

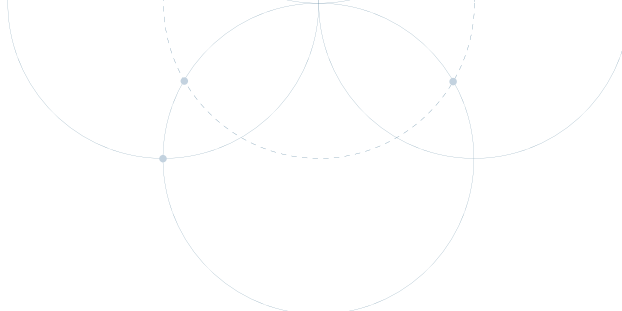


# MAPPING THE MICROBICIDE EFFORT

A Companion to the *Microbicide Development Strategy*



**Alliance for Microbicide Development**  
March 2007



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## ACKNOWLEDGEMENTS

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As described in the *Introduction*, this document is the combined product of reporting by more than 30 leading microbicide research, development, and advocacy organisations during 2006. First acknowledgements, therefore, go to the many individuals who took the time to compile and present this information at the Alliance for Microbicide Development meeting in March 2006, and then to review this document in December 2006 to ensure updated and accurate reporting.

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# INTRODUCTION

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*Worldwide, women account for nearly half of all new HIV infections each year and, in parts of the world, that proportion rises steadily. For many women, for many reasons, abstinence, sexual fidelity, or condom use are not feasible strategies for reducing their vulnerability to HIV and sexually transmitted infections (STIs). Microbicides are a new class of products being developed to address this clear and urgent need, and microbicide development efforts have been growing and accelerating. More funders have stepped forward to provide support and, each year, there is new scientific progress and knowledge to report. Yet as the microbicide field expands in scale and diversity, all stakeholders are challenged to advance their work in a larger and more complex arena.*

## **Background**

### *Microbicide Development Strategy*

In 2004, the donors funding the first wave of microbicide effectiveness trials met to discuss ways to learn as much as possible from those trials and enhance information-sharing and harmonisation across the microbicide field. The formation of a Microbicide Donors Committee and the idea of the *Microbicide Development Strategy* emerged from recognition of substantial changes across the microbicide field. Microbicide science had advanced; a few pharmaceutical companies had taken significant steps toward some level of involvement; an increase in the number of donors had elevated overall funding levels; candidate products were poised for large trials; and advocacy efforts had steadily raised attention to the microbicide agenda in general. All this highlighted the importance and urgency of more strategic communication, coordination, and allocation of resources.

The goal of the *Strategy* was to identify the most critical gaps in global efforts to develop and deliver microbicides, highlight the main obstacles to resolution of these gaps, and recommend priority actions for overcoming them.\* Four Working Groups were formed to pursue that goal in the areas of basic sciences and pre-clinical development, clinical research, manufacturing and formulation, and commercialisation and access. Priority Gaps and Actions were organised into the key areas requiring additional basic and applied knowledge, more comprehensive or systematic approaches, greater leadership and participation, expanded physical infrastructure and human capital, and/or increased funding or other resources. The result of what was a year-long

\* *Table A1* in the *Appendices* to this document summarises the gaps identified and the actions recommended by the Working Groups, informed by additional expertise and review throughout the *MDS* process. For a full account, readers are urged to go to the Alliance web site ([www.microbicide.org](http://www.microbicide.org)), where the entire *MDS* is available as a PDF; hard copies and/or CDs are also available from the Alliance. For commentary or questions on the *MDS*, or to request hard copies, contact the Alliance at: [info@microbicide.org](mailto:info@microbicide.org); tel +301-587-9690.

process of consultations involving more than 100 experts from more than 60 organisations was the *Microbicide Development Strategy* document formally launched at the XVI International AIDS Conference in Toronto in August 2006 and, since then, widely distributed.

### *Mapping the Microbicide Effort*

When the first draft of the *MDS* was presented to the Donors Committee in London in November 2005, they suggested that the *Strategy* could be even more valuable to donors, researchers, developers, and advocates if there was an additional complementary exercise that would “map” current and immediately prospective activities in the microbicide field against the priorities identified. In response to that request, the Alliance invited key organisations working in microbicide research, development, and advocacy to take the opportunity of the Alliance’s Annual Meeting in March 2006 to report on their activities, using the framework of the *MDS* Priority Gaps. Additional organisations were contacted thereafter with the same invitation. In November, a draft document chronicling those reports was sent to all organisations for review and updating. Altogether, more than 30 organisations have responded and *Mapping the Microbicide Effort* is the result of this process.

### **The Intent and Structure of This Document**

The goal of the Mapping Exercise is to generate a succinct yet comprehensive review of the current work and future plans at key organisations engaged in microbicide research and development. It is intended to be a “living” document, to be updated regularly using a similar data-collection and review process, so it serves a pulse-taking function for the microbicide field without requiring that the *MDS* itself be rewritten in full. As the first of this sort of review, *Mapping the Microbicide Effort* is meant to contribute to ongoing dialogue, to encourage fresh perspective and synergistic activity, and, for areas that are emerging or where there is relatively little activity, to encourage new attention and investment. Ultimately, this document is a “catalogue of opportunity”, describing specific areas of work that must be supported now to hasten the day when safe, effective, acceptable, and affordable microbicides are used to prevent HIV worldwide. It is our hope, in its next iteration, to integrate the Mapping Exercise with the work of the HIV/AIDS Vaccines and Microbicide Resource Tracking Group, so that it can assist in providing useful and targeted information about the levels of funding required to implement priority actions in a way that can guide investment with maximum efficiency and effectiveness.

*Mapping the Microbicide Effort* is divided into five chapters, the first four responding to each of the *MDS* Working Group areas of focus. The fifth chapter, “Looking Ahead”, first attends to a theme that cross-cuts all of the Working Group areas: the monitoring and advocacy that contributed so importantly to bringing the field to where it is today. The chapter then proceeds to “What Is Needed Now”, which lists the areas that were highlighted during the

mapping process as remaining neglected and/or demanding more urgent and particular attention over the coming year. These include: support for basic and pre-clinical research and focus on key emerging questions; increasing the number and diversity of microbicide candidates in the development pipeline and ensuring their rational advancement through that pipeline; organising and sharing data on markers and models; exploring alternative approaches to clinical trial design; analysing measures of adherence and strategies for consumer research in clinical studies; scaling up capacity at clinical study sites and using available resources more strategically; and compiling data and fostering forums for communication and information exchange.

### **Caveats**

Because it is a first attempt, the authors know that they cannot have achieved utter completeness or even close to perfect balance across all the ongoing and planned work to find a safe, effective, and affordable microbicide for the many worldwide who could benefit from it. This is, like that work, an “effort”, and we ask our readers for their tolerance and all suggestions about how it might be strengthened and made as useful as possible to all concerned.

### **With Appreciation**

The progress of the microbicide field was made possible by dozens of groups and hundreds of researchers and advocates, who in turn were supported by a growing number of donors, both from the public and private sectors. Because there are too many to name in the body of this document, the groups, individuals, and donors engaged in the microbicide development effort are listed in the *Appendices* to this report, with the effusive appreciation that they all deserve.



## BASIC SCIENCES AND PRE-CLINICAL DEVELOPMENT

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### PRIORITY ACTIONS

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*Microbicide Development Strategy, p.28*

- Develop and validate *in vitro* and *in vivo* model systems suitable for carrying out the types of experimental studies needed to address the key scientific questions
- Identify, develop, and validate biomarkers that correlate with relevant *in vivo* properties
- Build and certify 2-3 Good Laboratory Practices (GLP) reference labs
- Establish mechanisms for bringing expertise from other scientific areas and settings into the microbicide field
- Establish expert task forces that work collaboratively on key issues

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### 1.1 Expanding the basis for microbicide discovery and design

*The fundamental ongoing need in the area of basic sciences and pre-clinical research is to expand the foundation of knowledge on which this research rests. The microbicide effort depends on the advancement of more and improved products in the pre-clinical pipeline. Designing those products relies on understanding the physiology and ecology of the genital tract—the roles of target cells for the transmission of HIV and other sexually transmitted infections (STIs), the protection afforded by innate and adaptive immune defences, and the ways in which microbicides might enhance or interfere with these dynamics. This knowledge is also needed to inform the development of model systems and surrogate markers of safety and efficacy to support rapid, efficient evaluation of new product concepts. Finally, innovative translational research technologies are required to allow researchers to rationally consider, screen, and advance the most promising ideas.*

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### CURRENT REPORTED WORK

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Scientists at research institutions and universities, small biotechnology ventures, and organisations such as CONRAD, the International Partnership for Microbicides (IPM), and the Population Council have shaped a substantial knowledge base for microbicide development.<sup>1,2,3</sup>

\* See Table A2 in the *Appendices* to this document for a summary list of microbicide candidates in pre-clinical development as of February 2007.

Much of this work was made possible by funding from public and philanthropic sector sources in Europe and North America, of which the most recent examples are the following:

- The **Foundation for AIDS Research (amfAR)**<sup>†</sup> awarded nearly US\$1 million<sup>‡</sup> for eight new grants to advance understanding and prevention of rectal HIV transmission, half of which will be dedicated to basic and translational research at Johns Hopkins School of Medicine, Magee-Womens Research Institute and Foundation, St. George's Hospital Medical School, and University Hospital Zurich.

- The **Bill & Melinda Gates Foundation** and **Wellcome Trust** gave a “Grand Challenges in Global Health” grant of US\$19.7 million to St. George's for design of novel antigens and delivery strategies for vaginal mucosal protection.

- The **European Commission (EC)** awarded US\$20 million to support the European HIV Enterprise (EUROPRISE), a Network of Excellence mandated to focus on vaccine and microbicide research. Coordinated by Karolinska Institutet, Novartis, and St. George's, the consortium will support research at 32 institutions in 10 European countries. The EC also funds discovery and translational research under two multi-year integrated projects, the European Microbicides Project (EMPRO) and SHIVA, and two Specific Targeted Research Projects (STREP), Allomicrovac and VirApt, together involving 85 partners at a funding level of US\$44 million.<sup>4</sup> New microbicide calls will come in 2007.

- The **National Institutes of Health (NIH)** issued a Request for Applications (RFA) for “MIP II”, the second round of its Microbicide Innovation Program (MIP), committing US\$3 million for FY2007 for 10-15 new R21/R33 phased innovation/development grants. NIH also issued an RFA for an additional US\$3 million for 2-3 new U19 grants under its Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP-HTM). Support for these programmes comes from the **National Institute of Allergy and Infectious Diseases (NIAID)**, **National Institute of Child Health and Human Development (NICHD)**, **National Institute of Mental Health (NIMH)**, and **Office of AIDS Research (OAR)**. These new awards will be added to the existing NIH portfolio of integrated efforts, which includes the Partnerships for Topical Microbicides and the STI-Topical Microbicide Cooperative Research Centers (STI-TM CRC) supported by NIAID's Division of Microbiology and Infectious Diseases (DMID).

## **1.2 Identifying, developing, standardising, and validating surrogate markers and models**

*Reliable and validated surrogate markers in defined models could help predict the clinical safety and efficacy of candidate microbicides prior to initiating large-scale clinical studies, thereby*

<sup>†</sup> For conciseness, this document will present the entire name of each entity cited at its first use, and thereafter use its acronym. (Full names and acronyms of organisations appear in the *List of Organisations Involved in the Microbicide Effort* in the Appendices to this document.)

<sup>‡</sup> For simplicity, all funding amounts are presented in US dollars.



*enhancing decision-making and reducing costs and risks at all stages of development. A central area of effort is therefore to identify potential correlates of HIV/STI exposure and microbicide use, safety, and efficacy; validate these across in vitro, animal, and clinical studies; and make these data centrally accessible to all researchers.<sup>5</sup> In the MDS, this area was flagged as a crucial cross-cutting topic of relevance for basic and pre-clinical science, clinical research, and product formulation and delivery.*

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## CURRENT REPORTED WORK

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Table 1 provides an overview of efforts to develop and test assays and models that could serve evaluation needs along the pre-clinical and, eventually, the clinical portions of the microbicide pipeline. Some of these efforts are explicitly meant to serve the microbicide field as a whole; others are geared towards furthering specific candidates, although those efforts may eventually be shared with the entire field through presentations at meetings, publications, or partnerships.

