes beyond protecting the commercial rights of potential manufacturers, **the evaluation team does not believe that USAID's current arrangement with the Population Council can produce the wide range of possible products requested by the Cooperative Agreement**

Though collaboration at the clinical stage is good, the evaluation team believes that the microbicide development effort will require the collaborative efforts of the many organizations with growing experience in the area of reproductive health and product development at the pre-clinical stage Unless a major drug company were interested — and there is no evidence of their commercial interest to date — no single organization is likely to be able to assemble the expertise needed to develop a vaginal microbicide rapidly **Much wider technical collaboration is needed at the pre-clinical stage if the goal of finding a wide range of possible products is to be met**

The Population Council's efforts to involve women's advocates from the earliest stages of product development has had limited concrete impact to date, owing largely to the absence of a product for clinical testing, **the involvement of women's advocates throughout product development has been a model for women's participation that will be critical in providing the most appropriate product to a given community** There is still a need for an international women's advocacy group, but the emphasis is now, as it should be, on greater consultation with local women's groups, as the Council is doing in Thailand

If USAID wishes to continue to support microbicide development by the Population Council, continuing scientific guidance must be provided USAID could provide this guidance by ensuring that the cooperative agreement has clearer specifications and mechanisms to assure USAID involvement in decision-making, organizing a technical advisory group, contracting with an organization with the expertise to provide oversight, making strong linkages to other USAID-funded activities with microbicide components (ie , CONRAD), or limiting USAID support to field trials and product distribution in conjunction with basic research funded by the National Institutes of Health and other organizations Options for future USAID support for microbicides are covered in a companion report, *USAID Microbicides Development*

The evaluation team believes that the Population Council has accomplished most of the tasks indicated in the Cooperative Agreement and Work Plans Some tasks were not completed because they were predicated on the availability of a compound for clinical testing, which was due to the weakness in preclinical development Though the lack of specificity and precision in both the USAID contractual documents and the Population Council's reports to USAID made it difficult to determine appropriate evaluation criteria, the team was able to evaluate the positive contributions of the Council, and the areas that were less successful in fulfilling the goals and spirit of the Cooperative Agreement

I. Background

1 1 THE NEED FOR A VAGINAL MICROBICIDE

Worldwide HIV/AIDS is transmitted predominantly through heterosexual intercourse, putting women at risk without the means to protect themselves As summarized in the Scope of Work for this evaluation, "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 " One of the most promising methods, in the absence of a vaccine, would be an intravaginal product that a woman could use as needed to prevent the transmission of HIV and, ideally, other sexually-transmitted pathogens that increase the risk of HIV transmission and have their own sequellae as well Such products, seriously envisioned only within the past decade, have been termed *vaginal microbicides* It is in the context of the urgent search for such products that the project evaluated here should be viewed

As the HIV/AIDS pandemic continues, women face a high risk of infection, particularly in the developing countries Consistent condom use, an effective and key primary prevention strategy, is not feasible for many women The 17-site study cited above 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 " Woman often have too little negotiating

power in their sexual relationships to insist on condom use, and too little power outside of these relationships to avoid partnerships that put them at risk It is apparent that women need prevention technologies that they can employ on their own initiative and without their partner's knowledge and/or consent

During the many years of work by NICHD and numerous national and international organizations on the development and evaluation of spermicides, including nonoxynol-9 (N-9) and menfegol, the importance of a product that would be microbicidal to pathogens, whether or not it was spermicidal, was not always appreciated By early 1989, at the CONRAD-sponsored "Heterosexual Transmission of AIDS" international workshop, researchers had begun to focus on the potential for utilizing spermicides/microbicides for the prevention of heterosexual transmission of HIV and other sexually transmitted pathogens The Population Council played a significant role in creating awareness of the potential importance of microbicides and pressuring donor agencies to recognize the need for alternatives to an AIDS vaccine

By 1993, when USAID's Microbicide Development Strategy was elaborated, much more research was being directed to the search for a vaccine against HIV — hopes that have been disappointed by subsequent events— and relatively little was directed to the development of spermicides and new agents to reduce vaginal or rectal transmission of HIV and other STDs Such research was critically needed, as were efforts to identify female-controlled prevention measures Efforts have intensified since then, but, given the uncertainly of AIDS vaccine development and the acceleration of the pandemic throughout much of the world, the need for a topical microbicide is at least as great today as it was in 1993

> *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* (Elias 1993)

The arguments advanced in 1993 by Christopher Elias of the Population Council and Lori Heise, founder of Women's Health Advocates for Microbicides (WHAM), as rationales for the development of microbicides (see box) are even more urgent today As HIV/AIDS spreads throughout the developing world primarily through heterosexual transmission, women remain at risk of contracting HIV The present incidence of HIV infection among women in sub-Saharan

Africa approaches that of men, and an estimated 90% of new infections are acquired through heterosexual sex (Mertens 1996 cited in Pfannenschmidt and McKay 1997) HIV in Asia is also spreading primarily through heterosexual contact An estimated 42% of the 21 8 million adults now living with HIV/AIDS are women, and the proportion is growing (WHO 1997) According to Vuylsteke (1996), "Women are not only becoming infected with HIV more frequently than men, they are becoming infected at a younger age " Gender inequality and the common practice of men visiting sex workers have strongly influenced spread of HIV (UNAIDS 1996)

1 2 INTEREST IN MICROBICIDE DEVELOPMENT AT THE PROJECT'S INCEPTION IN 1993

In 1991 the Population Council established an internal Microbicide Working Group whose strategy paper was endorsed by the organization's Board of Trustees the following year, when the Council convened a consultative meeting in New York of about 50 scientists and women's health advocates from a wide range of institutions Also in 1992, the Population Council received a grant from the National Institute for Child Health and Human Development (NICHD) for contraceptive research, including contraceptive microbicides

The Population Council was not the only institution, however, with interest and capability in vaginal microbicide development Other agencies with strengths and interest in microbicide development in 1993 included

- NICHD and NIAID, which were considering increasing their support for research aimed at the development of new topical spermicides/microbicides and the evaluation of existing spermicides in animal models and in clinical trials,
- Family Health International, which was evaluating microbicides containing nonoxynol-9 (N-9) for efficacy against STDs, studying the safety of vaginal suppositories containing N-9, and preparing a Phase III study of an N-9 film,
- University of Washington, which had tested a sponge containing N-9 and found it to be ineffective in preventing HIV transmission,
- USAID's CONRAD project, managed by Eastern Virginia Medical School, which had been involved in the design, development, and evaluation of spermicides, and had studied the *in vitro* characteristics of more than 130 products (today this number has grown to 500),
- National Cancer Institute, which screens many compounds for anti-HIV activity,

- World Health Organization, which had completed a study on the safety of a foaming tablet containing menfegol and was starting Phase II studies with a gel containing N-9, and
- Medical Research Council (MRC) of the United Kingdom, which was engaged in preclinical evaluation of microbicidal products

In the private commercial sector, several companies had successfully developed spermicides, but they had not yet shown an interest in providing major support for the development of these products as microbicides

In 1992-3 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 had staff 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 continuing commitment to working with women's advocacy representatives

Compared with other organizations, the Population Council possessed several elements that gave it a competitive advantage for USAID funding (1) It had a real plan to establish a close working relationship with women's health advocates, a collaboration that had been sorely lacking in previous contraceptive development work, (2) It was aware of the potential utility of polyanionic polysaccharides in HIV prevention, and (3) It had contributed to the study of mechanisms of sexual HIV transmission However, the Council lacked experience in the design and conduct of clinical trials with spermicides and their *in vitro* evaluation And it lacked actual experience in vaginal product development

1 3 PRODUCT DEVELOPMENT STEPS FOR A MICROBICIDE

Product development proceeds through a series of steps, some of which can overlap if, as in this case, the need is particularly urgent First is the identification of potentially effective compounds which are then screened for stability and activity under a range of conditions that may be found in nature Those that are still promising must then be tested further in a variety of formulations that might be acceptable and affordable to the user To avoid delay for FDA approval, necessary in almost all cases unless the product is developed and used exclusively outside the United States, plans for FDA-required testing should begin at this

point Collaboration with a potential manufacturer should also begin early in the process

In vitro tests are typically followed by animal studies Those few products that still appear promising at this point can then go on for clinical testing in humans for safety, tolerability and efficacy Behavioral studies of acceptability and desirability by the potential users are also needed at this stage Human testing is necessarily limited, however, until a suitable product has been identified

In 1993, the activities that would have to be carried out to develop and test microbicides were in active discussion by scientists in the reproductive health scientific community The International Working Group on Microbicides (IWGM) formalized its recommendations for microbicide identification and testing in 1994 (see Figure 1)

Figure 1 Recommended *in vitro* tests for microbicide activity*

for activity against HIV

- Laboratory-adapted HIV virus in T-cell lines
- Laboratory-adapted HIV virus in peripheral blood mononuclear cells
- Clinical HIV isolates (depending upon the microbicide and the mechanism of action, it may be appropriate to include drug-resistant isolates)
- Activity against cell-associated virus
- Antiviral activity in semen and if possible, vaginal fluids or in an *in vitro* system that is physiologically appropriate

for activity against other sexually-transmitted pathogens

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- *Haemophilus ducreyi*
- *Trichomonas vaginalis*
- Herpes simplex virus

for activity against other vaginal organisms

- *Lactobacillus crispatus*
- *Candida albicans*

*** International Working Group on Vaginal Microbicides, AIDS 1996, Vol 10 No 8**

II. USAID Support for Microbicide Development

2. 1 THE COOPERATIVE AGREEMENT WITH THE POPULATION COUNCIL

Following preliminary discussions with USAID, the Population Council submitted to USAID's AIDS Technical Support Project (ATSP) in 1993 a five-year workplan to accelerate microbicide development through a coordinated program of research, development, and product introduction The proposal outlined a cooperatively funded multi-donor effort, estimated to require $8 4 million over five years The Swedish Government and the Rockefeller Foundation had agreed to contribute to this effort

On September 1993, USAID's Office of Health and Nutrition awarded a cooperative agreement to the Population Council to support microbicide development Cooperative Agreement Number HRN-5972-A-00-3022-00 was finalized on October 8, 1993 The project's formal title is "The Development and Evaluation of Microbicidal Compounds for Intravaginal Use in Preventing the Sexual Transmission of HIV "

The cooperative agreement supported continued research in microbicide development, including compound screening, preclinical testing, and development of an Investigational New Drug (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 Figure 2 outlines the specifications of the Year One Work Plan

Figure 2 Highlights of the 1993 Cooperative Agreement between USAID and the Population Council — Year One

Purpose "to provide financial support for the Recipient's program entitled 'Microbicide Research, Development and Introduction' "

- Perform *in vitro* screening of potential microbicides for activity against HIV and other STD pathogens and to analyze their anti-fertility effects
- Prepare formulations of screened compounds (dextran sulfate and carrageenan mentioned), including gels, creams, foams, and suppositories
- Conduct preclinical testing in rat and rabbit models of formulated compounds for chemical stability, vaginal irritation, and toxicity
- Prepare data required by the FDA for an IND application for clinical testing in year 2
- Test the acceptability of existing, approved vaginal spermicidal preparations (N-9)
- Organize and participate in meetings related to microbicides research, including con-sultative meetings with women's health-advocacy groups and with clinical ethicists

Period August 1, 1993 - July 31, 1994

Reports

- Standard financial reports as listed
- A technical report at the end of the period describing progress on basic and clinical research as well as outcomes from all consultative meetings supported
- Provide one copy of all scientific publications no later than when submitted for publication and "give serious consideration to any comments received from the A I D Project Officer " USAID reserves the right to disclaim endorsement of opinions expressed and to disassociate itself from sponsorship or publication Otherwise, USAID support will be acknowledged Provide two additional copies of publications and lists to A I D , POL/CDIE/DI

USAID role "A I D anticipates substantial involvement and collaboration during the course of this Agreement including monitoring of the direction of the work, particularly in regard to the potential interrelationships with other projects "

Funded under the AIDS Technical Support Project, the Microbicides Project began in August 1993 with an initial allocation of US$199,431 for the first year During 1994 USAID extended the cooperative agreement and added $800,000 for

the next two years In 1996 USAID increased the ceiling of the cooperative agreement and added $600,000 more to cover a fourth year's work

Thus, USAID has allocated $1 6 million to the project over four years and two months (Aug 1993-Sept 1997) Of this amount, $1,136,866 had been spent by December 31, 1996, the remaining funds are expected to be expended by September 30, 1997 At that time, the project will end unless USAID allocates additional funds or initiates a new project Some project activities are funded by other donors, so it is expected that portions of the work funded by USAID will continue under other funding sources in any event

Figure 3 Scope of Work Details Added in Subsequent Years

For Years 2 and 3 (8/1/94 - 7/31/96)

- *In vitro* testing for Chlamydia specified
- A gel formulation of iota carrageenan selected for further testing, including efficacy against Chlamydia and HSV in mice, for anti-fertility tests both *in vitro* and in animals, and Phase I testing for safety and acceptability in very low-risk women at four ICCR clinics in Australia, Chile, the Dominican Republic, and Finland
- Preclinical studies to be completed should permit filing of IND with FDA in June 1994
- Phase II studies (probably in other sites with higher risk rates) should begin in Year 3
- Studies of women's acceptability of 3 formulations (gel, film, suppository) of existing, approved vaginal preparation of the spermicide N-9 to be tested in six clinic sites (Cote d'Ivoire, Zimbabwe, Sri Lanka, 2 in Thailand, and New York City)
- A consultation for formulation chemists in planning clinical testing

For Year 4 (14-month period, 8/1/96 - 9/30/97)

- Mouse model testing of potential microbicides for anti-chlamydia efficacy
- Mouse model testing for efficacy against HTLV-1
- Development and testing of new synthetic antibody compounds
- Site preparation in Thailand for large-scale efficacy trials and associated behavioral research
- Completion of the five-site study of women's preferences regarding three N-9 formulations for presentation at Vancouver AIDS meeting
- User studies addressing women's perceptions and men's attitudes
- Continued collaboration (joint meetings, reports, sharing of research protocols) with WHAM

2 2 THE ROLE OF OTHER DONORS

Additional "unrestricted" funding for research in microbicides was also provided by the Swedish International Development Cooperation Agency and by the Rockefeller Foundation Swedish assistance totaled $510,000 from 1993-97 The Rockefeller Foundation contributed $310,000 over this period and has committed an additional $200,000 for 1997-9 (see Table 1)

Two other donors provided funding for microbicide research by the CBR The Mellon Foundation contributed $400,000 during 1995-97, it has committed an additional $200,000 for 1997-98 The National Institutes of Health has provided about $250,000 annually since 1993, and continued funding at this level is expected through project year 2001-2

The Australian Agency for International Development (AusAID) contributed U S $11,000 to support a formulation preference study in Thailand The Robert H Ebert Program on Critical Issues in Reproductive Health and Population, administered by the Population Council, provided $31,000 to support formulation preference studies in Mexico, Thailand, and Minnesota, U S A

During the four years that USAID funded the project, the Population Council's total expenditures on microbicides research totaled $4 1 million Although less than the Council's original request for $8 4 million over five years, the original budget request had included more than $3 million for clinical trials Thus the funds available for preclinical studies and other research were close to the Council's original estimates During the four years of USAID funding (Office of Health and Nutrition and Office of Population combined), USAID contributed 44% of the total expenditures on microbicide research

III. Preclinical Microbicides Research: Expectations and Findings

3 1 Product Identification and Screening

3 1 1 Screening Process

Based on the project's Work Plans, the Population Council was expected to undertake the following steps

- Continue development of a cell-culture model for mucosal transmission of HIV,
- Screen for activity against other STD pathogens,
- Repeat evaluations of formulated products, and
- Carry out in vitro analysis of potential anti-fertility effects of dextran sulfate and carrageenan

A stated goal of the Population Council's project on Microbicide Research was " identification and evaluation of a wide range of vaginal microbicide products including those that would allow conception while still providing protection against RTIs " Given this expectation, it would be reasonable to assume that some type of formal screening process would be established during the initial years of the project

A screening program of this type is typically comprised of a series of well-defined assays conducted in a predetermined sequence While the assays employed may

be modified over time to reflect pertinent scientific advances, the basic screening tests are generally carefully defined through the generation and use of standard operating procedures (SOP) to ensure reproducibility and quality control For a potential vaginal microbicide, the appropriate in vitro preclinical studies should include a thorough assessment of drug activity against HIV, employing a variety of different cell types and virus isolates In addition, preclinical studies should examine the ability of the product to function in the vaginal environment as well as its potential impact on that environment A more detailed description of preclinical assessments relevant to the development of a vaginal microbicide is provided in Figure 5

The goal of the preclinical screening process is to provide sufficient information about product activity and toxicity to determine if a compound is an appropriate candidate for clinical testing Some of these studies will be dictated by regulatory requirements, but additional information may be desired to facilitate ranking of products if more than one viable candidate is identified In most drug discovery/development programs data from the primary screening assays are used to guide subsequent testing based on preset guidelines (i e , a decision tree or flow chart) The outcome of the preclinical studies then provides the basis for the decision to move on to clinical testing

With respect to the Population Council CBR's in vitro screening process, it is not clear that a standardized or formal screening program was designed or initiated by the CBR The CBR laboratory has demonstrated that it can evaluate compounds for activity against HIV in primary and continuous cell lines It has also demonstrated the ability to conduct basic in vitro drug activity studies with *C trachomatis* (chlamydia), HTLV-1, *N gonorrhea* and HSV However, the application of these assay systems and the depth to which any individual candidate compound has been evaluated appear to follow no obvious pattern or plan

Figure 4 Laboratory Steps in Microbicide Development (according to the Population Council CBR)

1 Assessing *in vitro* inhibition of HIV
2 Screening in animal models
3 Testing for toxicity and mutagenicity
4 Compliance with regulatory requirements

The CBR virus laboratory has performed *in vitro* screening of potentially microbicidal compounds in a HIV/cell culture model Two assays to assess the effect of microbicidal compounds on *C trachomatis* and *H ducreyi* infection were developed Evaluations of formulated products were not presented to the evaluation team, but

it was mentioned that addition of Carbopol to N-9 decreases N-9's activity, suggesting that the model has been used to assess formulated products too

No data were presented to permit the evaluation team to determine whether "mucus penetration tests and other appropriate tests" assessing the spermicidal potential of dextran sulphate and carrageenan had been conducted (as promised in the SOW May 1993) It was mentioned that these tests are normally contracted out to third parties, but there was no indication that this had been done and the results were not presented

In addition to the work prescribed in the SOW, the Council has developed several animal models to study the transmission of sexually transmitted pathogens

1) HSV-mouse model
2) HTLV-1 mouse model
3) *C trachomatis* mouse model
4) Murine Leukemia (MuLV) virus mouse model

Whether these models are predictive of the transmission of HIV or other STD pathogens in human transmission is unknown, but it appears that the combined use of these assays has led to the identification of four or five leading compounds for further testing

One or two carrageenans
PR-39, a 39 aminoacid protregrin
Prophenin, a 79 aminoacid protegrin
Mucibodies (under investigation, but a compound for testing has not yet been identified)

It should be noted that, following a Phase I study of its safety, testing of one of the carrageenans (PC 213) was stopped on the basis of data from the *C trachomatis* mouse model only, and without SIV macaque model evaluation The rationale for this decision by senior management of the Council was not convincing to the team

It was mentioned that another product has been identified that does not have the problems of the PC 213 model, but it was unclear at the time of the evaluation whether it is undergoing further testing and whether an IND is being prepared for the alternative to PC 213 The alternative product is probably a lambda carrageenan, but it could also be a N-9/polysaccharide product (p 8, PC document 15 June 1997) This was not clear during the meetings with the Population Council staff

The Population Council has been integrally involved in the International Working Group on Microbicides (IWGM) since its 1993 inception In this role, Population Council staff coauthored the 1996 manuscript on AIDS entitled, "Recommendations for the Development of Vaginal Microbicides " Figure 1 summarizes the procedures identified by the IWGM as important to the identification and testing of candidate compounds

Figure 5 Considerations in the Preclinical Assessment of Activity for Prospective Vaginal Microbicides Intended for Use to Prevent the Sexual Transmission of HIV

I Recommended *in vitro* activity assessments conducted with the active ingredient(s)

A Dose response curves showing the full range of biological activity against
1 Cell-free and cell-associated virus
2 Laboratory-adapted and clinical virus isolates grown in human PBMC and fresh monocyte-derived macrophage (MDM) cultures (to include viruses that are T-cell tropic, monocytotropic and dual tropic, SI and NSI phenotypes, HIV-1 and HIV-2) Inhibitory activity in T cell lines and in vitro non CD4+ cell lines can be used to supplement but not replace data generated in primary PBMC and MDM cultures All in vitro activity assessments must include parallel cytotoxicity controls conducted under identical conditions
3 Representative virus isolates from each of the major clades, with an emphasis on B, E, O and A

B Impact of the following on the in vitro activity profile against HIV
1 Low pH and sequential pH shifts (from 3 5 to 7 and back)
2 Seminal plasma, cervicovaginal sections
3 Inoculum size (i e , MOI)
4 Drug interaction studies (for products with more than one active ingredient)

C Mechanism of drug action and time course of kil l
1 Definition of drug activity with respect to target site and mode of action e g , direct virucidal effects, blocking activity, disruption of replication
2 Time course of action (i e , time course of kill for virucidal agents, pretreatment or exposure time requirements for non virucidal blocking agents, persistence of agents that inhibit replication)

D Effect on other STDs and opportunistic pathogens of the lower reproductive tract
1 Should include both bacterial and viral STDs such as *N gonorrhoeae, C trachomatis, T pallidum, T vaginalis, H ducreyi*, HSV, CMV, EBV, and HPV (or suitable alternative)
2 Opportunistic pathogens should include *E coli, C albicans* and representative microorganisms that contribute to bacterial vaginosis

E Effect on vaginal environment
1 Impact on normal flora, with an emphasis on H_2O_2-producing lactobacilli
2 Miscibility with cervicovaginal secretions and seminal plasma
3 Mucospissic effects
4 Contraceptive effects

II Recommended *in vitro* activity studies conducted with the formulated product

A Miscibility with seminal plasma and cervicovaginal secretions
B Product stability at pH extremes and at extremes of temperature, humidity, etc
C Impact of formulation on in vitro activity against representative virus strains
D Formulation impact on condom stability
E Contraceptive effects of the final formulation

The lack of Standard Operating Procedures (SOPs) in place for any of the assays, despite the fact that some have been described in publications, suggests that candidate products are being tested using assays that are still under development, and that the assays rather than the products may be the focus of investigation This may also reflect commitments made to other funding agencies (e g , NIH) While these efforts have merit with respect to the pursuit of basic science questions, contributions to the USAID-funded drug discovery effort have been minimal to date

Although one product made it to Phase I testing as noted above, many tests critical to determining the viability of a candidate product, such as stability at low pH, have not been done This is unfortunate in light of the existing consensus on which tests should be used to evaluate the properties of new products It can be argued that the science supporting these tests is evolving, however, if we wait for the science to catch up, we may have missed the opportunity to promote the use of products that could save lives Most scientists recognize the necessity of using current technology to test these products in an effort to enter promising candidates into clinical testing

Based on the limited number of products discussed in the briefing package and at the site visit, it appears that drug discovery per se was not a priority during the first 3 ½ years of this project The primary compounds of interest (sulfated polysaccharides, dextran sulfate and the carrageenans) were under consideration for development as microbicides prior to the initiation of the USAID project This class of drugs is also being investigated by other groups N-9, the second of four products listed in the updated product development plan, was also being evaluated as a potential vaginal microbicide in preclinical and clinical studies before the microbicides project began Two new product types have emerged from the Council's screening effort Both of them have potentially formidable preclinical development issues to address prior to clinical testing At the time of this review it is not clear that active recruitment and screening of new candidate compounds is occurring