The following is a list of additional details provided by respondents to the Mapping Exercise about activities related to the development of surrogate markers and model systems:

- The **Centers for Disease Control and Prevention (CDC)** has evaluated eight microbicide candidates in its epithelial cell line model and in cervicovaginal and colorectal explants. CDC plans optimisation of two multiplex assays for studying response to microbicide application in non-human primates (NHP); a quantitative ELISA format comprising 19 different cytokines and chemokines; and a cellular gene expression profile comprising 22 markers of cellular apoptosis, activation, and cytokine expression. Milestones in 2007 include an NHP study to compare topical products with known toxicity profiles that could provide guidance for a similar approach during human trials, and continuation of ongoing collaboration with sponsors to screen candidate products in NHP models.
- **CONRAD** is planning animal studies to determine whether CD4+ T-cells, dendritic cells, or macrophages are the initial targets for HIV transmission; whether initial capture of virus by the vaginal epithelium promotes access to HIV-1 target cells; and whether vulnerability to HIV transmission is influenced by natural persistence of immune-activated vaginal target cells, stage of reproductive cycle, microflora fluctuation, and/or immune responses.
- **INSERM, Istituto Superiore di Sanità (ISS), Institute of Tropical Medicine (ITM), and Leuven Catholic University** recently completed a two-year US\$1 million project to develop an *in vitro* epithelial model for microbicide evaluation, funded by the Agence Nationale de Recherches sur le SIDA (ANRS).
- **IPM** is developing models for safety and efficacy in non-human primates and smaller animals for assessing cytokine expression. IPM is focused on comparative evaluation of candidate microbicides combining entry and fusion inhibitors, and is supporting work on an

**TABLE 1 MODELS TO EVALUATE CANDIDATE TOPICAL MICROBICIDES ACROSS THE DEVELOPMENT PIPELINE**

MODEL TYPES	ADVANTAGES	LIMITATIONS	RESEARCH INSTITUTIONS WORKING WITH THESE MODELS
Innovative screening tools	<p>Rapid screening of promising compounds before evaluating in more labour-intensive and time-consuming models</p> <p>Potential that inclusion of measurements of innate immune mediators and changes in intrinsic antimicrobial activity might provide biomarkers to predict safety</p> <p>Increasing recognition of contribution of non-HIV STIs promotes value of assessing activity against those infections</p>	<p>Possibly premature disqualification of compounds whose value might be enhanced by formulation and/or combination with others</p> <p>Measurement of non-HIV STIs as trial endpoints is complex</p>	<p>Agence Nationale de Recherches sur le SIDA (ANRS)</p> <p>Boston University School of Medicine</p> <p>Dartmouth Medical School</p> <p>Drexel University College of Medicine</p> <p>Harvard Medical School/Brigham and Women's Hospital</p> <p>Indevus Pharmaceuticals</p> <p>Microbicide Quality Assurance Program and Southern Research Institute (MQAP/SRI)</p> <p>Mount Sinai School of Medicine</p> <p>University of Central Florida</p> <p>University of Pennsylvania School of Dental Medicine</p>
Tissue explant models (e.g., vaginal, cervical, colorectal, tonsil)	Model providing surface for gel and interaction among multiple cell types	Cell and tissue availability, sample size, viability, function, and isolation from systemic elements	<p>ANRS</p> <p>Centers for Disease Control and Prevention (CDC)</p> <p>Dana-Farber Cancer Institute</p> <p>Drexel University College of Medicine</p> <p>Harvard Medical School</p> <p>Institute of Tropical Medicine (ITM)</p> <p>Istituto Superiore di Sanità (ISS)</p> <p>Leuven Catholic University</p> <p>MatTek Corporation</p> <p>Mount Sinai School of Medicine</p> <p>MQAP/SRI</p> <p>St. George's Hospital Medical School</p> <p>University of Pennsylvania</p> <p>University of Pittsburgh/Magee-Womens Research Institute and Foundation</p>
Small animal models (e.g., HIV/HuPBL-SCID mice)	Model of <i>in vivo</i> vaginal challenge; direct detection of potential microbicide toxicities	Correlation not yet confirmed with dynamics of human transmission and protection	<p>INSERM</p> <p>Institute of Human Virology, University of Maryland School of Medicine</p> <p>Johns Hopkins Bloomberg School of Public Health</p> <p>ReProtect, Inc.</p> <p>Southern Research Institute (SRI)</p> <p>University of Alabama at Birmingham</p>
Non-human primates (e.g., SIV or SHIV/ macaque model)	Similar cervicovaginal and rectal environments to humans; defined challenge models	Cost and availability; correlation not yet confirmed	<p>California National Primate Research Center (NPRC)</p> <p>CDC</p> <p>CONRAD</p> <p>MQAP/SRI</p> <p>Tulane NPRC</p> <p>University of Texas Southwestern at Dallas</p> <p>University of Washington NPRC</p>
Evaluation tools for clinical trials (e.g., lab monitoring and proficiency testing, assessing innate immunity/inflammatory processes, evaluating adherence to protocol)	Quality assurance monitoring tools essential for detection/correction of deviations in pre-analytical/analytical/post-analytic processes at on-site laboratories	Lack of comparative assessment, consensus, standardisation, and coordinated training strategies	<p>Dartmouth Medical School</p> <p>Indevus Pharmaceuticals</p> <p>MQAP/SRI</p> <p>Mount Sinai School of Medicine</p> <p>Population Council</p> <p>University of Central Florida</p> <p>University of Pittsburgh/Magee-Womens</p> <p>Medical Research Council of South Africa, HPRU</p>

RT-SHIV macaque model for testing NNRTI-containing products and a PCR-based assay to detect and quantify SHIVs in a mixed challenge stock.<sup>6</sup>

- The **Microbicides Development Programme (MDP)**, supported by the UK Medical Research Council (MRC) and Department for International Development (DFID), is undertaking investigation of cytokine profiles as surrogate markers, and will expand this work to compare *in vitro* and *in vivo* cytokine responses using Luminex® technology for measuring multiple analytes.

- The **Microbicide Quality Assurance Program (MQAP)**, first established by NICHD and supported by NICHD and NIAID, comprises: 1) an Explant Model Project, with five laboratories using three tissue types to compare and perhaps standardise pre-clinical testing protocols<sup>7,8</sup>; 2) an Innate Immunity Project, evaluating soluble innate factors in genital secretions from HIV-positive and -negative women to determine possible associations with HIV transmission; and 3) a Cytokine Advisory Group, with 12 laboratories assessing cytokines as biomarkers of inflammation, their reproducibility across laboratories, and potential for establishing a “pre-proficiency” cytokine panel.<sup>9</sup> All data are entered into the Microbicide Research and Development Portfolio (MRDP) for collation and analysis.<sup>10</sup>

- The **Microbicide Trials Network (MTN)** has a Network laboratory that performs a range of *in vitro* tests for microbicides and their activity against HIV, sexually transmitted pathogens, and constituents of the vaginal flora. Assays used to evaluate activity of microbicides against HIV include cellular assays and cervicovaginal and rectal explant models. The MTN laboratory also incorporates assessment of cytokines and other innate immune factors in its Phase 1 microbicide studies. These measures of potential genital tract inflammation will be correlated with clinical assessment and colposcopy in Phase 1 studies and with safety and effectiveness outcomes in larger trials.<sup>11,12</sup>

- **NIAID’s Division of AIDS (DAIDS)** provides ongoing contract-supported resources for: *in vitro* screening of candidate microbicides; antiviral testing (HIV, HSV); chemical synthesis; pharmacokinetics; and toxicology evaluations including NHP safety and efficacy determinations, rabbit vaginal irritation testing (RVI), reproductive toxicity, and carcinogenicity.

- **NIAID’S Division of Microbiology and Infectious Diseases (DMID)** supports the STD Prevention Primate Unit for pre-clinical evaluation of topical microbicides and vaccines at the University of Washington. Results from this contract are coordinated with the NHP testing programmes supported by DAIDS.

- The **Population Council** continues its ongoing efforts to optimise techniques to isolate epithelial and dendritic cells, and refine assays that measure transfer of virus to these cells.

- **ReProtect, Inc.** has developed animal models for various assessments of cell-associated HIV, chlamydia, herpes, and gonorrhoea; a model for assessing the role of low vaginal pH in impeding HIV transmission; and a model allowing direct detection of microbicide-induced toxicities that paradoxically enhance susceptibility to infection.

### 1.3 Ensuring collaboration and engaging new expertise

*Two of the recommended actions of the MDS Basic Sciences and Pre-clinical Working Group were formative: establishing mechanisms for attracting expertise from other scientific areas and settings into the microbicide field, and convening expert task forces to work collaboratively on key issues.*

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#### CURRENT REPORTED WORK

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The members of this Working Group who made these recommendations, and some of the experts who advised them, are leaders within organisations that have actively recruited and encouraged new engagement of a range of academic and industrial experts. The productivity of those recruitments is evident, yet forging research-focused collaborations that bridge areas of expertise and engage new disciplines has been, so far at least, challenging and infrequent. There are two examples to date that respond to these two recommended actions:

- **CONRAD** and the **Alliance** co-sponsored a conference on the discovery and early validation of biomarkers for evaluating vaginal microbicides and contraceptives. The first of its kind in the microbicide field, the meeting convened experts within that field and from complementary fields to explore the status and potential of biomarkers of semen exposure, cervicovaginal inflammation, and HIV/STI infection. The meeting also established linkages for continuing interaction and expanded collaborations, and is generating a report for wide distribution.<sup>13</sup>
- Investigators in the **MTN** and the **Adolescent Medicine Trials Network (ATN)**, which is supported by **NICHD**, **NIDA**, and **NIMH**, have forged a collaborative relationship to design and conduct microbicide clinical trials in the United States. This collaboration will help bring ATN's experience in conducting clinical trials with adolescents, as well as with sites capable of enrolling adolescents, into the MTN clinical trials effort.

### 1.4 Building and certifying GLP reference labs

*The MDS signalled the need for two related activities: establishment of a centralised specimen bank containing clinical samples and associated data from past, current, and future safety trials; and establishment of centralised facilities with Good Laboratory Practices (GLP) certification that could provide researchers with standardised analytical tools.*

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#### CURRENT REPORTED WORK

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- The **Microbicide Quality Assurance Programme (MQAP)** is the only reported effort that explicitly responds to the second of these identified needs, although work planned within the MTN has clear potential for response in this area.
- The MTN is exploring strategies for strategic conservation of clinical samples and associated data. Still, establishment of such capacity is site-dependent, demanding, and costly, so initiatives in this area remain essentially unattended.



## CLINICAL RESEARCH

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### PRIORITY ACTIONS

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*Microbicide Development Strategy, p.48*

- Develop inventory of potential research sites/assessment of readiness, to be shared with product developers and sponsors
- Increase capacity of clinical research sites to recruit, train, and retain staff
- Document full costs of ongoing clinical studies
- Develop transparent processes whereby clinical research sites can seek to implement studies with different sponsors and investigators
- Develop new local and international consensus statements for responsibilities and standards of care in HIV prevention research
- Expand efforts to document and evaluate research methods for measuring behaviours related to sex and condom/product use
- Create international database of safety and other data from all microbicide products and studies
- Establish ongoing dialogue between trial investigators and regulators

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### 2.1 Building clinical research infrastructure and capacities

*To accelerate the development of microbicides (and HIV vaccines, pre-exposure prophylaxis, and other new and potential HIV prevention interventions), there will have to be ongoing investment in clinical space and services, central laboratory and data-processing capacity, and appropriately qualified and experienced clinical research staff. Of comparable importance is the parallel need for local communities to be informed partners in clinical research, and for steady leadership throughout that will engage individuals and constituencies in the development endeavour.<sup>14 15</sup>*

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### CURRENT REPORTED WORK

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Clinical research infrastructure and staffing for ongoing or prospective microbicide research is being supported and mobilised in more than 20 countries and 60 clinical research sites by more than 15 international organisations (see *Table 2* on p.14 and *Table A3* in the *Appendices* of this

document for further information). As of December 2006, four candidate microbicides were in Phase 2B and Phase 3 trials involving more than 23,000 study participants in 10 countries.<sup>7</sup> Seven more candidates are in earlier stages of clinical testing, generating data that could lead to more large-scale trials in the next few years. Some of these efforts are linked through international networks and partnerships; in 2006, for example:

- The **European Developing Countries Clinical Trials Partnership (EDCTP)** announced an international capacity-building effort for microbicide clinical research sites. Beginning in 2007, EDCTP will allocate approximately US\$18.5 million to partnerships with the UK Medical Research Council (MRC/UK), London School of Hygiene and Tropical Medicine (LSHTM), and Academic Medical Center/University of Amsterdam (AMC), to support seven clinical sites in Africa.

- The EC announced a three-year (2007-09) award to the **IPM**, including support to the **Institute of Tropical Medicine (ITM)**, for development of up to eight trial sites in Kenya, Rwanda, South Africa, and Zimbabwe, and for associated efforts to build community participation in the work of those sites.

- The **NIH Microbicide Clinical Trials Network (MTN)** rests on the foundation laid by its predecessor, the **HIV Prevention Trials Network (HPTN)** which, between 1999 and 2006, had completed five microbicide trials at nine sites (eight in the United States and one in India) and implemented important assessment and preparedness work at eight sites in Africa. The MTN proposes to complete 14 clinical trials of microbicides between 2006 and 2013 at 12 African sites and five US sites, and will carry forward both HPTN 035, the large effectiveness trial of BufferGel<sup>®</sup> and PRO 2000, and HPTN 059, a Phase 2 study of 1% Tenofovir gel.

## 2.2 Improving use of clinical research infrastructure

*Building human resources and physical infrastructure is not enough. There is consensus around the urgency of finding and applying clinical research approaches that would use existing and future infrastructure more efficiently. Attention is turning to alternative research designs: “minimalist” approaches to clinical research (rapid site assessment and training, limited scientific questions, relatively small enrolment numbers for test-of-concept studies) and “maximalist” approaches (extensive multi-year preparatory studies, pre-trial assessment of incidence and retention, large efficacy trials involving product-to-product comparisons and many nested sub-studies). Other actions that increase efficiency of research approaches include optimising sharing across trials to curtail unproductive redundancy, establishing reproducibility and validity of assays from multiple laboratories, and standardising in other areas that require such coordination to be maximally effective.*

<sup>7</sup> In late January 2007, the number of Phase 3 trials decreased to three with the closure of the cellulose sulphate trials.