3 1 2 Use of Research Findings on Spermicide Analysis and HIV to Develop Screening Protocols

The in vitro screening tests employed by the CBR were very basic at the start of the program (i e , use of laboratory isolates grown in continuous T-cell lines), but they have been adapted over time to reflect more contemporary methods of drug evaluation CBR's capabilities now include the use of clinical virus isolates and

primary monocyte/macrophage cultures, as well as its own cervical cell model to screen candidate compounds for anti-HIV activity While the relevant *in vitro* laboratory protocols have evolved over time, the process has been relatively slow, and is not up-to-date based on current scientific understanding of factors that may contribute to HIV transmission For example, the screening process does not include the use of virus strains from clades other than B Data from previous vaccine trials have demonstrated that this is an essential evaluation step for compounds that are based on antibody recognition, such as the proposed "mucibodies" and possibly for other agents that block the process of target cell binding and/or fusion Given the fact that clade B is not the predominant virus type present in many developing countries, this may be a particularly important variable to consider in a microbicide screening program Screening candidate compounds against a number of different strains of HIV-2 is also strongly recommended

It should also be noted that the recent explosion of research in virus entry mechanisms has produced several new assays that focus on early virus infection events that could be used in a screening program These assays have apparently not been investigated by the CBR Unfortunately, these more specific inhibitors of HIV may also be among the best candidates for non-spermicidal microbicides, a product type that is of great interest to developing countries

The CBR has dedicated a substantial amount of time and effort to the development of the cervical cell infection model, despite the fact that this is a CD4-, transformed cell line with unproven relevance to the process of virus transmission in vivo It is clear that the Council intends to continue to emphasize this model its recent research proposal states that the cervical cell line ME-180 will be a focal point for the preliminary screening process for new candidate compounds A number of recent findings suggest that, while the model may have value as part of a more broad spectrum screening program (e g , for characterization of nonspecific inhibitors of virus binding), it may not represent a process that actually takes place in vivo Documented human infections have demonstrated that HIV infection can occur in the absence of a cervix, and animal model studies have confirmed this observation In addition, virology studies conducted in the monkey model have not demonstrated virus replication in vaginal or cervical epithelia, even as early as two days post-infection The primary target site for virus replication within the first week of infection has been shown to be Langerhans cells in the vaginal epithelium, a finding consistent with the preferential transmission of monocytotropic virus strains during sexual transmission in humans

Another important concern with respect to the use of the ME-180 cell line as a screening tool is the fact that it is a transformed cell line Our understanding of the process of early events in HIV infection has increased substantially in the last year, particularly as it relates to cofactors involved in virus binding and entry HIV-1 clearly has the ability to utilize other cell surface proteins in addition to, or in some cases in place of, CD4 to facilitate binding to a host cell Since the process of transformation can result in changes in cell surface proteins, the transformed cell line ME-180 may differ substantially from normal cervical cells It is therefore possible that a transformed cervical cell line could support virus binding whereas a normal cell may not under similar conditions The differences in cell surface protein expression on the ME-180 cell line compared with nontransformed cervical cells has not been investigated In addition, the ability to infect a cell line or primary cell type in vitro does not necessarily indicate that infection can, or does, take place in vivo

The evaluation team noted that, despite the overriding concern expressed by Council staff that the main objective of microbicide development should be to prevent HIV infection (Elias and Heise 1993), the anti-HIV activity of some of these compounds has not been determined When asked what compounds they had tested for activity against HIV, the Population Council staff produced the list in Figure 6

Figure 6 Compounds Screened for Effectiveness against HIV Using In Vitro and Animal Models

Sulfated Polysaccharides
Dextran, DEAE-dextran, dextran sulfate, lambda carrageenan, iota carrageenan, kappa carrageenan, fucoidan, chondroitin sulfate A, heparin, heparan sulfate, de-N-sulfated heparin, pentosan polysulfate

MMD Compounds
Six compounds

Glycomed Compounds
Twenty sulfated compounds

Surfactants
Tergitol (N-9), benzalkonium chloride, C31G

Antibodies to HIV
Twelve different monoclonal antibodies, sera from HIV positive subjects

Mucibodies
Four mucibodies

Cell Adhesion Molecules
CD11a, CD18, ICAM-1, CD58, CD2, CD4, VLA4, VLA5, SLex, L-selectin, E-selectin, CD26, CD44, HLA-DQ, HLA-DR + DQ, CD31 and E-cadherin

Sugars
Glucose, galactose, galactose-6-sulfate, fructose, L- and D-fucose, mannose, mannose-1-phosphate, mannose-6-phosphate, mannitol, sorbitol, N-acetylglucosamine, N-acetylgalactosamine (galNAc), N-acetylneuraminic acid, glucuronic acid, galacturonic acid, mannuronic acid, lactose, maltose, sucrose and mannan
-

Other Compounds
Proflavine (3,6-acridinamine), Chloroquine, Polyvinyl pyrrolidone, Diethyldithiocarbamate, Glutathione, Chlorophyllin

[END OF FIGURE 6]

In conclusion, there has been some evolution in the screening assays used for *in vitro* evaluation of drug activity, but the process has been slow and appears to be driven by basic science interests rather than a focused effort on drug discovery Too much emphasis has been placed on the ME-180 model system, and not enough on *in vitro* modeling of factors known (or believed) to contribute to the sexual transmission of HIV

3 1 3 In Vitro Screening Against Other STDs

CBR staff stated that they attempt to evaluate the effectiveness of each candidate product in inhibiting the following organisms in addition to HIV

HTLV-1
HSV
HPV
C trachomatis
N gonorrhoeae
T pallidum
H ducreyi
T vaginalis

Although a complete list was not provided, it does not appear that all products under investigation have been tested against all microbes In addition, there did not appear to be any established order for testing of compounds or of pathogens Many of these decisions appeared to be influenced largely by the availability and enthusiasm of the laboratory person working directly on a given assay

CBR staff presented to the evaluation team conceptual descriptions of several assays for HSV, *C trachomatis*, HIV, and HTLV-1 It was not clear, however, whether assays against HPV, *T pallidum*, *H ducreyi*, and *T vaginalis* have been developed Most of the experiments are "plaque" assays using the human cervical epithelial cell line ME180 and testing whether a given compound has the ability to inhibit infection with a given organism In brief, graduated concentrations of the compounds were added to a constant volume of organism, and the combination was inoculated onto monolayers of the cell preparation Infection was detected by a cytotoxicity assay specific to the pathogen being tested

Minimal information was provided regarding the specifics of the procedures, including variations in incubation times The investigators stated that they had not tested any of the compounds for pH stability or effects on normal vaginal flora, including *L crispatus*, or on *C albicans* In fact, when the evaluation team asked about the pH issue, they were told that in vitro models such as these are always run at neutral pH No test for pH stability of compounds was mentioned There are no plans to test whether a candidate compound would penetrate cervical mucus, and none of the compounds had been tested in combination to assess the potential for any synergistic or antagonistic effects

An assay to measure the ability of compounds to inhibit the adhesion of *N gonorrhoeae* was described briefly This assay seemed primitive, and investigators could not explain how adhesion was differentiated from intracellular presence It was not included in the list of assays already used to test microbicidal compounds, suggesting it is in the early phases of development

At the time of the evaluation, HSV appeared to be one of the assays that has been developed to an advanced degree Investigators have even included semen to determine its effect on the system The *in vitro* model for *C trachomatis* also appeared to be highly developed

At present, the preclinical testing scheme employed by the Council for activity against other STD organisms is not performed on a consistent basis and is relatively limited in scope Epidemiologic studies have demonstrated that infection with other STDs, in particular those that cause ulcerative lesions, can

increase the risk of HIV acquisition during intercourse with an infected partner In addition, high-risk populations such as commercial sex workers also tend to be at increased risk for acquisition of other STDs Consequently, it is important to know what effect, if any, a candidate compound may have on other sexually transmitted disease organisms An effective preclinical screening program for potential vaginal microbicides should include an evaluation of drug activity against the full range of bacterial and viral STDs known to occur in populations at high risk for HIV infection This should include not only HSV, *N gonorrhea*, *C trachomatis*, and HTLV-1, the organisms currently used by the Council, but also *T pallidum*, *T vaginalis*, *H ducreyi*, CMV, EBV, and HPV (or suitable animal virus alternative) While this is not the primary goal of the microbicides screening program, it is an important safety assessment given the frequency with which these diseases coexist in populations at high risk for HIV In addition, knowledge about the activity of a product against other STDs may be useful in prioritizing compounds for further development, as well as for selection of potentially beneficial drug combinations

In addition to the impact of other STDs on HIV transmission, recent studies have found that perturbation of the normal flora (e g , bacterial vaginosis) can also increase the risk of HIV transmission In the interest of maintaining good vaginal health, drug effects on normal flora (i e , *Lactobacillus* species) and opportunistic pathogens such as *E coli*, *C albicans* and representative microorganisms that contribute to bacterial vaginosis should also be determined

3 1 4 Animal Models in the Product Development Plan

Animal model studies can provide valuable information about drug activity and the impact of formulation on product efficacy These studies are particularly useful for the assessment of combination products that rely on more than one active ingredient, compounds that mediate activity through cell protection (as opposed to direct virucidal effects), or when characteristics of the formation may contribute in a significant manner to product efficacy

Animal models for *C trachomatis* and herpes simplex virus may be acceptable for formulation research for products that are nonspecific inhibitors of HIV and also show equivalent levels of activity against each of these two organisms Products that are not active against HSV or *C trachomatis* cannot be evaluated in these models for formulation effects on drug activity If the impact of formulation product activity is a potential concern for an HIV-specific blocking agent, the Council does not appear to have any type of model system (*in vitro* or *in vivo*) in place or planned to try to assess it The two retrovirus models currently under

development (HTLV-1 and MuLV) are unlikely to be useful for this purpose Apart from the evaluation of relatively nonspecific blocking agents that act on enveloped viruses in general, these models will only be useful for the assessment of selected compounds that act on replications steps that are relatively conserved within the retroviridae (i e reverse transcription) This is a drug type in which the Council has expressed no interest It should also be noted that these models are essentially redundant and, with the possible exception of testing drugs that act after cell infection, offer little benefit for a microbicide screening program beyond that provided by the HSV animal model

At the present time preclinical animal models that simulate sexual transmission of HSV and *C trachomatis* are being used by the Council for product testing Also under development are two retrovirus models based on viruses not directly related to HIV (HTLV-1 and an unspecified MuLV) The evaluation of drug activity in the HSV and *C trachomatis* animal models should prove useful in the development of new microbicides However, the retrovirus models under development are not closely related to HIV-1 in terms of virus entry mechanisms or the resulting disease state induced These models are unlikely to be of any use in the evaluation of HIV-specific blocking agents

A general overview of the importance and difficulties of animal testing (for chemical stability, vaginal irritation, and toxicity in rat and rabbit animal models) was provided by the CBR Models are chosen based on cost, reliability (not generalizability), time to detection of infection, and time to next experiment A given product must block transmission of two out of three, although it is not clear whether this refers to three pathogens or three assays for HIV All models employ progesterone pretreatment, vaginal inoculation with a moderate dose of pathogen, vaginal inoculation of microbicide, and evaluation for signs suggestive of infection The incubation times were not described

The Population Council's HSV mouse model has been worked out in great detail The scant data presented suggested that, of the polysaccharides, high molecular weight ones worked better than low molecular weight ones, and that the carrageenans worked poorly Carbopol was added to the carrageenans The addition of semen to the system appeared to decrease HSV transmission When animals were evaluated for timing of infection with relation to stages of estrous cycle, 35% of animals inoculated in diestrus became infected, 11% when inoculated in proestrus, and none when in either estrus or metestrus It was mentioned that 20 times the inoculum of HSV was required to achieve rectal infection, but no data were presented during the presentation to the team to support this