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## CURRENT REPORTED WORK

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- CONRAD, Family Health International (FHI), NIH, the Population Council, and the US Agency for International Development (USAID) are attempting to streamline protocol development, clearance, and implementation processes to implement all their clinical studies more efficiently.
- CONRAD, IPM, and MTN are implementing new budgeting and cost reporting methods to better predict and control expenditures.
- The CTWG (often referred to as the “Quick” Clinical Trials Working Group due to the relative speed of its founding), led by the Alliance, has launched an exploration of alternative clinical trial designs. Its purpose is to link the knowledge of trialists and statisticians outside the microbicide field with the specific challenges faced in current and future trials of microbicides. This includes, but is not limited to, collaboration with a forthcoming Institute of Medicine committee examining methodological challenges in HIV prevention trials.
- FHI and IPM are collaborating on approaches to measure HIV and STI incidence more accurately before clinical trials begin, to ensure that calculated study recruitment and retention rates and follow-up duration are sufficient to determine effectiveness.
- FHI and MTN are writing guidelines to address trial participant drop-out rates caused by pregnancy and false-positive pregnancy tests,<sup>16</sup> and work is proposed for the design and acceleration of Segment 3 and carcinogenicity studies of microbicides to evaluate microbicide safety in pregnant women.
- The Global Campaign for Microbicides (GCM) is preparing guidance for clinical researchers for engaging community stakeholders; has begun a project to anticipate ethical requirements for control group interventions as new prevention strategies are determined to be partially effective; and, with the HIV/AIDS Vaccine Ethics Group (HAVEG) at the University of KwaZulu-Natal, is hosting an expert consultation to chart ways to resolve scientific and ethical-legal challenges posed by collecting data from adolescents.<sup>17 18</sup>
- IPM and VivoMetrics have developed a dynamic clinical trial cost model to aid in planning Phase 3 trials. The model includes: study size, statistical parameters, enrolment projections, and number of sites; costs associated with salaries, laboratory procedures, and facilities; and returns estimates of study size, overall timeline, timeline of participant visits, and cash flow.<sup>19</sup>
- NIAID’s DAIDS and DMID held a workshop to enhance standardisation across sites around the diagnosis and reporting of adverse events (AEs) encountered in topical microbicide trials. The outputs from that meeting—three detailed, graded tables for female and male genital toxicity and rectal exposure toxicity—are being widely shared and their application is already planned for three forthcoming trials.

**TABLE 2 MICROBICIDE CLINICAL RESEARCH SITES AS OF FEBRUARY 2007****Clinical sites supported for current or potential microbicide research\***

COUNTRY	SITES
Australia	Melbourne Sexual Health Centre
Belgium	Institute of Tropical Medicine, SGS Biopharma Research Unit
Benin	Centre National Hospitalier Universitaire, Projet SIDA 3
Botswana	BOTUSA Project
Ethiopia	Addis Ababa University
India	Jehangir Hospital, NARI/ICMR, St. John's Medical College, YRG Care
Kenya	Kenya Medical Research Institute (KEMRI)
Malawi	Lilongwe Central Hospital, Queen Elizabeth Central Hospital
Madagascar	Centre National de Recherche sur l'Environnement (CNRE), University of Antananarivo
Mozambique	Manhiça Health Research Center (CISM) Mavalane Hospital, Maputo
Nigeria	National Institute for Medical Research (NIMR/Nigeria), University of Ibadan, University of Port Harcourt
Rwanda	Projet Ubuzima
South Africa	Africa Centre for Health and Population Studies (ACHPS), CAPRISA, Farmovs-Parexel Clinical Pharmacology Research Unit, Medical Research Council HPRU, Orange Farm Clinic, RK Khan Hospital, University of Cape Town, University of KwaZulu-Natal, University of Limpopo/MEDUNSA, University of the Western Cape, University of the Witwatersrand RHRU
Tanzania	African Medical and Research Foundation (AMREF), Kilimanjaro Reproductive Health Project, London School of Hygiene and Tropical Medicine (LSHTM), National Institute for Medical Research (NIMR/Tanzania)



Thailand	Chiang Rai Health Club
Uganda	Makerere University Faculty of Medicine, Uganda Virus Research Institute (UVRI)
UK	St. Mary's Hospital
US	Baystate Medical Center, Bronx-Lebanon Hospital Center, California Family Health Council, Columbia University, Eastern Virginia Medical School, Emory University, Johns Hopkins Bayview Medical Center, New York University, Ohio State University, Oregon Health and Science University, University Hospitals of Cleveland, University of Alabama at Birmingham, University of California San Francisco, University of Cincinnati, University of Colorado at Denver, University of Pennsylvania, University of Pittsburgh Medical Center, University of Texas Southwestern Medical Center
Zambia	Kamwala Health Centre, University Teaching Hospital
Zimbabwe	Seke South Clinic, University of Zimbabwe

### Examples of organisations supporting clinical sites for microbicide research\*

Academic Medical Center, University of Amsterdam (AMC)  
 Adolescent Medicine Trials Network (ATN)  
 Centre for the AIDS Programme of Research in South Africa (CAPRISA)  
 Centers for Disease Control and Prevention (CDC)  
 CONRAD  
 European and Developing Countries Clinical Trials Partnership (EDCTP)  
 Fogarty International Center (FIC)  
 International Partnership for Microbicides (IPM)  
 London School of Hygiene and Tropical Medicine (LSHTM)  
 Microbicide Trials Network (MTN)  
 Microbicides Development Programme (MDP)  
 National Institute of Allergy and Infectious Diseases (NIH/NIAID [DAIDS and DMID])  
 National Institute of Child Health and Human Development (NIH/NICHD)  
 Population Council  
 Medical Research Council, South Africa (MRC/ZA)  
 Medical Research Council, United Kingdom (MRC/UK)  
 Wellcome Trust  
 World Health Organization (WHO)

\* See Table A3 in the *Appendices* for a summary of clinical trials as of February 2007. Further information on clinical studies and research sites is available at the Microbicide Research and Development Database (MRDD) on the Alliance web page, [www.microbicide.org](http://www.microbicide.org), and the NIH-sponsored [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

## 2.3 Improving measurements of behaviour

*Clinical trials of microbicides rely heavily on participant self-reports of sexual behaviour, condom use, and microbicide use. Yet self-reported data are subject to many forms of bias that can create uncertainty about the validity of trial results. This means that efforts to identify and standardise measures and surrogate markers that provide objective confirmation of HIV risk, exposure, and product use are of pivotal importance.*

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### CURRENT REPORTED WORK

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The shared wisdom at this point is that combinations of qualitative and quantitative approaches to motivating and evaluating study participant adherence to protocol are most likely to improve participant engagement and continuation in the trial, enhance protocol compliance, and generate plausible data. Groups leading the current effectiveness trials are engaged in various efforts towards these objectives:

- FHI has developed a training tool for clinic staff in qualitative behavioural research methods.
- MDP is collecting case report data on adherence and behaviour from all participants at regular intervals. Information is checked against applicator returns. This is complemented by more detailed data from a representative sub-sample in each site, covering the same period of sexual activity, and collected through coital diaries and in-depth interviews. These data are “triangulated” and any inconsistencies are followed up and resolved.
- MTN will continue assessment of adherence in sub-studies linked with protocols HPTN 035 and 059, integrate behavioural research into all its clinical studies, and build its capacity to do this through its Behavioral Research Committee (BRC) with support from NIMH.
- The **Population Council** is evaluating and comparing two data-capture modes: participant face-to-face interviews, and direct data entry by participants using Audio Computer-Assisted Self Interviews (ACASI).

The *Basic Sciences and Pre-clinical Development* section of this document urges attention to identification of biomarkers of product safety and efficacy, and their validation in clinical trials. It is similarly important to find other biomedical technologies that can be used in the trial context to quantify risk of exposure and product use and, in some cases, compare the results of such technologies with self-reported data:

- CONRAD has explored Prostate-Specific Antigen (PSA) as a possible biomarker of semen exposure and sexual activity, and reported on this work at the recent Biomarkers Conference.<sup>20</sup>
- IPM reports research on an ‘intravaginal accelerometer’ assay in a biocompatible silicone elastomer.

- The **Population Council** has developed and validated a dye process that indicates whether an applicator has actually been used vaginally.<sup>21 22</sup>

However, sexual behaviour hardly occurs in a vacuum. Thus, several groups are working not only to find better ways to measure trial-related behaviour, but to understand the contexts in which that behaviour takes place and the variables that affect it. For example:

- The **Research Foundation for Mental Hygiene, Inc. (RFMH)** and **Wayne State University** received awards in the latest round of amfAR grants for studies of HIV risk behaviour of relevance for understanding and preventing rectal HIV transmission.

Finally, there is the issue of synthesising the outputs from these various channels of effort, an imperative frequently remarked but to date unevenly implemented.

- The **CTWG** is collaborating on design of a consultation that will systematically compile and assess approaches used in HIV prevention trials to enhance as well as measure participants' adherence to clinical trial procedures and to product use. The consultation will determine what behavioural interventions and/or measures worked, what did not, how future trials can strengthen adherence and its measurement, and how this experience can or cannot be extrapolated to various forms of microbicide delivery for HIV prevention.

## 2.4 Ensuring HIV treatment and care

*Standards of care in clinical research settings have long been a focus of ethics discussions, with many meetings and papers commissioned by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO), among others.<sup>23 24</sup> Building on this dialogue and broader efforts to make HIV treatment available, the past two years have seen increases in institutional commitments and funding pledges to ensure HIV treatment and other related health care to individuals who either cannot participate in HIV prevention research because they are already HIV-positive or who seroconvert during the course of research.*

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### CURRENT REPORTED WORK

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All international research sponsors describe plans to monitor access and provision of treatment and care at the local level, and to strengthen site-specific protocols and commitments to treatment and care. This work includes monitoring and conducting site-to-site comparisons of referral protocols, treatment utilisation rates, quality of care, and health outcomes of seroconverters. More specifically:

- The **Centre for the AIDS Programme of Research in South Africa (CAPRISA)**, **IPM**, **MTN**, and the **Population Council** are in discussions with international HIV treatment and treatment research programmes (AIDS Clinical Trials Group [ACTG], Clinton Foundation, US President's Emergency Plan for AIDS Relief [PEPFAR], and the Global Fund to Fight

AIDS, Tuberculosis and Malaria) about how to fund treatment and care at HIV prevention research sites. There are precedents: CAPRISA, for example, already has an AIDS treatment programme funded by PEPFAR and the Global Fund that makes treatment and care available at all three of its clinical research sites.

- **CONRAD** and the **MTN Foundation** are incorporating into their clinical research strategies plans for allocating funding to ensure treatment and care at trial sites where required but not otherwise available.

- The **GCM**, **WHO**, and a number of advocacy groups working in HIV prevention research are engaged in global policy and advocacy to advance dialogue and build mechanisms and linkages for care in clinical research settings. GCM has a multi-disciplinary group tasked with designing durable mechanisms for use by research sponsors to ensure HIV treatment access for individuals identified as HIV-positive during clinical studies and, in consultation with the **Alliance** and the **CTWG**, is surveying to document standards of care at microbicide clinical research sites.<sup>25 26</sup>

## 2.5 Understanding consumer preferences and product use

*Understanding consumer preferences, needs, and levels of demand is at the epicentre of microbicide development. Microbicide formulations, packaging, and marketing all necessitate research on the context of whether, how, and how frequently consumers will use these products—consumers who will be, to a great extent, women living in settings heavily impacted by HIV. Understanding these consumers and their purchasing decisions in the context of gender and sexual relationships, in particular their social and cultural settings, will be crucial. And, because health care providers may act as consumer gatekeepers and procurement by public sector agencies may weigh heavily in global demand, factors affecting decision-making by these significant players must also be taken explicitly into account.*

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### CURRENT REPORTED WORK

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Over the past decade, what has been referred to as “acceptability research” was primarily theoretical or limited to small early-stage trials. This work and overall progress in the field make it both possible and necessary to evaluate product acceptability in much larger populations in later-stage clinical studies.<sup>27 28 29 30 31</sup> While such trials do not mirror conditions in which products will actually be used, they offer a distinctive and critical opportunity to collect data on likely consumer preferences and potential use, which could inform potential marketing and messaging. Thus:

- **All current late-stage trials** include some collection of data on microbicide acceptability and user perspectives, information that in most cases had also been gathered in earlier trials to

inform product development and, in some cases, in pilot studies prior to trial initiation. Some trial implementers also include limited efforts to do exit surveying whose purpose is to better understand trial participation and gather data that might help interpret primary, “intent-to-treat” analyses.

Yet going beyond such trial-specific acceptability research presents challenges. Large effectiveness trials are complex and hard to manage, and clinical researchers and site staff worry about data volumes and their own abilities to collect and analyse more data of any kind, even given incentives for doing so. This means that every increase of this data-gathering, whether biological, biomedical, or behavioural, must be considered strategically and with great care.

## 2.6 Increasing dialogue and information-sharing

*Communication among microbicide clinical researchers will have to be ramped up as new microbicides enter clinical evaluation, Phase 3 trials of microbicides and other prevention approaches increase in number, pressures on site capacities mount, and results from all effectiveness trials become available. The MDS urged the compilation of critical bodies of data, data-sharing, and dialogue among researchers around key issues and flagged as essential the need for ongoing dialogue between researchers and regulatory agencies with respect to further advancement of these products and, perhaps, the articulation of new clinical trial designs.*

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### CURRENT REPORTED WORK

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- **Voxiva**, with support from USAID through a grant to IPM, will set up an Asia-specific clinical trials portal as a companion site to its Africa Clinical Trials Portal ([www.africaclinicaltrials.org](http://www.africaclinicaltrials.org)). Both portals are intended to provide detail on trial sites as a basis for assessment of site capacity and potential for partnering.
- The CTWG (the “**Quick**” Working Group), led by the Alliance, is the first Working Group established under the aegis of the Microbicide Donors Committee, consisting of the leaders of all of the current later-stage microbicide trials. Meeting regularly to facilitate exchange of experience and learning from studies, the Group has inventoried commonalities and differences across all major elements of the respective clinical research protocols and precipitated establishment of a “Super Data-safety Monitoring Committee” (DMC), an independent group charged with reviewing the key safety outcome measures in ongoing and planned effectiveness trials. The CTWG has taken on hard common issues, including assessment of HIV incidence in trial sites and the implications of trial participant pregnancies, and most recently served as a nexus for considerations around the closure of the cellulose sulphate trials. As indicated elsewhere in this document, forthcoming work for this Group will focus on exploration of trial design options and the synthesis of critical behavioural data.



## MANUFACTURING AND FORMULATION

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### PRIORITY ACTIONS

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*Microbicide Development Strategy, p.70*

- Form a manufacturing, formulation, and supply logistics information exchange forum
- Expand consumer research to better understand consumer preferences, demand, and potential use of microbicides
- Support expansion of microbicide formulation groups
- Support innovation in formulation designs
- Conduct international market research in a variety of consumer markets and among major public sector purchasers to assess acceptability of various packaging and distribution methods at varying levels of projected efficacy and pricing
- Compare various formulations and delivery systems by means of a systematic, coordinated research effort involving paired *in vitro* and *in vivo* studies
- Assess products in development, using an expert team to identify commonalities and commercialisation issues, reduce processes to lowest common denominator, and speed commercial industrialisation
- Fund process development and scale-up of drug substances and product
- Develop strategic and tactical product development and marketing plans
- Identify large-volume manufacturers in low-cost regions and generate cost-of-goods projections
- Engage with national regulatory agencies in countries conducting efficacy studies before, during, and after studies, to achieve commercial licence in those countries

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### 3.1 Developing microbicide formulations

*Defining formulations that are both possible and preferable is crucial to microbicide development, yet, except for relatively few pioneering efforts, innovation in this area has been scantily attended and supported. More recently, researchers have been offering new ideas about formulation options: compounds with much more specific biological targets or novel mechanisms of action, new semi-solid or solid suspensions to hold and deliver these compounds, and new delivery devices such as*

sponges, diaphragms, cervical barriers, rings, and applicators. Yet many of these remain largely conceptual—described but not tested, or evaluated only in small quantities in laboratory-based evaluation and small animal models.

Table 3 organises some of these concepts in a way that might inform collaborations around their exploration and, as appropriate, their systematic implementation, since a major effort is needed to combine good ideas and convert them into well-characterised and consistently produced products for clinical evaluation.

**TABLE 3 FORMULATION GOALS FOR TOPICAL MICROBICIDES**

	ACTIVE PRODUCT INGREDIENTS (APIs)	DELIVERY SYSTEMS
<b>Formulation components</b>	Vaginal defence enhancers (such as acid buffering agents), surfactants, and antiviral agents (such as entry/fusion inhibitors and replication inhibitors)	Semisolids (gels, lotions, ointments, creams), solids/capsules, vaginal rings and sponges, cervical caps, diaphragms, applicators
<b>Formulate what is possible</b>	Select APIs with antimicrobial specificity, bioactivity, and likely safety and potency at appropriate volume and concentration	Select physical properties that will allow a functional barrier (to protect tissue) and/or API deployment and delivery (e.g., appropriate microbicide distribution and retention so that the active ingredient is released at the right time, place, and concentration)
	Ensure manufacturing feasibility by characterising the product's components and physical properties (e.g. miscibility, solubility, rheology, viscosity, stability), developing manufacturing processes and capacity, and manufacturing quality control procedures	
	Conduct <i>in vitro</i> and animal model studies of pharmacokinetics and pharmacodynamics to measure dissolution, bio-adhesion, distribution, safety, activity, and/or efficacy	
	Conduct clinical studies to evaluate safety (e.g., measurements of absorption or inflammation); the appropriate application site and volume; genital tract dissolution, bio-adhesion, and distribution; interaction with vaginal fluids and with semen; and clinical antimicrobial activity and efficacy	
<b>Formulate what is preferable</b>	Develop formulations that can be used and packaged in ways that will meet the preferences and needs of women and men around the world	

## CURRENT REPORTED WORK

- CDC is supporting development of gel formulation of Truvada™, a combination of tenofovir (a nucleotide analogue) and FTC (a nucleoside analogue) for *in vitro* and NHP evaluation. CDC has also completed an initial primate safety and size-fit study of a prototypic vaginal ring, and during 2007 will collaborate in manufacture of a UC-781-containing vaginal ring and evaluation of its efficacy in an NHP SHIV challenge model. In addition to screening compounds for collaborating partners, CDC is also conducting imaging studies to evaluate potential colorectal delivery and distribution of candidate microbicides.

- CONRAD is continuously screening and evaluating potential compounds for further pre-clinical evaluation as potential microbicides. Over the next four years (2007-2011), CONRAD plans to develop vaginal sponges, drug-releasing cervical caps, and advanced gel formulations, as well as combinations of these products. For each new product, CONRAD will correlate physical-chemical and structural properties with vaginal tissue absorption, secretion, and permeability. In 2007, CONRAD plans to do *in vitro* rheologic profiling with MRI studies.

- IPM has funded formulation experts and developed a GMP-compliant facility that can physically characterise and produce long-acting gels in sufficient quantities for Phase 1 and 2 studies. With this capacity, IPM is testing multiple dosage forms and formulating combinations of active product ingredients such as NNRTIs, NRTIs, R5 blockers, entry inhibitors, and polyanions, some in-licensed from pharmaceutical partners. In 2006, separate consumer use studies of three gel formulations were completed among women in Kenya, South Africa, and Zambia.<sup>32</sup>

- NIH, through its IPCP-HTM programme and the **Partnerships for Topical Microbicides**, and through general R01 grants in support of HIV researchers, continues its support for cutting-edge studies of baseline physiology and product transport, as well as development and biophysical evaluation of novel microbicide formulations at several research institutions including: Duke University, Johns Hopkins University, University of Pennsylvania, and University of Utah.<sup>33 34 35 36 37</sup>

- Osel, Inc., now that it has steady support from NIH and CONRAD, is able to focus attention on the challenges of formulating lactobacilli-delivered microbicide compounds.

- The **Population Council** has developed two new combination products—PC-815 (Carraguard® + the NNRTI MIV-150, which is targeted to HIV prevention) and PC-710 (Carraguard® + zinc, which may show efficacy in preventing herpes infection), and has conducted comparative studies of vaginal retention of these products in humans and non-human primates. In 2007 the Council will test PC-815 in Phase 1 trials in men and women, and file an Investigational New Drug (IND) application for PC-710 with regulatory agencies.

## Delivery Technologies

At the March 2006 Alliance Annual Meeting, where the *Microbicide Development Strategy* gap analysis and Mapping Exercise were discussed, several participants noted that the area of applicator technologies had been overlooked as an area for priority action. All the microbicides presently in large-scale clinical trials are delivered vaginally with the use of pre-filled single-use plastic applicators. However, for subsequent product iterations, different designs and packaging will be needed for both vaginal and rectal application and for different markets and consumer populations. While potential consumer preferences and likelihood of regular product use are



undeniably important factors to consider in formulation, cost is also critical. All delivery methods and devices constitute a significant product cost component that has to be considered from the outset.<sup>38</sup> Despite its importance, work to develop delivery technologies that meet these imperatives remains in its early stages.

- **IPM** is evaluating alternative delivery methods and devices for combination microbicides, including semisolids, solids, vaginal ring technologies, and applicators using new materials, and plans new studies of vaginal rings and gels to evaluate the distribution of product in the vaginal environment using MRI techniques.<sup>39</sup>

- **PATH** has completed cost analyses comparing different applicator designs, has done a scan of potential applicator manufacturers in South Africa and India, and is planning a study to determine cost “break points” for manufacturing different applicator designs, including pre- and user-filled applicators as well as cervical barriers. **PATH** is also doing initial product development for a dose-metered applicator that would allow users to fill and dispense the correct dose.

- **PATH** and **FHI** have also solicited guidance from the **US Food and Drug Administration (FDA)** on regulatory pathways for substituting alternative applicators for those used in the current trials. The FDA responded with guidance on the data that would be required, including data on user compliance and acceptability of the alternative applicator, which could be collected using a placebo.<sup>40</sup> **PATH** intends to facilitate further dialogue on this issue and, based on the FDA input, is actively evaluating the acceptability of a user-filled applicator and in 2007 plans to conduct further evaluations of this applicator with a microbicide.

- **ReProtect, Inc.**, has developed a novel reusable, one-size-fits-all diaphragm-like device trademarked **Duet™**, a platform technology for delivery of vaginal microbicides, spermicides, and vaginal therapeutics. **Duet** is likely to be first marketed as a contraceptive product with **BufferGel®**, a microbicide now in a late-stage clinical trial for HIV prevention, and is being evaluated in acceptability trials in Africa.

- The **Research Foundation for Mental Hygiene, Inc. (RFMH)** was just awarded an amfAR grant for development of a standard rectal microbicide delivery device. Work will begin in 2007.

### **3.2 Preparing for scaled-up manufacturing and commercialisation**

*In the 2005-2006 MDS process, experts flagged two serious gaps in microbicide production. The first was the difficulty associated with manufacturing and financing the product needed for clinical testing, an especially sizable challenge for large trials. The second—and not unrelated—gap was the prospective lack of infrastructure for low-cost/large-capacity production once a given candidate is found effective in clinical trials. At such time, the strategic planning and*

*infrastructure for manufacture and marketing must already be established, so that the traditional lag time between product licensure and market availability can be reduced—an issue of particular concern in the context of a deadly global epidemic.*

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## CURRENT REPORTED WORK

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- **CONRAD, IPM, and the Population Council** have begun to explore and actively evaluate options for low-cost, large-volume manufacturers for small molecule and polymeric microbicides scale-up and industrialisation in Canada, India, and South Africa.
- **IPM** also is also planning a worldwide survey and targeted audits of clinical manufacturing organisations.
- **Osel, Inc., Mapp Biopharmaceutical, and St. George’s** are attempting to address manufacturing challenges for protein microbicides.
- Companies that developed the microbicides presently in clinical trials—**Gilead Sciences, Indevus Pharmaceuticals, and ReProtect, Inc.**—have begun planning for scale-up but are hampered by limited resources.

### 3.3 Sharing product development information

*As microbicide development efforts have proliferated and experience has begun to accumulate, the need for a centralisation of all formulation work, delivery technologies, and manufacturing imperatives has become clearer. Collaboration is needed so that detailed information about formulations, manufacturing options, and pre-clinical and clinical data is readily shared across institutions.*

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## CURRENT REPORTED WORK

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- The **Alliance**, through its ongoing tracking of relevant published and “grey” literature, conferences, trade journals, and public media; its website, weekly *News Digests*, and *Alerts*; *The Microbicide Quarterly*; and its Microbicide Research and Development Database (MRDD), consolidates and reports a wide range of product development information and analysis.
- The **Microbicide Research and Development Portfolio (MRDP)**, established by **NICHD** and managed by **Social & Scientific Systems, Inc.**, interfaces with the Alliance MRDD and gathers, consolidates, and exchanges information about candidate microbicides as the basis for its efforts to develop, standardise, apply, and validate pre-clinical assays and analytic methodologies.
- **Product developers**, including **CONRAD, Gilead, Indevus, IPM, Population Council, ReProtect, and Starpharma**, with varying degrees of formality and regularity, communicate among one another and reach out to other product developers.



## COMMERCIALISATION AND ACCESS

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### PRIORITY ACTIONS

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*Microbicide Development Strategy, p.94*

- Draw in a new pool of expertise in key areas such as marketing and financing
- Fund demonstration projects that introduce and scale up access to existing and emerging prevention technologies
- Develop plans, protocols, and budgets to make products available in study communities after Phase 3 studies
- Develop forecasting and impact models of demand and costs to inform manufacturing scale-up and procurement decisions
- Determine how existing financing mechanisms for public goods can be applied and adapted for microbicide manufacturing scale-up, purchase, marketing, and delivery
- Engage regulatory experts to map registration and regulatory pathways, including strategies for over-the-counter status
- Develop a commercialisation and access planning working group to define business plans and roles for moving products from research to widespread use
- Clarify intellectual property arrangements for Phase 3 products, and determine implications for preferential pricing
- Launch research and education initiatives for key policy and communication challenges

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#### 4.1 Forecasting costs, demand, and commercialisation and access needs

*Without a proven product (and with a variety of mechanisms of action in the clinical or late pre-clinical parts of the pipeline), it is difficult to estimate the costs of product manufacture, procurement, and delivery. It is also difficult, despite accumulating data about microbicide acceptability and potential consumer interest, to integrate such data with market data on other analogous health products in order to extrapolate some kind of market forecast. Yet this sort of forecasting and normative work cannot wait, since it will be pivotal to plans for scale-up and informing policy and advocacy for donor and government financing for microbicides.*

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## CURRENT REPORTED WORK

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- The London School of Hygiene and Tropical Medicine (LSHTM) HIVTools Research Group, in partnership with the GCM, has worked for several years on population-based models to evaluate the likely impact of introducing microbicides of varying efficacies into different epidemiological settings. The models have been used in several ways: to develop case studies of possible microbicide impact in Benin, India (Karnataka State), and South Africa (Hillbrow, Johannesburg); to explore the potential impact of condom substitution at both the individual and population levels; and to assess the relative importance of microbicide STI-efficacy in reducing HIV-risk.<sup>41</sup> A dynamic version of the model is being prepared as a reference for policymakers and regulators.