The *C trachomatis* mouse model has also been well tested Of note is that the model uses a vaginal swab in its test for infection This is problematic for two reasons First, *C trachomatis* does not infect the vagina, but only the tiny area of endocervical cells Second, in both mice and humans it has been well documented that upper genital tract infection (pelvic inflammatory disease) can occur even when the lower genital tract tests normal Experiments have shown that nonoxynol-9 appears to inhibit infection Unfortunately, none of the carrageenans did so In fact, iota carrageenan appeared to *enhance* infection, perhaps a function of its viscosity or concentration All testing was stopped on this compound once this problem was identified

The investigators described a model to test *H ducreyi* on the backs of two different rodent models, the rabbit and the nude mouse Their model is primitive, but suggests that one of the carrageenans appears to inhibit infection The biggest problem with their model is that skin abrasion is required for infection

As previously discussed, two retrovirus models are under development, both of which are based on oncogenic viruses that are unrelated to HIV-1 (HTLV-1 and MuLV) These viruses cause a lymphoproliferative disease (cancer of the immune system), that differs in a number of important ways from the immune deficiency induced by HIV-1 In addition, these non-lentiviruses differ with respect to virus binding and entry events, as well as regulatory mechanisms that contribute to the process of productive virus infection and spread While HTLV-1 is itself an STD, the need for a model specifically to evaluate drug activity against this virus is debatable

While the SIV/SHIV model has its drawbacks, at present it may be the most effective way to assess the impact of formulation on drug activity It would be appropriate for the Council to have access to this model for compounds that are active against these virus constructs For products that are based on inhibition of the virus RT or other early steps in HIV replication it may be possible to use either the FIV or the SIV model to assess drug activity and formulation impact These models should also be available either through a collaborative effort or a contract mechanism as part of this drug development program

3.1 5 Antimicrobial Peptide Studies

A brief discussion of several new microbicides was presented by the CBR Antimicrobial peptides included the protegrins, magainins, and defensins Two of the protegrins (PR-39 and prophenin) are in the early phases of preclinical testing and have shown activity against *C trachomatis* These peptides are inactivated

by serum and unfortunately have not been tested for stability in vaginal fluid or seminal plasma Finally, a description of mucibodies was presented Limited attention appears to have been given to the importance of tertiary structure in inhibition of HIV infection, and no thought given to using potentially superior multivalent antibody technology

It is possible that bioengineered antimicrobial compounds, or naturally occurring antimicrobial peptides, could prove to have some utility in the formulation of new vaginal products Ultimately, it may be important to look at the impact of new vaginal products on this natural form of protection However, there are a number of potential problems with the development of this type of compound that have not been investigated by the Council, including stability in the vaginal environment when added as an exogenous component, impact on the vaginal ecosystem and immune responses at pharmacologic (as opposed to physiologic) concentrations, and antigenicity These concerns notwithstanding, there is no clear reason at this point in time to discontinue the evaluation of these compounds, but further development should not displace the drug discovery process

The potential impact of genital tract secretions on product activity is an important consideration in the evaluation of new microbicides In the future consideration should be given to expanding this aspect of the preclinical screening process to look more closely at drug activity in the presence of cervicovaginal secretions as well as semen In addition, the ability of a product to penetrate CVS (i E , miscibility), should be determined

3 1 6 Decision-making and Management of Preclinical Research

The process by which the Population Council ranks potential candidate compounds is based on a formula that includes the following variables

- HIV efficacy (estimated)
- STD efficacy (estimated)
- Future production costs (estimated)
- Stability
- Formulation issues
- Contraceptive potential
- Scope for Council role
- Available literature

As outlined to the evaluation team, decisions to advance a potential microbicide through preclinical development are made by the Microbicides Project Co-Director CBR, perhaps in limited consultation with his International Programs Division counterpart

The direction of the preclinical research program conducted at the Population Council appears to have been influenced strongly by other sources of funding, including grants given for basic research and assay development Personal research interests may also play a role in this decision process Despite some substantial setbacks, the primary focus of the Council's research efforts -- sulfated polysaccharides -- has not changed since the time the original funds were granted, and relatively few additional candidates have been identified for possible development

The evaluation team is concerned with the composition of the "product selection" committee Only one of four members has pharmaceutical company experience The Microbicides Project Co-Director at CBR has no such experience and has devoted most of his recent productive research to animal and in vitro models of STD infectivity The team is not convinced that the product development plan as presented in table form by the Population Council is realistic For example, a Phase II study of a sulfated polysaccharide is scheduled to begin in I/98 and a Phase III study in III/98 Operationally this is very difficult, if not impossible, suggesting little appreciation/knowledge of product development The behavioral research component appears to be much further advanced than the product component

Aside from the CBR's Microbicides Project Co-Director, it is not clear that any other staff have had any significant input into the preclinical drug development program There is also no indication that current research into HIV transmission events has had a substantial influence on the Council's work in regard to the preclinical drug screening process The input of other scientists within the Council as well as others actively involved in research in this decision-making process would be extremely useful

3 2 FORMULATION

The Population Council's Work Plan indicated the intention to formulate into preparations appropriate for intravaginal use compounds selected on the basis of in-vitro screening Gels, creams, foams, and suppositories were mentioned, as well as the intention to continue to improve the formulations of these compounds

Formulation technology for vaginal products is exceedingly difficult when compared to the formulation of oral or injectable products Too little research has been carried out, so the technology is only now being developed

While the Population Council has considerable experience with the formulation and delivery of steroids and of some peptides, the evaluation team could find no support for the statement that "the CBR laboratories have extensive experience in the formulation of vaginal products " The nature of vaginal products demands a different technology and experience from that currently in place at the CBR This shortcoming is indirectly acknowledged by CBR's desire to hire a chemist for formulation research None of the Council's products that have made it to the market (such as long acting progestagens for contraception, IUDs, and skin patches for hormone replacement therapy) is intended for vaginal administration

The formulations used in Phase I studies will probably not work with other products of high molecular weight Unless the individuals involved truly understand formulation technology, it is hard to expect people who have worked primarily on steroids and small peptides to develop the vaginal formulations needed Thus the expertise of the current staff of the Population Council is likely to be inadequate to the task of new formulations

The wording of the original Work Plan suggests that in 1993, eight formulations had been made for two polysaccharides (presumably PC 213 and dextran sulphate) During the evaluation team's visit, no evidence was presented that the Population Council has continued to work on the formulation of those two compounds or, indeed, of any other compounds selected through in vitro testing On the other hand, it was mentioned that a vaginal ring is being formulated to deliver a microbicide (likely a protegrin or an antiretroviral) Vaginal rings to deliver products intravaginally have been the objective of design efforts to deliver steroid hormones for 25 years and have so far led to the development of only one commercially available product Other formulation work at the Council was also related to non-microbicidal products, such as steroids

The evaluation team found it difficult to evaluate the quality of the formulation program for two reasons (1) preparation of a limited number of formulations (only one has been clinically evaluated), and (2) the predilection of the Population Council staff to present information in terms of generalities rather than specifics The latter criticism can be extended to both oral and written presentations in just about every area of product development On p 5 of the Population Council's written responses to questions sent on 6/15/97, for example, item 6 states "Used the herpes simplex mouse model to optimize a carrageenan-based formulation for

retroviruses " It is difficult to determine the nature of optimization because, on the very next page, it is stated that "PC 213 comprises a sulfated polysaccharide derived from iota carrageenan, which naturally forms a gel when mixed with water We decided to evaluate PC 213 in a gel formulation since it did not require any further manipulation or addition of excipient ingredients " This appears to have been an observation rather than an outcome of scientific experiment

Verbal and written documentation from the Population Council leave the strong impression that the overall operational strategy has been to do all of the preclinical and clinical research internally, with the need to develop in-house capabilities in all areas In the long run this approach may be good for the Population Council, but it is not necessarily good for the funding agencies The Microbicides Project has done little to utilize the capabilities of other organizations

IV. Clinical Microbicides Research: Expectations and Findings

The original Scope of Work included the intention to prepare an IND application for at least one product and to identify six sites for clinical studies through the ICCR In addition, an acceptability study to assess women's perspectives on N-9 preparations was planned

An IND was obtained for PC 213 (an iota carrageenan), and a Phase I study was conducted with the product before further development of the product was stopped The formulations preferences study was carried out in five centers The results were presented at the International Conference on AIDS in Vancouver in June 1996 but have not been published so far

The ICCR network sites intended to assess the safety and efficacy of N-9 containing products mentioned do not appear to have been selected On the other hand, a site to do a Phase III evaluation of a microbicide is being assessed in Thailand, and four sites for the same purpose are being assessed in South Africa

4 1 Phase I Testing (Safety)

At the time of this evaluation, only one Phase I microbicide trial has been carried out by the Council In a study of PC 213 (iota carrageenan) at five ICCR sites 25 patients used the product daily for seven days The product was reported to be well tolerated with minimal side effects No data were collected on dispersion

4 2 PHASES II (EXPANDED SAFETY), III (EFFICACY), AND IV (POST MARKETING)

No product has been available for testing in these phases, except for N-9, whose testing was included in the original Work Plan and is still under consideration To date there has been no opportunity for these phases of testing, but the Population Council has been preparing a site in Thailand and exploring possible sites in South Africa in anticipation of a Phase II/III study

The Population Council has clearly put a great deal of thought into study site preparation for potential Phase III studies Its criteria for potential sites include a supportive government and local community, an area of high annual HIV incidence (probably > 1%), predominantly heterosexual transmission, an accessible population, adequate laboratory facilities, a stable organizational environment, and experience with and existing infrastructure to support high-caliber research

Once a site is selected, it takes at least one year to prepare the site for clinical trials Site preparation entails both community studies and work with local clinicians Community studies include collecting information on women's perception of their risk of contracting HIV risk as well as men's sexual behavior their wife's pregnancy and postpartum period Researchers also hold consultations with women's and community groups To prepare clinical sites, researchers must review existing laboratory facilities, train staff to do record keeping and conduct the informed consent process, and establish baseline rates of condom use and STD prevalence in the potential study population

The Population Council has identified two potential sites for microbicides trials Chiang Rai, Thailand and South Africa The Thai site meets all the Council's criteria for site selection The Thai government and the local community are stable, open, and very supportive of research of this nature HIV prevalence for antenatal women is 7 1% Data on Norplant® and the Copper-T IUD from sites in Thailand were of sufficiently high quality to be used to gain FDA approval The U S Centers for Disease Control and Prevention (CDC) has been working in Chiang Rai for more than six years and has now assigned an epidemiologist to work there CDC and the Population Council have already collected copious data regarding the social, behavioral, and biomedical characteristics of this population, including prevalence figures from various groups for all major sexually transmitted infections Focus groups have been held at several sites within the Chiang Rai metropolitan area, and interest in participating in microbicide trials is high The infrastructure of the region, including laboratory capacity and access to

healthcare, is highly developed Relations between the Ministry of Public Health, the CDC, and the Population Council are outstanding Dr Christopher Elias of the Population Council resides in Bangkok Communications and transportation are excellent There is no local university and no US-based university research projects in place in this area

The proposed study design for the Thai site would enroll seronegative pregnant women into the study and follow them for several years Due to cultural traditions most Thai women do not have sexual relations during pregnancy or for several months postpartum During this period, their husbands may seek sexual gratification elsewhere, thereby increasing their risk of acquiring HIV Since newly infected men appear to transmit most effectively during the first few months after seroconversion, women resuming sexual activity following childbirth may be at highest risk for acquiring HIV then

A major concern regarding the Thai site, which is also recognized by the Council, is that HIV incidence may be too low for a manageable sample size This population has already demonstrated its ability to adopt condom usage rapidly For example, most military men now report consistent use of condoms with non-primary sexual partners (although few use condoms with their wives) This rapid behavior change has been reflected in a precipitous drop in HIV incidence among military men HIV incidence rates could fall even lower if men begin to use condoms at home as well as with non-primary sexual partners For the ethical conduct of a microbicides trial, subjects must be counseled to use condoms at home If they comply with this advice, incidence rates could decline further, thus reducing the power of the study