- Also in anticipation of Phase 3 study results, the LSHTM is collaborating with the Microbicides Development Programme (MDP), which has policy research as part of its mandate and funding, to develop a policy brief on reconciling different understandings of efficacy and effectiveness as applied to microbicides trials and counselling messages.

- The LSHTM, also in partnership with the MDP, is developing a framework for cost projections for distributing microbicides, analysing national costs data from Population Services International (PSI) to estimate the costs of adding new products to social marketing programmes; and conducting a study in Johannesburg on willingness-to-pay that could inform discussions of pricing and market segmentation. If and when candidate microbicides in Phase 3 trials demonstrate any efficacy, MDP will revise these projections to reflect the characteristics of those products.

- ReProtect has supported development of cost projections for both BufferGel® and Duet™.

### 4.2 Defining licensing and intellectual property arrangements

*Each of the candidate microbicides now in development has a unique set of intellectual property constraints and considerations based on its origin, history of investment, and other issues. To avoid delays in global scale-up of access to effective microbicides, some advocates have argued for greater effort now to define intellectual property rights, licensing agreements, and technology transfer arrangements for products currently in Phase 3 studies.*

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## CURRENT REPORTED WORK

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- CONRAD has obtained non-exclusive public sector licences for UC-781, and Cyanovirin-N so that those products can be developed and made globally available as microbicides. CONRAD anticipates that this will ensure the mandatory favourable public sector

pricing and availability of these drugs, especially for UC-781, which is in the portfolios of several different organisations.

- **IPM** has in-licensed four compounds royalty-free to develop, manufacture, and distribute for use as microbicides in resource-poor countries, and ensures that all products being developed by IPM have clearly defined intellectual property and costing information.
- The **MDP** anticipates, given its agreement with **Indevus**, that intellectual property arrangements will not be an impediment to access and low pricing of PRO 2000 in developing countries. Currently, MDP and Indevus contract with a South African company, Lekoko PMC, for production of PRO 2000 gel for clinical research in that country.
- **Population Council** contracts provide that partnering companies such as Medivir will receive no royalties for sales of Carraguard® and related combination products in developing countries.
- **ReProtect**, as a commercial entity, carefully monitors intellectual property as a matter of standard procedure and is the holder of patents on BufferGel® and Duet™.

### 4.3 Clarifying pathways for regulatory review and product registration

*In an effort to design better products and test them more efficiently, microbicide researchers are developing new combination microbicides and new clinical study designs to screen and evaluate these products. Beginning in 2007, data will be released from the trials of microbicides in efficacy studies, as well as trials of other new prevention interventions, notably cervical barriers, HSV-2 treatment, and tenofovir used as pre-exposure prophylaxis (PrEP). This means that it is not too soon for regulatory agencies to be prepared to review data on all proposed products and study designs.*

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## CURRENT REPORTED WORK

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- **CONRAD** is working with the Government of India to facilitate eventual registration of microbicides at such time as a product is determined to be effective in a Phase 3 study.
- **IPM** has engaged a group to evaluate current microbicide efficacy study design requirements and actively engage experienced regulatory professionals to develop a strategy for addressing specific questions related to licensure. Research has been completed on regulation policies in Brazil, Canada, South Africa, Switzerland, the United States, and the European Commission.
- **MDP** plans to work with **Indevus** to seek licensure simultaneously in the United States and in trial countries (South Africa, Tanzania, Uganda, Zambia) if PRO 2000 is shown to be effective.

- **PATH** is working with Southern African regulatory bodies to determine regulatory recommendations for incorporating alternative delivery devices such as user-filled applicators into introduction strategies for this region.
- **ReProtect** regularly interfaces with the US FDA regarding contraceptive and HIV claims for BufferGel®; other developers and sponsors also engage in regular communication with the FDA on a case-by-case basis as needed in the course of advancing their candidate products.
- **WHO** has a particularly important role in this work: in collaboration with the **Alliance**, **CONRAD**, and, most recently, the **IPM**, WHO convened a series of global and regional policy dialogues with national regulatory authorities. These dialogues have recommended further action to facilitate national review of dossiers and approval of new products; support of national regulatory agencies with technical reviews; and capacity-building for national partners through provision of guidelines, rosters of experts, and trainings.

#### 4.4 Demonstrating commitments to access

*To have an impact, prevention products must be available. Unfortunately, there remains an enormous gap between the need for proven prevention technologies such as male and female condoms, clean syringes, and perinatal HIV treatment to prevent mother-to-child transmission (PMTCT), and access to those technologies.<sup>42</sup> Many organisations around the world are struggling to ensure such access, but none have fully embraced the mandate to ensure widespread availability of the newest products in high-need settings.*

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### CURRENT REPORTED WORK

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- **CAPRISA**, with support from **PEPFAR**, is strengthening its capacity for supply and distribution of HIV-related medicines and pharmaceutical products in South Africa, and notes that this programme could potentially include microbicides once they are licensed for use.
- **IPM** is supporting a study to model the impact of different introduction strategies in a range of settings and, in concert with a number of advocacy colleagues, is advocating for microbicide introduction to be included in plans for scaling up HIV/AIDS services in general. **IPM** has also commissioned a study to examine the likely funding requirements for introduction of future microbicides and assess the potential of existing and emerging funding mechanisms to meet these needs.
- **IPM** has also developed an important conceptual framework and timeline to sequence efforts needed for microbicide access, recommending parallel activities in early clinical research through to product launch and initial scale-up of microbicides.<sup>43</sup>

## 4.5 Engaging new expertise and energy

*Although a number of organisations do work that is directly or indirectly relevant to informing commercialisation, access, and introduction strategies, it will be ever more important, as commercialisation and access issues become more immediate, to engage new organisations and expertise in areas such as financing and marketing that typically lie outside the purview and experience of public sector and scientific research institutions.*

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### CURRENT REPORTED WORK

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- The consulting firm **HLSP** has been commissioned by IPM to initiate a study on the estimated costs of introducing microbicides in various scenarios.
- **MDP** will conduct exit interviews in a representative sub-sample of participants, to assess the accuracy of the adherence and behavioural data, and to explore acceptability and willingness to pay in order to inform future marketing strategies.
- The **Population Council** has set a date in early 2007 for a “Day of Dialogue” to explore insights and evidence from the introduction of other products in the fields of contraception, HIV/AIDS, and selected consumer product marketing and commercialisation efforts, and to learn from experience and identify key features that could inform the introduction of microbicides.

Public health policymakers also need to be made aware of the progress of microbicide clinical research, the policy options and evidence for needed decisions related to partially effective microbicides, and the potential impact of introducing microbicides as an additional strategy for HIV and STI prevention. Reported work to address policy and impact planning includes:

- The **Alliance**, traditionally in its own work and publications and as a core member of the **HIV Vaccines and Microbicides Resource Tracking Group** with the **AIDS Vaccine Advocacy Coalition (AVAC)**, the **International AIDS Vaccine Initiative (IAVI)**, and **UNAIDS**, regularly reviews and annually distributes the results of its survey of all global investment in and expenditures on microbicide research, development, and advocacy. The Tracking Group’s Report on 2006 funding is in preparation for late spring 2007 publication.
- The **Alliance**, as part of its forthcoming Annual Meeting, has designed, in conjunction with product developers, a panel discussion on the challenges facing developers over the next three years, including assessment of product safety (*e.g.*, long-term toxicology studies), assessing efficacy (*e.g.*, additional HIV trials that might be required by regulatory authorities), and industrialisation (*e.g.*, manufacture of registration batches, NDA submissions, commercial scale-up, and global plans for manufacture, registration, and distribution).

- MDP is communicating the potential impact of microbicides by using results from its modelling work, and is ready to integrate any data about partial or full clinical efficacy into these impact models if and when these data become available. MDP is also planning a desk study of communication issues related to partial effectiveness of family planning products.

#### **4.6 Convening a working group on commercialisation and access**

*During the 2005-2006 process of developing the MDS, the Commercialisation and Access Working Group recommended creation of a permanent working group to continue identifying strategic and collaborative work in this rapidly evolving area. Such a group could contribute to the field by identifying and attracting new expertise, building further momentum on issues of commercialisation and access, catalysing industrialisation planning for products, defining industrialisation plans and roles, monitoring progress, and exchanging information. It could also support political and public health decision-making by focusing attention and resources on modelling public health impact, the integration of fully or partially efficacious microbicides in a hierarchy of other HIV prevention, and health promotion interventions.*

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#### **CURRENT REPORTED WORK**

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- No work has been reported that responds to this recommendation.



## LOOKING AHEAD

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*The purpose of this document is to respond to the request by the Microbicide Donors Committee for a “map” of current and immediately prospective activities projected against the priorities identified in the Microbicide Development Strategy. It is intended as a living document, to be updated regularly as a pulse-taking function for the microbicide field. The hope is that Mapping the Microbicide Effort will provide a platform for ongoing dialogue, encourage fresh perspectives and synergistic activity, and, for areas that are emerging or where there is relatively little activity, attract new attention and investment.*

*As indicated in the Introduction to this document, the purpose of this closing chapter is to highlight issues and themes such as monitoring and advocacy that cross-cut the “Current Reported Work” identified through the Mapping Exercise, point to corresponding areas of emphasis for the coming year, and suggest some possible ways to implement those.*

### **Monitoring and Advocacy**

As the Mapping Exercise attempts to show, the microbicide effort now encompasses an ever-widening range of individuals, institutions, and partnerships engaged in work that enjoys a broader and more diverse funding base than ever before. This present reality might not have been attained—or at least would have been much slower in coming—had there not been almost a decade of different kinds of advocacy for, and monitoring of, the microbicide field: its achievements, requirements, challenges, and opportunities.

As work on the *Microbicide Development Strategy* proceeded, the issue was raised that the centrality of monitoring and advocacy had not been sufficiently addressed. Monitoring and advocacy actions cut across the different research and development areas of the microbicide effort, and have been instrumental in such areas as: extending and deepening the community of support for basic, translational, and clinical research; expanding intellectual and capital investments across the entire microbicide enterprise; insuring that those investments are well made; contending with disappointments and constraints; and harnessing all efforts toward the common goal of safe, effective, acceptable, affordable, and readily available microbicides.

Thus, a decision was made to form a “Microbicide Development Strategy Civil Society Working Group” that would explore the role of civil society in microbicide research, development, and eventual creation of a market for microbicides, and generate a companion document to the *MDS* that would propose Priority Actions to enhance monitoring and advocacy across the entire microbicide trajectory. The Working Group has been meeting by conference call and in person since 2006, and a report will be available in summer of 2007.

In the interim, the “Current Reported Work” section that follows provides information on specific monitoring and advocacy achievements and activities in 2006 and planned for 2007 that:

- **Encourage national and global collaborations** among researchers, government agencies, and prevention advocates to bridge multiple areas of expertise in support of microbicide-related science;
- **Foster information-sharing across institutions**, again nationally and globally, so that many scientific questions and activities can be pursued jointly or in explicit parallel, and so that there is greater accountability and transparency with respect to allocation of resources; and
- **Integrate the commitment to microbicides into policies and advocacy for global health**, particularly policies and advocacy that first, seek to advance health in developing countries, and second, advance research and development of both microbicides and new technologies for HIV prevention broadly considered.

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## CURRENT REPORTED WORK

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In 2006:

- The *Microbicides 2006* conference in Cape Town in April, and the XVI International AIDS Conference (*AIDS 2006*) in Toronto in August, were bright markers of progress in microbicide coalition-building, policy dialogue, and sharing of knowledge. *AIDS 2006* comprised a breadth of microbicide-related topics and communicated a global AIDS agenda that embraced microbicides as a central goal. In addition, at both conferences, advocates from Africa, Asia, Europe, and North America presented and compared strategies to mobilise public support for microbicides.<sup>44</sup>
- Advocacy efforts secured commitments in the declarations emanating from the 5th United Nations General Assembly Special Session on HIV/AIDS (UNGASS+5) and the G8 Summit in support of development of microbicides and other innovative prevention technologies.<sup>45 46</sup>
- Advocacy efforts and the leadership of Graça Machel contributed to the establishment of the **Women’s Leadership Network for Microbicides**, whose goal is to promote global advocacy for development of and access to microbicides for women in resource-poor nations.
- In Canada, the **Microbicides Advocacy Group Network (MAG-Net)** developed a national Microbicides Action Plan, a multi-sectoral strategy—the first of its kind—that articulates the contributions Canada can make to support microbicide development and delivery.<sup>47</sup>
- The **Nigeria HIV Vaccine and Microbicide Advocacy Group (NHVMAG)** convened stakeholders to develop a consensus proposal for a standard of care in Nigeria for application in HIV prevention technology research in general.<sup>48</sup>

- In South Africa, advocates and clinical research sponsors are engaged in ongoing dialogue with national and provincial media and health authorities, and regularly share information with the **South African Medicines Control Council (MCC)**, to ensure updated understanding of clinical research. Independently, several community advocacy efforts are working to build a supportive environment for microbicide research, development, and access in South Africa.<sup>49</sup>
- Advocates made presentations and exerted a variety of efforts to mobilise additional support for microbicides within the **European Union** and the **African Union**.<sup>50 51</sup>

#### In 2007:

- The **African Microbicides Advocacy Group (AMAG)** will expand its work as a coalition of microbicide advocates from organisations and institutions based and/or working in various African countries, including its participation in global forums, its active *eForum*, and pursuit of an African-driven agenda.
- **AMAG** and **Journalists Against AIDS-Nigeria**, in collaboration with **AVAC**, **GCM**, **IAVI**, and **IPM**, will train and mentor African journalists whose beat includes new prevention technologies.
- The **Alliance**, **AVAC**, **IAVI**, and **UNAIDS** will persist in their joint efforts as the **HIV Vaccines and Microbicides Resource Tracking Working Group**, which systematically collects, analyses, and disseminates information on public sector, philanthropic, and commercial investments in and expenditures on microbicide and vaccine research, development, and advocacy.<sup>52</sup> The Group's purview will expand in 2007 to cover all new HIV prevention technologies: male circumcision, pre-exposure prophylaxis (PrEP), herpes suppression, and vaginal barriers.
- **GCM**, in concert with the **Alliance** and **IPM**, continues to convene the **Microbicide Media and Communications Initiative (MMCI)**, a working group composed of communications experts, scientists, and clinicians, whose purpose is to shape approaches to the communications challenges posed by large effectiveness trials in resource-poor settings and, soon, to provide on-site communications support at clinical research sites throughout the world.

## WHAT IS NEEDED NOW: SUGGESTED AREAS OF EMPHASIS FOR 2007-2008

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The following is a list of areas, identified in the process of reviewing current reported work for the Mapping Exercise, that are recommended for further attention and activity and offered here as a focus and emphasis for the microbicide field in 2007-2008.

### **1. Continue support for basic and pre-clinical research and sharpen focus on key emerging questions**

The optimal approach to preventing sexually transmitted HIV infection overall remains undetermined and there is consensus that no single approach will be sufficient in itself or for all populations in all contexts. With specific respect to microbicides prophylaxis, large questions persist regarding the best targets for interrupting HIV transmission and the balance between the safety of any candidate, for uninfected and infected women and their partners, and its likelihood of efficacy.

Support for basic and pre-clinical research is already generating vital insights into areas crucial to microbicide development<sup>53 54 55 56 57</sup>, insights that press at the boundaries of the unknown, inspire a wealth of ideas for potential applications, and provide a base for the long-desired ability to compare candidates with similar profiles.<sup>58</sup> The productivity of these efforts is well illustrated in *Table A2* in the *Appendices*, which provides a snapshot of the pipeline of microbicides now in pre-clinical development.

As some of the current clinical trials draw to their close over the coming months and new microbicides advance into later-stage trials, questions could emerge around the sufficiency of the scientific inquiry that preceded their entry into the clinic, the informative and predictive value of such safety measures as colposcopy and other assessments of toxicity, the unknown role of the inflammatory response, and fresh challenges such as the potential for development of drug resistance associated with new candidate classes.

### **2. Increase and rationalise the number and diversity of microbicide candidates, as well as their advancement through the development pipeline**

There is another, absolutely essential message in *Table A2*: The number of microbicide candidates in advanced pre-clinical development (*i.e.*, close to entering the clinic) is small and, given the typical ratios of attrition in pharmaceutical development, the earliest portion of the pipeline is fairly narrow. Thus, the *MDS* argued for expansion of the pipeline to include a wider array of

candidates that would act on different targets in different ways, individually or in combination.<sup>59</sup> The MDS also noted that such expansion would require a shared process for expanding and managing the pipeline that would proceed iteratively, using evolving assessment algorithms and selection tools.

Such a process will depend heavily on strategic communication and coordination among developers and donors, and on a consensus approach to pipeline management and investment. The NIH Office of AIDS Research has made a firm public commitment<sup>59</sup> to support establishment of a “Microbicide Research Working Group” that would serve such purposes, following the pattern of the AIDS Vaccine Research Working Group. Refinements or variations to this approach are in early discussions but there is no time to waste. While funding for microbicide research and development has grown, it remains insufficient, particularly with respect to support for the later-stage clinical trials where large investment decisions need to be considered and calibrated with special care.

### **3. Organise and share data on markers and models to assess their relative merits and limitations, and to conceptualise areas of emphasis for new approaches**

Many areas of drug development are focusing on a perceived need for surrogates or biomarkers for product safety and efficacy, but microbicide development is particularly burdened by the total lack of validated pre-clinical or Phase 1 clinical markers of safety and by the lack of sufficient or validated animal models for predicting efficacy. Absent such markers and models, the testing of candidate microbicides that will satisfy licensure requirements must make a large presumptive leap from relatively small safety trials directly into large-scale trials of effectiveness.

Ultimately, only clinical efficacy data will be the arbiter of the validity and utility of any biomarker, assay, or model. To reach that point, however, there must be efforts now to compile and share standardised comparative data on microbicide candidates, notably those now in clinical evaluation or soon to enter such testing. As for biomarkers, it now seems unlikely that such approaches will consist of a single indicator but, instead, will comprise several biomarkers and depend on changes in indicator levels prior to and following exposure rather than on absolute concentrations or amounts. The *MDS* recommended the collection of clinical samples from clinical studies for retrospective validation of assays and putative markers, but no systematic activity in this area was reported.

While more may be unknown than known, some pieces of a foundation have been laid for collaborations around the search for surrogates and biomarkers. The same can be said for pre-clinical assays and models where, as *Table 1* in Chapter 1 suggests, there is proliferation of

work and where the potential for pre-clinical screening of candidate compounds so importantly resides. There is a real need to support and lead a clearly identified, well-supported, coordinated process by which these assays and models could be assessed, individually and comparatively, with respect to their potential contribution to rational evaluation of new candidates. Some of this assessment could be designed to build on the outcomes of current trials to determine which assays and markers may have predicted safety or efficacy. All this, in turn, could provide a platform for standardisation and harmonisation, at least for candidates with similar mechanisms of action, across basic research laboratories as well as laboratories participating in clinical trials.

#### **4. Explore alternative approaches to designing microbicide clinical trials that will be more resource-sparing without compromising the power required for product licensure**

Experience with the current microbicide effectiveness trials and the challenges encountered—the implications of trial participant pregnancies, dynamic incidence rates, participant adherence to protocol, and, again, the lack of sufficient interim measures of safety and efficacy—have provoked attention to the advisability of fresh thinking about microbicide trial design in general. Even though large effectiveness trials may ultimately be required, there is accumulating urgency around exploration of alternative trial designs earlier in the clinical sequence that might provide more knowledge and inspire more confidence in the eventual and perhaps obligatory leap to very large studies.

#### **5. Analyse and evaluate measures of protocol adherence and consumer preferences in current clinical studies with the goal of developing a core set of measures of adherence and strategies for additional consumer research**

Much depends on this. If behaviours relevant to protocol adherence are not reliably determined in effectiveness trials, drawing conclusions about product efficacy may prove tenuous. Looking beyond the clinic, additional consumer research in the context of clinical studies could assess which formulations, delivery mechanisms, and packaging are preferred by research participants and their partners. Clinical study sites also offer settings where strategies for microbicide health messages and potential social marketing approaches could be evaluated and compared. For example, exit interview strategies and even formal exit surveys could be conceptualised and approaches compared and analysed as a way to extract as much understanding as possible from effectiveness trials.

Yet, despite hard work in this area, it has lagged with respect to strategic investment, coordination, practicality, and systematic evaluation of what is truly informative and replicable in a trial context. There are several reasons for this. First, as is the case for pre-clinical models

and assays, it is still too early for validation of measures of adherence to trial protocol to have occurred in any persuasive way. Second, large effectiveness trials are already challenging to manage, and clinical researchers and site staff worry understandably about data volumes and staff capabilities for collecting additional data in the course of a trial, even when such data might be critical to eventual trial interpretation and analysis. Third, clinic staff may be even less likely to have time or incentives for implementing systematic exit interviews.

Thus, behavioural and social scientists charged with shaping data collection strategies and instruments must be focused and thrifty about what they ask and profit as much as possible from work that has gone before.

## **6. Scale up capacity-building efforts at clinical research sites and strategically conceptualise, sequence, and support the use of those sites**

Few sites in the world have the human resources or physical capacity to rapidly recruit thousands of women into microbicide efficacy trials or even parallel Phase 2 trials. Multiple large-scale studies of microbicides and other new HIV prevention interventions, including but not necessarily limited to HIV vaccines and pre-exposure prophylaxis, will demand dozens of clinical research sites, tens of thousands of research participants, and, therefore, substantial increases in investment in trial site capacity, community engagement and support, and innovative study designs. In addition, in the communities where microbicide studies are recruiting participants, there may be limited access to basic health services in general and HIV treatment and care in particular. These limitations present both ethical and economic challenges that will have to be somehow accounted for in trial design and budgeting.

In 2007 and beyond, there must be growth in the numbers of clinical research sites, in the capacity of staff and infrastructure to absorb and manage the work required, and in the provision of comprehensive health care and HIV treatment to study participants who require them. Sequencing prevention research activities and maintaining site resources must be explicitly managed, yet there is no readily available inventory of present or prospective sites for HIV prevention research in general, nor any mechanism for coordinating or even communicating systematically about the optimal development and use of such sites.

There is also the question of the financial resources needed to strengthen existing sites, establish new ones, and maintain their functioning during intervals between trials, a question that is impinging on some major decisions about trial site awards. Once those decisions are made, the total picture of current and prospective trial sites presented in *Table 2* in Chapter 2 should be updated and reviewed with respect to present and potential capacity, availability of appropriate research populations, and probable levels of HIV incidence against which to project the impact of any preventive intervention.

## **7. Compile data for information exchange and foster forums for communication among developers working on:**

- **the challenges of manufacture and formulation of candidate microbicides, and**
- **issues of commercialisation and access**

Two *MDS* Working Groups laid out 18 Priority Actions in the areas of manufacturing and formulation, and commercialisation and access that constitute much of the process of industrialisation. For new technologies, this “critical path” from laboratory to patient is, particularly and typically, rate-limiting, erratically funded, and highly underrated by the scientific community.<sup>60</sup> The Mapping Exercise identifies considerable effort in all these areas, yet there is much more to be done.

For products already in effectiveness trials, the most immediate concerns are clarification of regulatory pathways, issues of intellectual property (IP), and licensing arrangements. Newer candidates, further back in the pipeline, will sooner and later face some of those same issues, but more imminently confront challenges in formulation and manufacture. Both will require different kinds of consumer and market research.

As for access, most microbicide developers have stated general commitments to access, but few of these commitments are yet backed by plans, funding, or actions. Specific plans and results are needed to ensure that future microbicides are accessible and affordable, beginning in study site communities and countries. Forecasting work on cost, demand, and other commercialisation and access issues can help to make these plans more realistic, and this work must be expanded and supported with comprehensive approaches and appropriate funding. Examples of some areas that need to be addressed within strategic plans are: 1) financing for manufacturing, marketing, and delivery; 2) outlining specific pathways for clarifying regulations, IP, and licensing; and 3) developing a set of marketing approaches based on market research.

There was consensus across both *MDS* Working Groups that much might be accomplished through ongoing task forces to address what is a broad and complex spectrum of needs and actions, drawing from new pools of experts in different fields to: 1) help develop the plans described in the preceding paragraph, and 2) confront specific technical areas, notably product formulation and manufacture.