It is prudent to continue considering alternative sites with a high sero-incidence India meets this criterion but local and national support for this type of research is lacking Some areas in eastern and southern Africa meet the initial criteria for site selection The weak infrastructure and logistics challenges found in Africa would be offset by high sero-incidence Also, researchers believe that sexual behavior among African men is less subject to change, compared with Asian men A potential problem in identifying sites in Africa is that dry sex or vaginal agents to enhance sexual pleasure are used in some areas, clinical trials in these areas may not be appropriate due to uncertainty regarding the interaction of a microbicide with commonly used products or the unwillingness of couples to use microbicides consistently

The Population Council has identified four potential sites in South Africa, from which one site would be selected for microbicides trials At the time of the team's evaluation, there was not sufficient information to determine whether the study

design being developed for Thailand would be used in South Africa If this is to be the case, differing cultural traditions between Thailand and South Africa should be factored into the study design

4 3 BEHAVIORAL RESEARCH

Two behavioral studies relating to microbicides development have been carried out by the International Programs Division The first was a study of formulation preferences carried out at five sites in four countries Its findings were presented in Vancouver in 1996, but have yet to be published In each study, a group of women not at high risk of HIV infection from multiple partners was recruited and asked to use, in sequence for one month at a time, each of three N-9 formulations — a gel, a film, and a vaginal suppository Participants kept coital logs, and researchers asked them about any side effects they experienced as well as which formulations they preferred Periodic examinations were performed to look for symptomatic local side effects The reports of the women were used to rank the three products for preferences

A presentation of the findings and methodology of the formulation preferences study by the International Programs Division staff, followed by discussion, revealed that this study has weaknesses that limit its usefulness First, as acknowledged, it used a product that is not ideal and is therefore of unknown relevance for a viable microbicide product Secondly, the participants were not randomly selected Many of them knew each other, so that analysis of the comments of the participants as individuals is questionable and ignores any group effect It is clear that there was a group effect one group decided they all wanted to use the same formulation at the same time rather than following the sequence of the study Thirdly, there is no way of knowing how representative these women may be, but the total sample size of 145 women from five sites does not allow the data to be used to generalize to any specific population Lastly, the degree of satisfaction or dissatisfaction seems not to have been analyzed If gels, generally the least liked formulation, turn out to be the most reliable, for example, it would be useful to know whether women dislike them to the point of being unwilling to use them, or whether they simply prefer the film, everything being equal Since everything is not likely to be equal among formulations, such information could be important

The study appears to demonstrate that five separate groups of women in five different sites differed in their formulation preferences The strength of this difference is uncertain, as is the meaning for individual women It is hard to

understand why five international sites were needed, why the women were not randomized, why the sequence of formulation use was not maintained, and why the data analysis seems to have ignored the effect of grouping The results were very modest by social science research standards Nevertheless, the study did represent a departure from the usual practice of developing a product for women and then seeking their views Whether the results prove useful in product development remains to be seen

The second study examined the attitudes of Mexican men toward the possible use of vaginal microbicides by their wives or partners The study was based on four focus group discussions Researchers first explained what a microbicide is and how it would be used in order to elicit participants' opinions The study did reveal aspects of men's attitudes and behaviors that facilitate HIV/AIDS transmission, and the concept of assessing men's attitudes directly (rather than simply asking women what their partners think) is to be commended Because methods to be used in this study had not been written up at the time of the evaluation team's visit to the Population Council offices, the quality of this behavioral research could not yet be assessed

At present the Population Council is carrying out behavioral studies in Thailand at antenatal clinics and during post-partum care to determine the risks perceived by HIV+ women while at the same time fostering their interest in participating in future clinical trials of microbicides Initial results are reported to show high levels of interest In addition, the Population Council is conducting behavioral studies of husbands whose wives have recently given birth to understand the men's viewpoints concerning microbicide use by their wives

V. Consultation and Collaboration: Expectations and Findings

The original Work Plan provided for the organization of, and participation in, meetings related to microbicides research, including consultative meetings with women's health groups and with clinical ethicists

5 1 Collaboration with Scientific Peers

> *[We] reaffirm our willingness to collaborate with the broader community of scientists and advocates in advancing this important agenda*
> (Population Council, Proposal to USAID, January 15, 1993, p 21)

Despite the stated commitment of scientific collaboration contained in the Council's original proposal (see box), the evaluation team found little evidence of such collaboration aside from scientific publications All indications were that the Population Council prefers, whenever possible, to carry out all scientific work in house, using its own staff The evaluation team was surprised at how little research collaboration was reported with laboratories having similar interests CBR staff do participate regularly in scientific meetings on microbicides and hence are knowledgeable about potential collaborators and new research methodologies

Collaboration with other institutions in the area of microbicides appears to be limited primarily to contacts with commercial companies and service/product

providers Little evidence of collaboration or even subcontracting to other institutions in microbicide development was presented to the team

5 2 COLLABORATION WITH WOMEN'S ADVOCACY GROUPS· WHAM

The Women's Health Advocates for Microbicides (WHAM), a group of international women's advocates, linked the Population Council's microbicides development efforts with the women's health community WHAM was formed in 1994 during an international conference organized by the Population Council and the International Women's Health Coalition The Population Council periodically provided WHAM members with information about microbicide development, and they advised the Council on issues related to clinical and behavioral research

The Population Council's goal of establishing a consultative process with women's groups regarding product formulation, the ethics of clinical trial design, and optimal approaches for product introduction was innovative, important, and worthwhile Given the history of distrust and acrimony between women's health groups and scientists working on reproductive health technologies, the collaboration between the Population Council and WHAM marked a significant change

> *Contraceptive methods are usually tested on poor women of the Third World who are particularly vulnerable given their limited access to resources and information Consent may mean nothing more than trust in the researcher*
> (Barroso 1995)

Women's groups in the South have a long history of distrust of contraceptive researchers This distrust extends to the Population Council, which these groups identify with a "Neo-Malthusian concern with overpopulation in developing countries" rather than user-controlled methods that promote women's autonomy (Barroso 1995) By establishing a dialogue with its critics, the Population Council gained useful insights into their perspectives and created a forum in which to explain its goals and methodologies related to microbicides development

The involvement of women was especially important to microbicides development because women have been largely ignored in clinical trials related to HIV/AIDS It was not until October 1992 that the CDC announced a case definition for AIDS in women (Rosser 1994) Inclusion of women in clinical

trials was mandated by federal legislation in 1993 Not until 1994 did the NIH undertake a major project to map the disease's course and signs in women (Benderly 1997) Thus the collaboration between the Population Council and WHAM focused new attention to the needs of women in the AIDS epidemic

Despite the accusations that it has ignored women's needs, the Population Council is recognized as a pioneer in promoting the user's perspective in the delivery of reproductive health services Past experiences with clinical trials point to the wisdom of incorporating the user's perspectives from the very inception of product development Only recently have Institutional Review Boards understood their "mandate for community consultation" (Knudson 1997)

The April 1997 Symposium on Practical and Ethical Dilemmas in Clinical Trials of Vaginal Microbicides, organized by the Population Council and WHAM, was considered by many participants to be a landmark event Researchers appreciated the opportunity to interact with women's advocates and thought that the meeting had advanced thinking on scientific and behavioral research Participants discussed new considerations for ethical guidelines to informed consent in the context of microbicide trials Some participants regretted that the meeting had not issued recommendations on difficult issues such as involving communities in trial design All in all, most participants--scientists and advocates alike--considered the meeting to be useful in advancing the microbicides agenda

Following the April 1997 symposium, WHAM members decided to disband, explaining that "a wider, more flexible network is needed--one whose membership is not restricted and whose focus is not on providing feedback or input to any one institution " (Letter from WHAM/Population Council Symposium Organizing Committee, June 24, 1997)

WHAM lacked the funds to exist as an independent entity It also suffered from its own internal problems Some WHAM members reportedly could not move beyond the history of contraceptive development and were opposed to use of all reproductive technologies Some women dropped out, and some women from the South felt that women from the North were over-represented

The Population Council plans to continue its consultations with women's advocates the both the international and national levels The Council plans to organize a consultation with Thai women's advocates and activists this fall In order to establish a consultative process with the women who could participate in clinical trials in Thailand, the Population Council hired a staff member who has been actively involved in one of the leading women's advocacy organizations Thus the Council is linking up with community organizations in Chiang Rai and

plans to obtain feedback regarding research plans and share research findings with them This collaboration is planned for South Africa as well

Although CBR staff stated that they had benefitted from interaction with WHAM members, WHAM has had no discernible impact on the products or research priorities of the CBR laboratory The evaluation team was not able to find evidence of written records of WHAM's comments on research protocols or program direction, raising the question of their importance to the research plans WHAM did influence the Population Council's behavioral research Council staff report that comments from WHAM members highlighted the difficulty of involving commercial sex workers The protocol for the formulation preferences study was altered and helped to focus on women at low HIV risk instead of commercial sex workers

VI. Project Organization and Management

6 1 Project Goals

USAID indicated, in its terms of reference for the evaluation team, that the Microbicide Project had three major goals

1 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),
2 Provision of public sector leadership to ensure that products once developed will be available and affordable to all the world's women, and
3 The incorporation of a range of women's perspectives in all the steps of the technology development process from the laboratory to the pharmacy shelf (USAID, 1997)

This statement of goals does not appear anywhere in the formal project documents, including the cooperative agreement and subsequent amendments

The original cooperative agreement with USAID was very general about the project's goals, tasks and deliverables (see Figure 2) The Population Council's initial proposal provided sketchy information about the planned activities to be funded by USAID, explaining that "Like all technology development, this process can be expected to be complex and iterative As it is essentially a task of 'discovery,' it is difficult to be more precise at this time " (Population Council, Proposal to USAID, January 15, 1993, p 20) Without a more detailed

description of the process that the Council would use to identify appropriate compounds, USAID had to rely on internal expertise to monitor the project and provide oversight

Successive Work Plans and amendments to the cooperative agreement maintained the same level of generality The Work Plans and budgets suggested that clinical research would begin imminently, but this schedule proved to be premature because a testable compound was not identified Because the Work Plans did not specify which activities were to be funded by USAID, the evaluation team found it difficult to identify the "deliverables" expected and provided under the cooperative agreement

6 2 MANAGEMENT AND STAFFING

Since its inception, the Microbicides Project has been managed at the Population Council by two project co-directors Initially the co-directors were Dr Christopher J Elias, Senior Program Association, International Programs Division, and Dr David M Phillips, Senior Scientist, Center for Biomedical Research When Dr Elias moved to head the Thailand office, Dr Charlotte Ellertson, Program Associate, assumed the co-directorship for the International Programs Division Annex E shows how the staffing of the Microbicides Program fits into the overall structure of the Population Council

Given its ambitious goals, the Microbicides Program appears to be understaffed At the CBR, 40 % of the project co-director's time is allocated to the Microbicides Program, only 10% is funded by USAID USAID funds support two full-time scientists (these positions are currently vacant, since both left the CBR in 1997) and two full-time research technicians Fifty percent of the project co-director's time is funded by USAID, the combined time of other headquarters professional staff adds up to less than one full-time person In the Bangkok Office, two professionals spend less than half-time each, supported by a half-time administrator Roughly speaking, the combined staff funded under the Microbicides Program is the equivalent of slightly more than seven full-time employees

The absence of readily available information regarding the Work Plan, budget, staffing and expenditures of the Microbicides Program suggests that overall management and oversight of the program could be strengthened Consultation with senior managers, outside technical experts or donors, can be increased As a

1994 evaluation of the Population Council's contraceptive development work stated

> *Beyond innovation and technical problem solving, good product development depends upon detailed management--careful attention to record keeping, schedules, budgets, resource leveling, logistics, and deadlines Multiple products, parallel development pathways, and a myriad of more-or-less uncontrollable external factors present a web of options demanding constant review and reassessment Wrong choices can mean costly delays, higher costs, and lost opportunities* (Harper et al 1994 46)

Without clear, detailed Work Plans and systems for periodically reviewing progress, the Microbicides Program cannot move expeditiously toward its goals