## IN CLOSING

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*In implementing this first round of Mapping the Microbicide Effort, a pattern emerged that respondents described in different ways. One description referred to “holes” in the microbicide development sequence, notably various sorts of translational research that were, for various reasons, only erratically supported. Another referred to large “bumps” in the critical path, pointing to constraints in the financing and manufacture of pilot materials for clinical testing as a prime example. Another wondered about “missing” issues such as the interrelation of HIV and non-HIV sexually transmitted infections and product safety in particular user populations.*

*This is, of course, what maps are supposed to do: that is, show where things are and where they are not, what leads to where or nowhere, and present at least some idea of what it might take to arrive. It is the hope of the contributors to this process that it will lead, speedily and clearly, to new collaborations within the microbicide field and beyond it, to conversations about new support strategies such as agile and minimally bureaucratic innovation grants, to active engagement in new coordinating efforts across the entire field of HIV prevention research, and to new ways of making decisions along the complete pathway of microbicide, research, development, and advocacy.<sup>61</sup>*

# APPENDICES

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## **A1. Priority Gaps and Actions, from the *Microbicide Development Strategy*, August 2006**

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### **PRIORITY GAPS**

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#### **BASIC SCIENCE and PRE-CLINICAL DEVELOPMENT**

- 1 In-depth understanding of vaginal physiology and ecology
- 2 Comprehensive knowledge about the biological and physiological nature of transmitting viruses
- 3 Understanding of microbicide-induced changes in genital tract immunity and transmission
- 4 Validated markers/models of genital tract immune response and inflammation
- 5 Pipeline enhancement through rational development and acquisition of chemical entities and targets
- 6 Clear strategy for optimal selection of actives for combination microbicides with multiple mechanisms of action
- 7 A means of determining delivery method properties required for efficacy, safety, and acceptability

#### **CLINICAL RESEARCH**

- 1 Appropriate study site capacity and study populations for effectiveness research
- 2 Recruitment and retention of suitably trained staff at clinical research sites
- 3 HIV treatment programmes that provide care for those who become infected during a study
- 4 Consensus about how to measure sexual behaviour and condom and product use
- 5 Accurate systems for estimating study costs and timelines
- 6 Information on surrogate markers for efficacy and safety to assist selection of products for Phase 2/3 trials

#### **MANUFACTURING AND FORMULATION**

- 1 Free and efficient information exchange among product developers at public meetings
- 2 Information on product attributes that will achieve or promote consumer acceptance including (but not limited to) the product formulation, dose, dose interval, drug delivery method, product administration route, primary and secondary packaging, product and packaging aesthetics, cosmetic and therapeutic benefits, pharmacokinetics and pharmacodynamics, safety, adverse event profile, level of effectiveness, and spectrum of activity

- 3 Optimal methods to formulate different classes of microbicide actives for product safety and effectiveness
- 4 Creative and practical package designs that will enhance consumer acceptance at low production cost
- 5 Information on product preferences for different groups of users
- 6 Commercial Business Plan on which to base commercial production planning

#### COMMERCIALISATION AND ACCESS

- 1 Consolidated information for experts in the field to create marketing strategies for topical microbicides
- 2 An accurate assessment of the capacity of drug and health commodity supply and distribution systems
- 3 Comprehensive information on cost and financing issues
- 4 Clear pathway to regulatory approval
- 5 Clear pathway for transition of a microbicide from research product to available, accessible public health product
- 6 Clarity about how IP issues affect private and public sector pricing
- 7 A policy awareness and commitment to microbicides, especially at national levels

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### PRIORITY ACTIONS REQUIRED

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#### BASIC SCIENCE and PRE-CLINICAL DEVELOPMENT

- 1 Develop and validate *in vitro* and *in vivo* model systems suitable for carrying out the types of experimental studies needed to address the key scientific questions
- 2 Identify, develop, and validate biomarkers that correlate with relevant *in vivo* properties
- 3 Build and certify 2-3 Good Laboratory Practice (GLP) reference labs
- 4 Establish mechanisms for bringing expertise from other scientific areas and settings into the microbicide field
- 5 Establish expert task forces that work collaboratively on key issues

#### CLINICAL RESEARCH

- 6 Develop inventory of potential research sites/assessment of “readiness”, to share among product developers/sponsors working in microbicides and other HIV/STI research
- 7 Increase capacity of clinical research sites to recruit/train/retain staff, using mechanisms such as increased core funding, network support, centres of excellence
- 8 Document full costs of ongoing clinical studies, as aid to investigators/funders/sponsors in planning future studies

- 9 Develop transparent processes whereby clinical research sites can seek to implement studies with different sponsors and investigators
- 10 Develop new local/international consensus statements for responsibilities/standards of care in HIV prevention research, including duration of sponsor commitment to provide care; care package offered to research participants/family members/those found ineligible to participate; sponsor commitments to treating research-related injury/illness and role in contributing to community health; and investigator roles/limits of responsibility
- 11 Expand efforts to document/evaluate research methods for measuring sexual behaviour and condom/product use, efforts to identify best practices across different studies and sites, develop consensus about when to use standardised behavioural measures vs. tailored or supplementary approaches
- 12 Create international database of safety and other data from all microbicide products and studies, organised to foster cross-comparison/detailed analysis of completed/ongoing/future studies
- 13 Establish ongoing dialogue between trial investigators and regulators to identify most efficient strategies for evaluating microbicide products, including use of potential surrogate markers/alternative study designs

#### MANUFACTURING AND FORMULATION

- 14 Form manufacturing/formulation/supply logistics information exchange forum
- 15 Expand consumer research to better understand consumer preferences/demand/potential use of microbicides
- 16 Support expansion of microbicide formulation groups
- 17 Support innovation in formulation designs
- 18 Conduct international market research in a variety of consumer markets and among major public sector purchasers to assess acceptability of various packaging and distribution methods at varying levels of projected efficacy and pricing
- 19 Compare various formulations and delivery systems through a systematic, coordinated research effort involving paired *in vitro* and *in vivo* studies
- 20 Assess products in development, using an expert team to identify commonalities and commercialisation issues, reduce processes to lowest common denominator, and speed commercial industrialisation
- 21 Fund process development and scale-up of drug substances and product
- 22 Develop strategic and tactical product development and marketing plan as a road map for bringing leading products to the public sector market, including timelines for gathering information on consumer-desired characteristics and other topics relevant to public sector marketing

- 23 Identify large-volume manufacturers in low-cost regions and generate cost-of-goods projections
- 24 Engage with national regulatory agencies in countries conducting efficacy studies before, during, and after studies, to achieve commercial licence in those countries even prior to FDA or EMEA approval, thus rewarding countries that participate in clinical evaluation and provide product faster where most needed

#### COMMERCIALISATION AND ACCESS

- 25 Work with product developers to create a new pool of expertise including social, private sector, end-user, community marketing, and advocacy, to craft strategies for marketing, product positioning, and consumer demand creation
- 26 Fund demonstration projects that introduce and scale up access by issuing RFP to demonstrate introduction/access to existing/emerging technologies (*e.g.*, female condom, diaphragm) in 5-7 potential “early adopter” settings
- 27 Develop plans/protocols/budgets to make products available in study communities after Phase 3 studies
- 28 Develop demand/cost forecasting/impact models to inform manufacturing scale-up/procurement/decisions
- 29 Determine how existing financing mechanisms for public goods can be applied/adapted to support microbicide manufacturing scale-up, purchase/marketing/delivery
- 30 Engage regulatory experts to map registration/regulatory pathways, including strategies for over-the-counter status
- 31 Develop commercialisation and access planning working group to define business plans/roles for moving products from research to widespread use
- 32 Clarify intellectual property arrangements for Phase 3 products, and determine implications for preferential pricing
- 33 Launch research and education initiatives for key policy and communication challenges (*e.g.*, initiative to define and communicate potential public health impact of partially effective microbicides, and to incorporate information about partial efficacy into broader education about risk reduction and any recommended hierarchy of use of health strategies)

Table A2. Microbicide candidates in pre-clinical development as of Feb. 2007\*

MECHANISM OF ACTION	CANDIDATE PRODUCT	DEVELOPER/RESEARCHER	STATUS*	
			D/EP	AP
Vaginal defence enhancers	Genetically engineered probiotics	National Institutes of Health (NIH)	X	
	Lactobacillus-delivered Cyanovirin-N	Osel Inc., University of Pittsburgh, NIH		X
	MucoCept HIV	Osel	X	
	Other engineered lactobacillus, <i>E. coli</i>	National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases	X	
	RANTES peptides	Osel	X	
	Single-chain anti-ICAM antibodies/ICAM-1	Osel	X	
Surfactants	Alkyl sulfates (surfactant and chaotropic agent)	Drexel University College of Medicine, Renaissance Scientific LLC	X	X
Entry/fusion inhibitors	Antibodies and fusion proteins (HIV, HSV, HPV), tobacco-derived/plant-based microbicides and mucosal STI vaccines	Arizona State University, Mapp Biopharmaceutical, NIH	X	
	ADS-J1	Southern Medical University, St. George's Hospital Medical School	X	
	Aptamers	University of California at Los Angeles, VirApt	X	
	Betacyclodextrin	Johns Hopkins School of Medicine, Meharry Medical College	X	
	bKLA	University of Wisconsin School of Medicine	X	
	BMS-806/378806	Weill Cornell Medical College (licensed to International Partnership for Microbicides [IPM])		X
	CMPD 167	Weill Cornell, IPM**		X
	Cyanovirin-N	CONRAD, NIH		X
	Cyclotriazadisulfonamides (CADA)	Rega Institute	X	
	DCM205	University of California at Davis	X	
	Flavonoids	University of Pittsburgh	X	
	Griffithsin, scytovirin	NCI	X	
	HPMCT	Novaflex Biosciences Inc., Drexel	X	
	ISIS 5060	ImQuest Biosciences	X	
	K5-N, OS(H), K5OS(H)	San Raffaele Scientific Institute	X	
	Lactoferrin/DC SIGN	University of Amsterdam	X	
	Mandelic acid condensation polymer (SAMMA)	Mount Sinai Medical School	X	
	"Molecular condom"	University of Utah	X	
	Nanobodies™	European Microbicides Project (EMPRO)		
	Novel delivery system of natural RANTES/Novasomes 7474	Institute of Human Virology, Advanced BioScience Laboratories	X	
	Optimised dendrimers	Starpharma, NIH	X	
	PEHMB	Drexel, Novaflex	X	
	Persulfated molecular umbrellas	Mount Sinai School of Medicine	X	
	Plant lectins	Rega Institute	X	
	Polybiguanides	Novaflex, Drexel, University of Medicine and Dentistry of New Jersey	X	

MECHANISM OF ACTION	CANDIDATE PRODUCT	DEVELOPER/RESEARCHER	STATUS*	
			D/EP	AP
	Porphyrins	Emory University	X	
	PSC-RANTES and additional recombinant RANTES analogs	Case Western Reserve University, NIH	X	
	Recombinant lactic acid bacteria (LAB)	Aaron Diamond AIDS Research Center	X	
	Retrocyclins	University of Central Florida	X	
	siRNA	Harvard Medical School, Rhode Island Hospital	X	
	Soluble DC-SIGN	Centers for Disease Control and Prevention (CDC)	X	
	TAK779	Institute of Tropical Medicine (ITM)	X	
	TatCD	University of Wisconsin School of Medicine, NIH	X	
Replication inhibitors	MC1220 (as lead compound in DABO series)	Idenix Pharmaceuticals	X	
	Thiourea-PETT derivatives	Parker Hughes Institute, Paradigm Pharmaceuticals	X	
Combinations (2 or more actives, or, 2 or more mechanisms of action)	BufferGel® with dendrimers (SPL7013 and optimised dendrimers)	ReProtect, Starpharma	X	
	CAP with UC781 or NCp7 nucleocapsid/zinc finger inhibitors	New York Blood Center, NIH	X	
	CVN-12pl chimeras and combinations, HNG-105	Drexel		
	Dolabellane diterpene	Instituto Oswaldo Cruz (FIOCRUZ), Universidade Federal Fluminense, Fundação Ataulpho de Paiva	X	
	M167, BMS, other ARV	IPM	X	
	PC-710 (Carraguard + zinc); ZCM (Carraguard + zinc + MIV-150)	Population Council	X	
	SJ3366	ImQuest	X	
	Tri-molecular microbicidal-immunising construct (MHC antigens, microbial HSP70, CCR5 peptides)	Allomicrovac	X	
Microbicides combined with devices	Duet™ cervical barrier	Johns Hopkins University		X
	Condoms with alkyl sulphate coating	Drexel	X	X
Uncharacterised mechanism(s)	CO (ciclo piroxolamine)	PATH	X	

\* D/EP=Discovery/Early Pre-clinical Development; AP=Advanced Pre-clinical Development. This list includes microbicides reported by Mapping Exercise respondents and/or documented in recent conference abstracts and/or published literature.

\*\* Other entry inhibitors (e.g., C52L, T1249, AMD3465) are reported to be in various stages of evaluation as topical microbicide candidates and/or components of potential combinations at several research entities (St. George's Hospital Medical School, Tulane National Primate Research Center, Weill Cornell Medical College) but their precise current status is undetermined.

**Table A3. Microbicide products in clinical trials as of Feb. 2007**

PRODUCT (DEVELOPER)	PHASE	SPONSOR(S) <sup>1</sup>	TARGETED ENROLMENT	SITES	STATUS
ACIDFORM™/Amphora™ (CONRAD; Instead, Inc.)	3 <sup>2</sup>	CDC; USAID; CONRAD	1600	Madagascar	Planned
BufferGel® (ReProtect, Inc.)	2/2B <sup>3</sup>	NIAID; Indevus Pharmaceuticals; ReProtect, Inc.	3100	Malawi, South Africa, USA, Zambia, Zimbabwe	Active recruitment
Carraguard® (Population Council)	1	Population Council	60	Thailand	Clinical studies completed <sup>4</sup>
	3	Population Council; USAID; Gates Foundation	6203 (adjusted)	South Africa	Enrolment completed
Dapivirine (TMC120) <sup>5</sup> (International Partnership for Microbicides [IPM])	1	IPM	18	South Africa	Clinical studies completed
	1/2	IPM	36	Belgium	Clinical studies completed
	1/2	IPM	112	Rwanda, South Africa, Tanzania	Clinical studies completed
Invisible Condom™ (Laval University)	1/2	CRI; Laval University; CHUL; CIHR	452	Cameroon	Active recruitment
PC 815 (Carraguard® and MIV-150) (Population Council)	1	Population Council	10	TBD	Planned
	1	Population Council	20	TBD	Planned
Praneem polyherbal vaginal tablet (Talwar Research Foundation)	2	National AIDS Research Institute (NARI)	TBD	India	Planned
PRO 2000 (Indevus Pharmaceuticals, Inc.)	2/2B <sup>3</sup>	NIAID; Indevus Pharmaceuticals; ReProtect	3100	Malawi, South Africa, USA, Zambia, Zimbabwe	Active recruitment
	3	Indevus Pharmaceuticals; MRC; DFID	9673	South Africa, Tanzania, Uganda, Zambia	Active recruitment
Tenofovir/PMPA gel (CONRAD; IPM)	2	NIH: NIAID/DAIDS; NICHD; NIMH; NIDA; Gilead	200	India, USA	Active recruitment
	2B	CAPRISA; USAID; CONRAD; LIFElab; Gilead; Family Health International (FHI)	980	South Africa	Planned
UC-781 (CONRAD)	1	CONRAD; CDC	90	Botswana, Thailand, USA	Planned
	1	CONRAD	TBD	TBD	Planned
	1	CONRAD; UCLA; NIAID	36	USA	Active recruitment
VivaGel™/SPL7013 (Starpharma Ltd.)	1	Starpharma; NIH	36	Australia	Enrolment completed
	1	Starpharma; NIH: NIAID, DMID	60	Kenya, USA	Active recruitment
	1/2	Starpharma; NIAID/DAIDS; NICHD	40	USA	Planned



<sup>1</sup> The Alliance uses the term “sponsor” as defined by the International Conference on Harmonisation (Guideline for Good Clinical Practice, 1996) as follows: “An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.” In this table, the listing in each cell of the “Sponsor(s)” column follows the order provided to us.