6 3 USAID OVERSIGHT

The cooperative agreement includes a provision regarding USAID's "substantial involvement" "A I D anticipates substantial involvement and collaboration during the course of this Agreement including monitoring of the direction of the work, particularly in regard to the potential interrelationships with other projects " (Cooperative Agreement HRN-5792-A-00-3022-00, p 5) In other USAID-funded projects with similar contractual requirements, USAID staff receive a regular flow of information regarding specific compounds under investigation and are consulted at key decision points affecting research plans USAID staff participate in all major technical meetings and review drafts of publications and working papers In the case of the Microbicides Project, however, USAID did not establish a close consultative relationship at the outset and did not institute additional requirements linked to incremental funding and amendments to the cooperative agreement

USAID has managed the project much like a grant, with few requirements or technical inputs The Population Council, from its side, viewed USAID's funding as "soft" money that had few strings attached as long as it contributed to microbicide-related research During the project's first three years, it was not clear exactly what USAID was paying for In early 1997 when USAID officials realized that other U S government agencies, notably NIAID and NICHD, were supporting related research at the CBR, an effort was made to identify who was paying for what The Population Council's irregular submission of vouchers for payment compounded the problem of tracking project expenditures, as well as the lack of specific dollar amounts and shared funding by donors in the Microbicide program

Factors that contributed to USAID's weak oversight include (1) confidence in the Population Council's work, based on its early leadership in advocacy for microbicides and its experience in product development, (2) the small amount of initial funding, (3) the Population Council's reluctance to provide detailed information in order to protect patent rights, (4) turnover in USAID staff responsible for project oversight, with three USAID project officers over a four-year period, and (5) the heavy workload of USAID staff Because the cooperative agreement required only an annual report, Population Council staff did not keep the USAID project officer apprized of day-to-day activities, problems encountered in the research, or even changes in Work Plans The USAID project monitor was not invited to the CBR's major ICCR technical meetings where decisions were reviewed, although staff from USAID's Office of Population did attend these meetings

6 4 DELIVERABLES

Although information available was incomplete, the evaluation team believes that the Population Council has accomplished most of the tasks indicated in the Work Plans for the Microbicides Project Table 2 lists the major tasks and indicates whether they have been completed Some tasks such as conducting clinical trials were not done because there was no product (other than N-9) to test

Table 2 Microbicide Project Activities Planned and Accomplishments

Scope of Work	Tasks Completed
Year 1 (Sept 1993-July 1994)	
In vitro screening of new compounds for HIV & other STDs	Developed two new assays to test cell blocking
Repeat evaluations of formulated products	Continued studies of PC 213 and carrageenan formulations
Improve formulations of 2 compounds	Studied PC 213 and carrageenan, but further testing needed
Begin preclinical studies of chemical stability, vaginal irritation, and toxicity	Conducted Phase I study of PC 213
Prepare IND application for FDA	Prepared IND for PC 213

Conduct study of acceptability of existing vaginal spermicides	Planned formulation preferences study, which was completed in June 1996
Organize and participate in several consultative meetings, including one with women's health advocacy groups and one with clinical ethicists	In May 1994 met with staff from the International Women's Health Coalition and the Pacific Institute for Women's Health, planned meeting to include ethical issues
Years 2 & 3 (Aug 1994-July 1996)	
Screen new compounds for STDs other than HIV and chlamydia	Tested compounds for their effect on gonorrhea and chancroid (*Haemophilus ducreyi*)
Repeat evaluation of formulated products	(Formulated products not available)
Test iota carrageenan in mice re effect on chlamydia and herpes simplex virus and anti-fertility effect	Done
Improve formulations of promising compounds	(Compounds still being tested)
File IND with FDA	IND for PC 213 was filed with the FDA on September 29, 1994
Conduct Phase I trials in Year 2 for carrageenan gel in 4 sites re irritation, acceptability and safety	Conducted Phase I trial of PC 213 in 5 sites during Jan -Oct 1995, testing discontinued due to concerns about impact on chlamydia
Begin Phase II trials in Year 3 at different clinic sites	Not done due to lack of product to test
Study acceptability of existing vaginal spermicidal products in Year 2 at 6 sites	Formulation preferences study conducted in 5 sites in 1995-96
Hold meetings with (1) clinical ethicists and (2) formulation chemists	WHAM members met with scientists, health experts, and policymakers in May 1994, meetings with ethicists were not reported
Year 4 (Aug 1996-Sept 1997)	
Test additional potential microbicides	Done (see Figure 6 for list of compounds screened against HIV)
Refine the mouse model	Done

Test microbicides for effect on HTLV-1 infection in mice	Work on HTLV-1 mouse model continues
Continue work on bioengineered microbicide "Font-1"	(Not reported)
Explore potential clinical trial site in northern Thailand and conduct systematic review of other possible sites	Thailand site preparation in progress, sites in South Africa were visited
Finalize study on N-9 formulation preferences	Paper on study findings completed in June 1997
Expand user-perspective research on men's attitudes toward vaginal products, women's risk perception, and peri-partum abstinence norms in northern Thailand	Research has been initiated
Convene symposium with WHAM, continue consultations with WHAM members	Convened symposium in April 1997, WHAM has disbanded but consultations with WHAM members continue

6 5 REPORTING REQUIREMENTS

The Population Council submitted Annual Technical Reports for the first three years of the Microbicides Project These reports do not always correspond to the project year's Work Plan and are often unclear about which activities were funded by USAID They were submitted within six months of the project year's end Since the cooperative agreement does not stipulate a deadline for these reports, this time lag would appear to be acceptable to USAID The fourth and final Technical Report is not yet due, since the cooperative agreement ends in September 1997

The cooperative agreement states that the Population Council will "provide one copy of the manuscript of any proposed publication to the A I D Project Officer not later than submission to the publisher " This review was designed to give USAID the opportunity to make comments on the manuscript and decide whether or not to be cited as contributing to the research in question It is not clear that these documents were consistently provided or that USAID ever made any substantive comments

The cooperative agreement requires quarterly financial reports to be submitted within one month of the end of the quarter None of Population Council's financial reports has met this deadline The 16 quarterly financial reports due through February 1, 1997 were submitted an average of four months late, and the report due on May 1 is now two months late

VII. Conclusions and Recommendations

7 1 Conclusions

7 1 1 Project Goals and Accomplishments

The three major goals of the Microbicides Project, as stated by USAID in the terms of reference for the evaluation team, are

1 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),
2 Provision of public sector leadership to ensure that products once developed will be available and affordable to all the world's women, and
3 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 evaluation team believes that the goals were, and remain, appropriate Given the continued urgent need for an effective vaginal microbicide, microbicide development remains a high priority for HIV/AIDS prevention programs The evaluation team believes that this goal is feasible if sufficient resources are invested and adequate technical oversight is provided to expedite the process and use resources efficiently

In assessing the Population Council's accomplishments over the four-year Microbicides Project, the evaluation team concludes that progress toward the three major goals has been below expectations The evaluation team believes that the Population Council's efforts to identify and evaluate vaginal microbicide products have been disappointing The Council's failure to find a viable microbicide to advance through the process of product development reduces the opportunity for achieving the other two goals Even more sadly, no systematic approach to microbicide development has emerged Continuation of the Council's current approach to microbicide development is unlikely to produce the desired product Donor investments in alternative research programs are likely to be more productive in developing a microbicide product for widespread use

Although the deliverables specified in the cooperative agreement between USAID and the Population Council and in subsequent amendments are vague in the extreme, the evaluation team concludes that the Council, as an experienced reproductive health product development organization well aware of the urgent need for a product, would have been expected to accelerate the development of an effective and acceptable vaginal microbicide using a "fast track," "state-of-the-art" product development approach Indeed, such a need for as rapid action as possible had been documented by the Council's non-laboratory staff (Elias, 1993 and 1995) This approach would include the use or development of systematic screening protocols, with SOPs spelled out and clear decision points and criteria The urgency of the need for a microbicide effective against HIV would require collaboration with scientific colleagues where that would speed the progress What was spelled out in the cooperative agreement was collaboration with women's groups, ethicists, and other concerned parties because this could not be assumed

The second goal--ensuring that any products developed are appropriate for developing countries--did not appear in the project Scope of Work or its amendments but is a clear responsibility of USAID and its contracted projects The Population Council and WHAM were effective advocates for microbicides in national and international meetings on AIDS Their representatives were invited to a briefing of Vice President Gore that included microbicides Because of the lack of a suitable product, however, little progress could be made in ensuring availability in the developing world The Population Council has interpreted affordability mainly as the public-sector price for any product This is a perspective that may miss other important aspects involved in the distribution of products to the poorest people who cannot afford a market price and are often most in need The absence of a product may make this a moot point

The third goal--incorporating women's perspectives in the product development process-- was the most innovative aspect of project activities The Population Council made considerable efforts to organize the Women's Health Advocates for Microbicides and did receive some input into the product development process Unfortunately, the fact that this process largely bogged down at the product identification and screening stage meant that WHAM had relatively little opportunity to advise on product formulation, clinical trials, and distribution plans Still, the Council's initiative in establishing WHAM has become a model of user participation in health product development It can be replicated in national and local settings, with appropriate adjustments to local conditions

One of the major accomplishments of the Microbicides Project has been to create awareness of the need for microbicides and their potential role in HIV/AIDS prevention The Population Council has played an instrumental and formative role in the process of developing and coordinating the international call for development of safe, effective, affordable microbicides for women throughout the world

In Table 2 the evaluation team listed the actual deliverables of this project as defined in the original Scope of Work and its amendments By this measure, the Council completed most of the tasks in its annual Work Plans Progress was impeded by the lack of a product ready for clinical trials

7 1 2 Preclinical Product Development Activities

As the overall preclinical research program of the Population Council is currently constructed, it is not likely to result in a microbicide product ready for Phase III clinical trials The preclinical drug screening program lacks a coherent, systematic approach A more clearly defined screening program that includes a data-driven decision tree to guide the sequential steps in the drug development process is needed The Council does not have an appropriate screening process established and would require additional time and resources to establish one Furthermore, if the basic research and assay development projects currently under way are continued, there would be insufficient manpower available to conduct an efficient, high-output screening effort

The Population Council's Center for Biomedical Research has demonstrated an ability to evaluate compounds for activity against HIV in primary and continuous cell lines as well as to conduct basic *in vitro* drug activity studies with *C trachomatis*, *N gonorrhea*, and herpes simplex virus It has developed animal

models for sexual transmission of *C trachomatis* and HSV that are potentially useful auxiliary screening tools

The evaluation team noted substantial variation, however, between the recommendations of the International Working Group on Vaginal Microbicides (IWGM) for *in vitro* activity testing (see Figure 1) and the components of the drug development process at the CBR Screening of candidate compounds for activity against HIV does not cover all the factors now considered relevant and testable, and testing against other STD pathogens and common vaginal flora is inconsistent and limited Specific deficiencies noted by the evaluation team include the following

- There appears to have been limited testing of laboratory-adapted HIV virus in peripheral blood mononuclear cells or of clinical HIV isolates in any of the models
- There was no description of any testing of macrophage tropic virus
- There was limited testing of antiviral activity in semen and no testing in vaginal fluids
- There has been limited in vitro testing of any compound against *N gonorrhoeae*, only preliminary animal model work against *H ducreyi*, and none against *T vaginalis*
- There has been no testing of activity against *L crispatus* or *C albicans*

The direction of research has focused on assay and model development rather than on passing the preclinical hurdles necessary to move microbicidal products into clinical testing It is here that the lack of a systematic product development process is most evident

The Population Council's original briefing materials and its 15 June 1997 memorandum placed a heavy emphasis on the creation of the cervical cell infection model for in vitro screening and on the development of alternative retrovirus animal models for formulation research The cervical cell infection model may prove to be a useful auxiliary screening tool as part of a series of in vitro assays, but it is not at all clear that this system "most accurately represents" the process of HIV sexual transmission, as suggested by CBR personnel While NIH laboratories have adopted a similar system for screening potential vaginal microbicides, it is not the primary screen for activity It is used as one component of a screening program that includes activity assessments carried out in traditional cell culture systems (both primary and transformed cell cultures) and its limitations are recognized Apart from the ME-180 model system, the in vitro work performed by the CBR has contributed less than the team would have expected to the microbicide development effort At the present time, the animal

models currently under development have not progressed to a point where they might be adopted by outside laboratories

The CBR has not always used state-of-the-art methodologies, a shortcoming that could be avoided with greater collaboration with other scientists Only the CBR s animal models of sexual transmission of *C trachomatis* and herpes simplex virus are particularly useful Coordination with other laboratories that have other assays is conspicuously lacking Even preliminary discussions with the FDA on required and recommended testing have not taken place

Formulation studies have been small and of little practical value to date The evaluation team is not convinced that the Population Council has the product development expertise needed to take a vaginal product beyond the identification stage to formulation and testing

7 1 3 Clinical and Behavioral Activities

Without a promising microbicide ready for testing, the International Programs Division of the Population Council has had a limited clinical agenda A small Phase I study of PC 213 (iota carrageenan) found the product to be non-irritating and well tolerated, but development of that product was stopped when it appeared to enhance the risk of *C trachomatis* (chlamydia) infection A four-country, five center study of N-9 formulation preferences was carried out, but the utility of the findings — a preference for a vaginal film or suppository formulation rather than a gel — is difficult to assess A related study of male attitudes toward microbicides in Mexico also produced information of uncertain utility Nevertheless, the two studies did explore new areas of research

IND application, also a responsibility of the International Programs Division, has been done for only one candidate product (PC 213) to date, and only a related lambda carrageenan is scheduled to enter the clinical evaluation process The Council is contemplating using the clinical testing site under development in Chiang Rai, Thailand for other (probably N-9) compounds

Council's development of clinical testing sites in Chiang Rai shows good collaboration with local women's advocates, Thai health officials, and researchers (such as the CDC) The steps taken to develop the Chiang Rai site may serve as a model for future work However, the need for additional testing sites at this point has not yet been convincingly demonstrated, since in the view of the evaluation team, product development is at this time, too far behind site development Also, the evolving epidemiology of HIV and prevention efforts in Chiang Rai suggest

that it may not suffice for a study with real statistical power and thus may not be appropriate Site development work has begun in South Africa but specific sites have not yet been selected

Acceptability studies and WHAM inputs appear to have had no impact on decisions regarding clinical testing, although they may become relevant to product formulation and research designs of clinical trials

7 1. 4 Internal Project Management and Collaboration

Microbicide development at the Population Council seems to lack systematic overall direction Management is diffuse, lacking a defined decision-making process and standard operating procedures for the laboratory work Clinical research decisions appear to be made largely by one person without other inputs or oversight

Overall staffing levels appear low for the project's ambitious goals The level of effort of the Microbicides Project staff is equivalent to slightly more than seven full-time employees The biomedical staff of the CBR are inadequate in numbers for the product development task at this point Two full-time scientists in microbicide development recently left and have not been replaced Needed are an immunologist and a microbiologist, an expert in vaginal products formulation, and other researchers with fresh, new ideas, knowledge of the latest techniques, and contacts with other scientists Some gaps in expertise could be filled through collaboration with other institutions, such collaboration would constitute a change in the Council's current *modus operandi* It seems premature to assess the size and adequacy of International Programs Division staff

Laboratory collaboration has been limited largely to contacts with industry, and the evaluation team considered the Council's hesitancy to collaborate or to provide real details to others to be a major weakness There even appeared to be minimal collaboration with other investigators at Rockefeller, Cornell, and other academic sites known for their work in this field

7 1 5 Collaboration with Women's Groups

Collaboration between the Population Council and WHAM had a significant impact in several critical areas

- initiating a working relationship between women's health advocates and scientists working to develop reproductive health products,

- directing attention to the need for female-controlled measures of HIV prevention that can be used without partner knowledge or consent,
- creating awareness that women must be included in clinical trials of products to prevent HIV/AIDS transmission,
- focusing social science research efforts on critical concerns of women and their reproductive health,
- advancing discussions between scientists and women's health advocates concerning the ethical questions in the clinical testing of vaginal products, and
- recommending improved ways of incorporating user (women) and community perspectives into site preparation for clinical trials in Thailand

The Council/WHAM collaboration had no impact on the ability of the Council to speed the discovery and production of a microbicide for testing Without a product to test, a critical gap persists However, collaboration with women's health advocates and community groups remains critical to any USAID-funded effort concerning women and AIDS

WHAM disbanded in May 1997 for a variety of reasons, including inadequate funding and too limited a mission (effectively relating only to the microbicide development efforts of the Population Council) These were external to the Population Council, however, and should not detract from the Council's pioneering and continuing efforts to find innovative ways to involve women The involvement of local women's advisors in Thailand is a model of a positive new approach

7 1 6 Management and Oversight by USAID

USAID has not exercised, or provided for, sufficient technical oversight It is true that its project management personnel were burdened with numerous other supervision responsibilities, and they were not always invited to technical meetings such as those of the ICCR at which technical decisions were made Even though USAID staff had technical expertise that would have benefitted the project, USAID did not insist that the Population Council involve them in technical decisions USAID managed the project as if it were a grant The "substantial involvement" called for in the cooperative agreement was not realized

The absence of technical direction from USAID has been compounded by a vague Scope of Work and deliverables Expectations and decision points requiring USAID approval are unclear Moreover, the Work Plans were not geared to

USAID funding levels, making it difficult to determine what USAID was paying for Even where the requirements were clear, however, as in required financial reports and advance copies of publications, USAID did not insist that the Council honor the terms of the cooperative agreement

7.2 RECOMMENDATIONS

Recommendation No 1 a. Continue to support the development of the lamba carrageenan the PC is readying for an IND

USAID should request the PC to have a pre-IND meeting with the FDA on the above carrageenan, and request the PC to share the comments by the FDA with USAID (or its appointed expert committee or TAG- *vide infra*)

Should the FDA consider the product to be workable, then the PC should prepare a workplan that should result in a rapid and succesful IND application This workplan would be be submitted to USAID and (after positive advice by its appointed expert committee) should be considered for (partial?) funding

After obtention of the IND, a new workplan for phase I/II evaluations (and possibly concurrent other testing like stability testing) would need to be submitted, and (after positive advice by its appointed expert committee) should be considered for (partial?) funding

After completion of the phase III workplan, a workplan for phase III evaluations (and possibly concurrent other testing like carcinogenicity or embryotoxicity) would need to be submitted, and (after positive advice by its appointed expert committee) should be considered for (partial?) funding

Recommendation No 1 b Explore alternative preclinical research approaches that would be more effective than continued collaboration with the PC

After four years of project experience the Population Council does not have a microbicide ready for field testing, and is unlikely to be able to identify and evaluate up to the IND stage several microbicides within the next five years The evaluation team therefore recommends that USAID examine alternative approaches to preclinical research, rather than funding the Population Council's Microbicides Program as currently constituted Options for USAID are to (1) collaborate with other government agencies that currently have efficient, broad

spectrum screening programs and formulation capabilities, (2) undertake a competitive contractual process in order to identify private-sector groups with expertise in microbicide screening and development, and (3) ask the CONRAD project to supervise preclinical research grants, if this would not constitute a conflict of interest on the part of the CONRAD project

Recommendation No. 1 b. Look at other areas than preclinical microbicide development in which USAID could more effectively exercise its comparative advantage. In other words, USAID might use its funding and extensive expertise in international health to support clinical development on subsequent marketing of microbicides, through its contractors and other partners

Recommendation No 2 Work more closely with other U S. government agencies and donors to increase support for microbicides research and avoid duplication The USAID Office of Health and Nutrition should consult more regularly with the USAID Office of Population, NIAID, NICHD and USAID-funded Cooperating Agencies to ensure a coordinated approach to microbicides development It should also strengthen linkages with international funding agencies to keep microbicide development on their agendas and to promote maximum collaboration and minimal overlap These contacts would help USAID Office of Health and Nutrition staff to be aware of the larger context of microbicide research and to decide on the Office's specific contribution to the larger microbicide endeavor

Recommendation No 3 Resolve questions regarding N-9 as a microbicide The question of the real utility of N-9 as a microbicide has not been fully resolved Since N-9 is the only product even close to market availability, the questions concerning its formulation and effect on HIV need to be resolved A study that avoids the weaknesses of past studies and has adequate statistical power should be conducted so that N-9 can be used in clinical trials or abandoned USAID should give high priority to ensuring that this study is initiated as soon as possible If USAID is unable to fund it, USAID should contact other donors to identify a funding source

Recommendation No 4 Require more detailed work plans and more regular reporting from grantees The USAID Office of Health and Nutrition should tighten up contractual requirements for microbicides projects The evaluation team recommends that the next contract/cooperative agreement be competitively procured, have a detailed work plan that reflects budget allocations, require more technical approvals from USAID, specify deadlines for reports, and specify more formal means of communication and input In future, all grantees should be expected to collaborate with other researchers, in order to ensure the highest

quality technical work USAID technical officers need to receive clear guidelines on project management

Before reviewing future funding requests for preclinical microbicides research from the Population Council, USAID should insist on (1) a much more concrete operational plan for a more focused, well-defined in vitro drug discovery effort, (2) evidence of product development expertise, (3) a structure that fosters collaboration with other researchers, and (4) establishment of an oversight committee of researchers actively involved in the field of microbicide research and/or drug development to help guide future research efforts funded by USAID The CBR requires technical oversight and guidance by an agency with technical understanding of all areas of vaginal product development Options include the creation of a technical advisory group (TAG) on microbicides, innovative arrangements with industrial firms with expertise in the area, and collaborative agreements with other agencies that have such expertise If a TAG is created, it should include women's health advocates to ensure transparency and coordinated advocacy, funds should be allocated to fund their travel to TAG meetings

The CBR should be asked to construct a clearly defined program, with a flow chart showing the assays that will be used for primary screening and follow-up studies The flow chart should be accompanied by established SOPs for each assay component and a description of the criteria that will be employed to determine the sequence of expanded preclinical testing of promising compounds The in vitro screening program should cover a broad range of compounds and should encompass all of the considerations discussed in Figure 5 to the extent possible At a minimum, this program should be capable of addressing all regulatory requirements for initiation of Phase I clinical testing The CBR needs much greater collaboration to expand the skill base and pace of the microbicide development effort Subcontracting or collaborating with other organizations having specialized skills should be considered

Recommendation No 5 Work more closely with the FDA The FDA welcomes pre-IND consultation on microbicides in order to expedite testing USAID-funded projects should take advantage of this assistance to clarify testing requirements

Recommendation No 6 Focus site development efforts on sub-Saharan Africa The site being developed by the Population Council in Chiang Rai is very likely to prove unacceptable The organization should work more intensively on sites in sub-Saharan Africa, or perhaps India where the epidemic is expanding

rapidly This includes developing collaborative arrangements with local scientists, women's advocacy groups, and community groups

Recommendation No 7 Consult women from multiple perspectives in all phases of clinical trials Women and their health care advocates from at least four perspectives should be involved in clinical trial preparation and analysis in the future These four perspectives are the developed world (the U S and other countries of the North), the developing world (the South), the national level where the study will be carried out, and the community Since advisory boards will not necessarily ensure adequate collaboration with women, USAID should explore options such as the following to involve women in a meaningful way in the entire microbicide development process

- Creation of advisory committees with a women's health advocacy perspective, including activists from the HIV/AIDS community, other women with continuing and vested interests, and those having direct patient contact,
- Provision of any advisory bodies with sufficient resources (secretariat, funding for travel to meetings, and clearly defined roles) to make independent contributions, and
- In the case of advisory groups affiliated with a USAID project, clearly defined relationships to ensure accountability, commitment and input

Recommendation No 8 Apply to other projects the lessons learned from collaboration with women's health advocates USAID should describe and share with other projects its experience with WHAM in an effort to encourage them to develop effective links of their own with women's health advocates These links should permit two-way communication so that scientists and other technicians can learn to listen to, and understand, the women's advocates in addition to keeping them informed

Annexes

Annex A: Scope of Work

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 it's 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 womens' 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 biodetergent 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 biodetergents, including nonoxynol-9, effectively inactivate HIV, there is no conclusive clinical data addressing protection against HIV infection Some studies, however, suggest that biodetergents 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 be 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 Lactobacillis 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 Praneem, (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 sulphated polymers have been evaluated for vaginal application in humans Investigators in London recently completed a vaginal safety study of varying dextrin-2-sulphate 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/macaque 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 Fontenot, 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

~~H~~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 Paises en Vias 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 Socia-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 *INCLEN Reproductive Health Working Group*, Chiang Mai, Thailand, January 1994

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

<u>David Phillips</u>

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

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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 Antibody 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)

E Women's Health Advocates WHAM Women's Health Advocates for Microbicides

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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, HNOffice
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

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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

CONRAD
Dr Henry Gabelnick
Director
CONRAD Program
tel 703-524-4744

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tel 703-524-4744

FHI
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Senior Epidemiologist
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National Strategies

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Chief, Contraceptive and Development Branch
National Institute of Child Health and Development
tel 301-496-1661

Dr Penelope Hitchcock
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National Institute of Allergy and Infectious Diseases
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Dr Zeda Rosenberg
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National Institute of Allergy and Infectious Diseases
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CDC
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Division of Reproductive Health, CDC
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Private Sector

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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: Evaluation Team Members

ANNEX B

List of Evaluation Team Members

Dr James Sonnemann, M D , M P H , served as Team Leader He has extensive experience in maternal and child health, project management in the USAID Health Sector, behavioral research as it relates to health sector planning, epidemiology, and data collection 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

Ms Jill Gay has written extensively on women's advocacy issues in the health field, and serves 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

Dr 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

Dr 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

Dr 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

Dr 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

Dr 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

Annex C: Contact List

ANNEX C 7/29/97

List of Persons Contacted

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Paul Delay, M D , Chief, HIV-AIDS Division, Office of Health and Nutrition
Felice Apter, Ph D , Research Advisor, Research Division, Office of Population
Jeffrey Spieler, M S , Chief, Research Division, Office of Population

Former USAID Staff

Dr Jeanine Buzy, former Technical Advisor to Population Council Microbicides Project, P O Box 1404, Bathurst, NSW, Australia Tel 063-376-649, E-mail jbuzy@ix net au

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C Elizabeth McGrory M P H Staff Program Associate
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Christopher J Elias, M D , M P H , Senior Staff Associate

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* Ms Amparo Claro, WHAM
Latin American and Caribean Women's Health Network
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* Dr Geeta Rao Gupta, President, International Center for Research on Women
Tel 202-797-0007
- Ms Lori Heise WHAM and Co-Director, Health and Development Policy Project
(see WHAM listing)
- Muriel Harris, WHAM and Past President, Society for Women and AIDS in Africa (SWAA), a regional network based in 28 African countries
(see WHAM listing)
- Judy Norsigian, Boston Women's Health Book Collective (see symposium listing)
- Cindy Pearson, Director, National Women's Health Network
Tel (202) 347-1140
- Henry Gabelnick CONRAD (see HTSP documents)
- Rebecca Cabral CDC
Tel (770) 488-5250
- Penelope Hitchcock, NIAID (See Symposium listing)
- Kate Irwin, CDC (See Symposium listing)
- Zeda Rosenberg, NIAID (See Symposium listing)
- Susan Wood, WHAM and International Women's Health Coalition (see WHAM listing)
- Allen Rosenfield Dean Columbia School of Public Health Allan Rosenfield
Dean Columbia University School of Pulic Health
600 W 168th St
New York New York
Tel (212) 305-3929
- Jodi Jacobson Health and Development Policy Project
(see listing for Lori Heise)
- Dr Barbara Brummer, Johnson & Johnson (See WHAM Symposium)
- Ms Julia Scott, Director National Black Women s Health Project
Tel (202) 835-0117

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Harper, Michael J K et al Final Evaluation of the Population Council Programmatic Grant LTS Corporation for the U S Agency for International Development Office of Population, April 1994

U S Agency for International Development "USAID Microbicide Program Strategic Evaluation and Development [Scope of Work for Evaluation Team] " Arlington, VA USAID, 1997

U S Department of State U S International Strategy on HIV/AIDS Washington, D C U S Department of State, Under Secretary of State for Global Affairs, July 1995

ANNEX D 7/29/97

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USAID Documents

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Bruce Judith 1987 Users perspectives on contraceptive technology and delivery systems Highlighting some feminist issues Technology in Society 9 359-383

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UNAIDS Family Health International [FHI] AIDS Control and Prevention Project [AIDSCAP] Harvard University School of Public Health 1996 "Vancouver AIDS conference spec al report The epidemic now current status and latest trends of HIV / AIDS in Africa -- a consensus update "AIDS ANALYSIS AFRICA Aug-Sep 6(4) 14-5

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Heise, Lori and Dr Chris Dr Chris Elias 1995 "Transforming AIDS Prevention to Meet Women's Needs A Focus on Developing Countries" Social Science and Medicine Vol 40, No 7, pp 931-943

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Irwin, Katy 1997 Telephone conversation with Jill Gay July 14

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Cabral, Rebecca 1997 Phone conversation with and email to Jill Gay July 14

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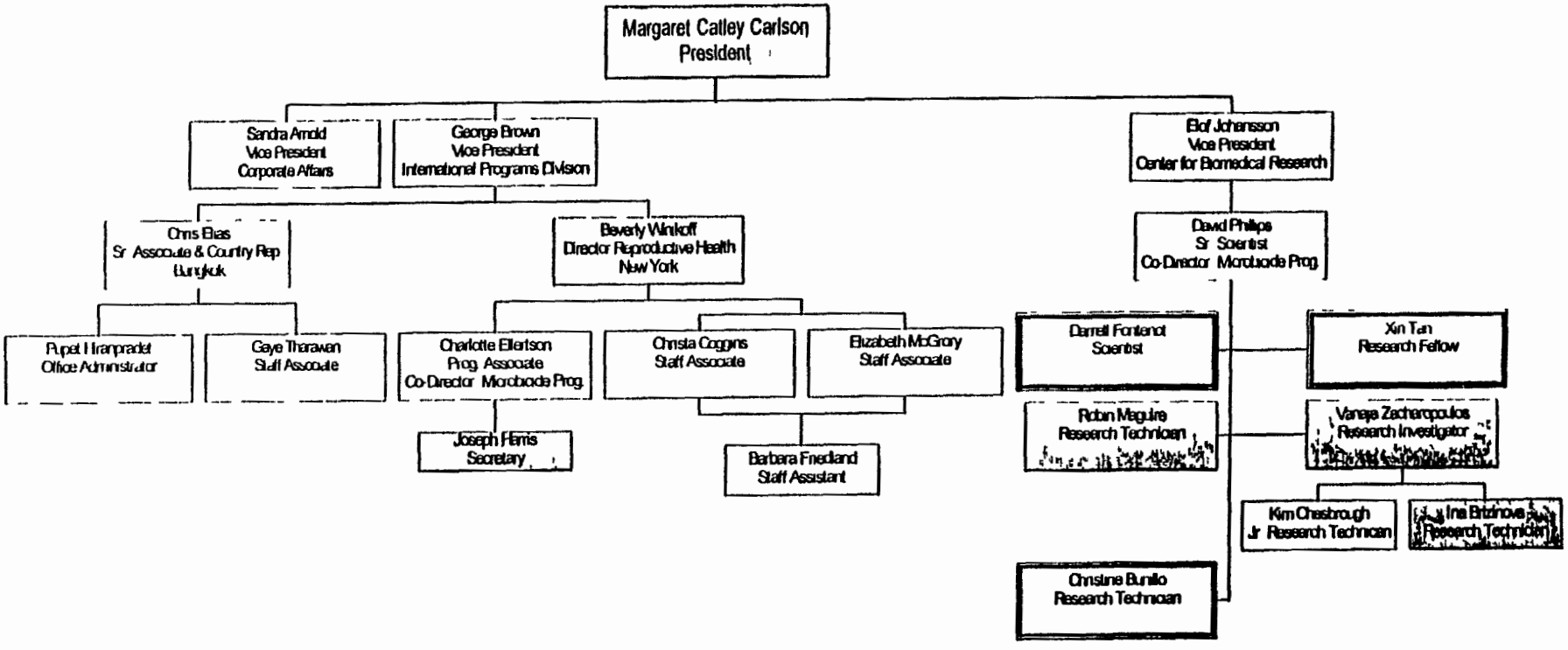
Annex E: Staffing Structure

Population Council Microbicides Program



Position not funded under Microbicide Program

Position vacant as of July 1997

Annex F: Microbicides Project Staff

Population Council – Microbicides Program
Salary Allocations

PROGRAMS DIVISION

George Brown, Vice President, Programs Division
Salary covered by unrestricted funds
(no funding from Microbicides Program)

New York Office

Beverly Winikoff, Director, Ebert Program
Salary covered by unrestricted funds
(no funding from Microbicides Program)

Charlotte Ellertson Program Associate
50% of salary covered by Microbicides Program
All microbicides funding from USAID

Christiana Coggins, Staff Associate
50% of salary covered by Microbicides Program
40% from USAID, 10% from Rockefeller

Elizabeth McGrory Staff Associate
16% of salary covered by Microbicides Program
All from USAID

Barbara Friedland, Staff Assistant to Christiana Coggins and Elizabeth McGrory
30% of salary covered by Microbicides Program
All from USAID

Joseph Harris Secretary to Charlotte Ellertson
No funding from Microbicides Program

Bangkok Office

Chris Elias, Senior Staff Associate
30% of salary covered by Microbicides Program
15% USAID and 15% Rockefeller

Punpet Hiranpradet Office Administrator
50% of salary covered by Microbicides Program
30% from USAID 20% from Rockefeller

Kanokwan Tharawan Staff Associate
50% of salary covered by Microbicides Program
30% from USAID 20% from Rockefeller

CENTER FOR BIOMEDICAL RESEARCH

Elof Johansson, Vice President
(no funding from microbicides)

David Phillips, Senior Scientist
40% of salary covered by Microbicides Program
30% from NIH, 10% salary from USAID

Darrell Fontenot, Scientist, (left in April 1997)
100% of salary covered by Microbicides Program
All from USAID

Xin Tan, Research Fellow (left in June 1997)
100% of salary covered by Microbicides Program
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Vanaja Zacharopoulos, Research Investigator
(no funding from Microbicides Program)

Robin MacGuire, Research Technician
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Christine Burrillo, Research Technician (left June 1997)
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Kim Chesbrough, Jr Research Technician
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All from Mellon

Ina Brizinova Research Technician (left June 1997)
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Annex G: List of WHAM Members

ANNEX G List of WHAM Members

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Annex G: Microbicide Publication List

PUBLICATIONS funded in whole or in part by USAID

International Programs Division

Coggins C Elias CJ et al A Study of Women s Preferences Regarding the Formulation of Over the Counter Vaginal Spermicides (submitted to *AIDS*)

Coggins C Madrigal M Llamas A Men's Attitudes Toward Vaginal Product Use Farmers and Taxidrivers in Mexico (will be submitted to *International Family Planning Perspectives* summer of 1997)

de Zoysa I, Elias CJ, Bentley M, Efficacy Trials of Vaginal Microbicides What HIV Prevention Services Should be Provided to Trial Participants? *WHAM/Population Council Symposium on Practical and Ethical Dilemmas in the Clinical Testing of Microbicides*, April 1997 (being prepared for publication)

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

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

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Elias CJ, Heise LL and E Gollub "Women Controlled HIV Prevention Methods " In *AIDS in the World II* Cambridge The Global AIDS Policy Coalition, 1996

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Tharawan K, Ellertson C and Elias CJ Men s and Women s Attitudes About the Use of a Potential Microbicide A Study in Chiang Rai, Thailand (being prepared for publication)