<sup>2</sup> This trial will evaluate the effectiveness of the diaphragm with ACIDFORM™ gel in preventing acquisition of *N. gonorrhoeae* and/or *C. trachomatis*. It is not intended to assess effectiveness for HIV prevention.

<sup>3</sup> BufferGel® and PRO 2000 are being tested in a single Phase 2/2B trial.

<sup>4</sup> Listed because while clinical studies have been completed, they are either still being analysed or publication is pending.

<sup>5</sup> IPM has planned feasibility, pK, acceptability, and safety trials to begin 1st through 3rd quarters 2007 with both vaginal ring and gel formulations of dapivirine (TMC120).

## A4. List of Organisations Involved in the Microbicide Development Effort

### PUBLIC, PHILANTHROPIC, AND COMMERCIAL SECTOR DONORS (2000-2006)\*

#### Public Sector Donors

Australia—National Health and Medical Research Council (NHMRC)

Belgium—Belgian Development Cooperation

Brazil—Ministry of Health/National STD/AIDS Program (NSAP)

Canada—Canadian International Development Agency (CIDA), Canadian Institutes of Health Research (CIHR), Health Canada

Denmark—Danish International Development Agency (DANIDA), Ministry of Foreign Affairs

European Commission—Directorate General (DG) Development, DG Research, European and Developing Countries Clinical Trials Partnership Programme (EDCTP)

France—Agence Nationale de Recherches sur le SIDA (ANRS), Ministry of Foreign Affairs

Germany—German Federal Ministry for Economic Cooperation and Development

India—Department of Biotechnology (DBT), Indian Council of Medical Research (ICMR)

Ireland—Development Cooperation Ireland (DCI)

Italy—Italian Ministry of University and Research, Ministry of Health/Istituto Superiore di Sanità (ISS)

Netherlands—Ministry of Foreign Affairs

Norway—Ministry of Foreign Affairs, Norwegian Agency for Development Cooperation (Norad)

South Africa—Department of Science and Technology (DST), Medical Research Council (MRC), National Research Foundation (NRF)

Sweden—Swedish International Development Agency (SIDA)/Department for Research Cooperation (SAREC)

UNAIDS (Joint United Nations Programme on HIV/AIDS)

United Nations Population Fund (UNFPA)

United Kingdom—Department of Health (DOH), Department for International Development (DFID), Medical Research Council (MRC)

United States—Centers for Disease Control (CDC), National Institutes of Health (NIH), United States Agency for International Development (USAID)

World Bank

World Health Organization (WHO)

#### Philanthropic/Private Sector Donors

Aids Fonds

amfAR (Foundation for AIDS Research)

Ford Foundation

Bill & Melinda Gates Foundation

John and Marcia Goldman Foundation

Richard and Rhoda Goldman Fund

Linda and John Gruber Foundation

William & Flora Hewlett Foundation

International AIDS Society (IAS)

\* Funding information for 2006 reported as of February 2007, and may not reflect all donations made in FY 2006.

John M. Lloyd Foundation  
 Kaiser Family Foundation  
 Moriah Fund  
 Parthenon Trust  
 Rockefeller Foundation  
 Turner Foundation  
 Wellcome Trust  
 World AIDS Foundation (WAF)  
 Small foundations, individual gifts, bequests,  
 and events<sup>†</sup>

### *Commercial Sector Donors*

Contract Lab Services  
 Glaxo-Wellcome  
 HTI Plastics  
 Indevus Pharmaceuticals  
 Janssen Pharmaceutica  
 Lancet Laboratories  
 Pannoc Chemie  
 Personal Products Company  
 Polydex Pharmaceuticals  
 Tibotec

## **PUBLIC AND NONPROFIT ORGANISATIONS, ENTITIES, AND RESEARCH INSTITUTIONS**

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Aaron Diamond AIDS Research Center	Case Western Reserve University
Academic Medical Center, University of Amsterdam (AMC)	Center for Health and Gender Equity (CHANGE)
Addis Ababa University	Centers for Disease Control and Prevention (CDC)
Adolescent Medicine Trials Network (ATN)	Centre de Recherche du CHUL (CHUQ)
Africa Centre for Health and Population Studies (ACHPS)	Centre for the AIDS Programme of Research in South Africa (CAPRISA)
African Medical and Research Foundation (AMREF)	Centre International de Recherches Médicales Franceville (CIRMF)
African Microbicides Advocacy Group (AMAG)	Centre National de Recherche sur l'Environnement (CNRE)
Agence Nationale de Recherches sur le Sida (ANRS)	Centre National de la Recherche Scientifique (CNRS)
AIDS Vaccine Advocacy Coalition (AVAC)	Centre National Hospitalier et Universitaire/Benin
Alliance for Microbicide Development (Alliance/AMD)	Chiang Rai Health Club
amfAR/Foundation for AIDS Research	Clinical Trials Working Group (CTWG/"Quick" Working Group)
Baystate Medical Center	Clinton Foundation
BioDesign Institute at Arizona State University	Cochin Institute
Boston University School of Medicine	Columbia University
BOTUSA Project	Commissariat à l'Energie Atomique (CEA)
Brigham and Women's Hospital	CONRAD
Bronx-Lebanon Hospital Center	Consejo Superior de Investigaciones Científicas (CSIC)
Brown University	Dana-Farber Cancer Institute
California Family Health Council (CFHC)	Dartmouth Medical School
California National Primate Research Center (NPRC)	Department for International Development/UK (DFID)
Cameroon Red Cross	Drexel University College of Medicine
Canadian Institutes of Health Research (CIHR)	

<sup>†</sup> Small foundations and individual donors are not listed in detail here because the total donated from this group represents less than 1% of all donations.

Duke University  
 Eastern Virginia Medical School  
 Emory University  
 European Commission (EC)  
 European and Developing Countries Clinical  
 Trials Partnership (EDCTP)  
 European Medicines Agency (EMA)  
 Family Health International (FHI)  
 Fogarty International Center (FIC)  
 Food and Drug Administration (FDA)  
 Foundation for Community Development (FDC)  
 Fundação Ataulpho de Paiva  
 Georgetown University  
 German Primate Center (DPZ)  
 Global Campaign for Microbicides (GCM)  
 The Global Fund to Fight AIDS, Tuberculosis  
 and Malaria  
 Harvard Medical School  
 HIV Prevention Trials Network (HPTN)  
 Hôpital de la Salpêtrière  
 Ibis Reproductive Health  
 Imperial College London  
 Indian Council of Medical Research (ICMR)  
 Indiana University  
 Institut Biomédical des Cordeliers  
 Institut National de la Santé et de la  
 Recherche Médicale (INSERM)  
 Institut Pasteur  
 Institute of Human Virology (IHV), University  
 of Maryland School of Medicine  
 Institute of Medicine of the National Academies  
 Institute of Tropical Medicine/Belgium (ITM)  
 Instituto Oswaldo Cruz (FIOCRUZ)  
 Istituto Superiore di Sanità (ISS)  
 International AIDS Vaccine Initiative (IAVI)  
 International Partnership for Microbicides (IPM)  
 Jehangir Hospital  
 Johns Hopkins Bayview Medical Center  
 Johns Hopkins Bloomberg School of Public Health  
 Johns Hopkins School of Medicine  
 Johns Hopkins University  
 Journalists Against AIDS-Nigeria  
 Kamwala Health Centre  
 Karolinska Institutet  
 Kenya Medical Research Institute (KEMRI)  
 Kilimanjaro Reproductive Health Project  
 King's College London  
 Laboratoire de Santé Hygiène Mobile  
 Laval University  
 Leuven Catholic University  
 Lilongwe Central Hospital  
 London School of Hygiene and Tropical  
 Medicine (LSHTM)  
 Louisiana State University  
 Magee-Womens Research Institute and Foundation  
 Makerere University Faculty of Medicine  
 Manhiça Health Research Center (CISM)  
 Mavalane Hospital, Maputo  
 Medical Research Council/South Africa (MRC/ZA)  
 Medical Research Council/United Kingdom (MRC/UK)  
 Medicines Control Council/South Africa (MCC/ZA)  
 Meharry Medical College  
 Melbourne Sexual Health Centre  
 Microbicide Development Strategy Civil  
 Society Working Group  
 Microbicide Quality Assurance Program (MQAP)  
 Microbicide Trials Network (MTN) and Foundation  
 Microbicides Advocacy Group Network (MAG-Net)  
 Microbicides Development Programme (MDP)  
 Mount Sinai School of Medicine  
 MRC/UK Clinical Trials Unit  
 MRC Social and Health Public Services Unit,  
 University of Glasgow  
 National AIDS Research Institute (NARI)  
 National Cancer Institute (NCI)  
 National Institute for Medical Research/Tanzania  
 National Institute for Medical Research/UK (NIMR)  
 National Institute of Allergy and Infectious  
 Diseases (NIAID)  
 National Institute of Child Health and  
 Human Development (NICHD)  
 National Institute on Drug Abuse (NIDA)  
 National Institutes of Health (NIH)  
 National Institute of Health/Mozambique  
 National Institute for Medical Research/Tanzania  
 National Institute of Mental Health (NIMH)

New York Blood Center  
 New York University  
 Nigeria HIV Vaccine and Microbicides Advocacy Group (NHVMAG)  
 Nigerian National Institute for Medical Research (NIMR)  
 Northwestern University  
 Office of AIDS Research (OAR)  
 Ohio State University  
 Orange Farm Clinic  
 Oregon Health and Science University (OHSU)  
 Parker Hughes Institute  
 PATH  
 Pennsylvania State University College of Medicine  
 US President's Emergency Plan for AIDS Relief (PEPFAR)  
 Population Council  
 Population Services International (PSI)  
 Projet SIDA 3  
 Projet Ubuzima  
 Queen Elizabeth Central Hospital  
 Queen's University Belfast  
 Rega Institute for Medical Research  
 Research Foundation for Mental Hygiene, Inc. (RFMH)  
 Rhode Island Hospital  
 RK Khan Hospital  
 Rush University Medical Center  
 San Raffaele Scientific Institute  
 Scripps Research Institute  
 Seke South Clinic  
 Southern Medical University (China)  
 Southern Research Institute (SRI)  
 St. George's Hospital Medical School  
 St. John's Medical College  
 St. Mary's Hospital (UK)  
 Swedish Institute for Infectious Disease Control  
 Tulane University National Primate Research Center (NPRC)  
 Uganda Virus Research Institute (UVRI)  
 Joint United Nations Programme on HIV/AIDS (UNAIDS)  
 United Nations General Assembly Special Session on HIV/AIDS (UNGASS)  
 United Nations Children's Fund (UNICEF)

United States Agency for International Development (USAID)  
 Universidade Federal Fluminense  
 Università di Cagliari  
 Università di Roma La Sapienza  
 Université de la Méditerranée Aix-Marseille II  
 University of Alabama, Birmingham  
 University of Antananarivo  
 University of Barcelona  
 University of Basel  
 University of California, Davis  
 University of California, Los Angeles (UCLA)  
 University of California, San Francisco  
 University of Cape Town  
 University of Central Florida  
 University of Cincinnati  
 University College London  
 University of Colorado, Denver  
 University Hospitals of Cleveland  
 University Hospital Zurich  
 University of Ibadan  
 University of Illinois, Chicago/College of Dentistry  
 University of KwaZulu-Natal  
 University of Leeds  
 University of Limpopo/MEDUNSA (Medical University of Southern Africa)  
 University of London  
 University of Maryland, Baltimore  
 University of Medicine and Dentistry of New Jersey  
 University of Milan  
 University of Minnesota  
 University of Munich  
 University of North Carolina  
 University of Oxford  
 University of Patras  
 University of Pennsylvania  
 University of Pittsburgh Medical Center  
 University of Port Harcourt  
 University of Reading  
 University of Siena  
 University of Southampton  
 University of Southern Denmark  
 University of Stellenbosch

University Teaching Hospital (UTH)/Zambia  
University of Texas Health Science Center, Houston  
University of Texas Southwestern, Dallas  
University of Texas Southwestern Medical Center  
University of Utah  
University of Washington  
University of Washington National Primate  
Research Center (NPRC)  
University of the Western Cape  
University of Wisconsin School of Medicine  
and Public Health

University of the Witwatersrand, Reproductive  
Health and HIV Research Unit (RHRU)  
University of York  
University of Zimbabwe  
Wayne State University  
Weill Cornell Medical College  
Women's Leadership Network for Microbicides  
World Health Organization (WHO)  
Y.R. Gaitonde Centre for AIDS Research and  
Education (YRG Care)

## **BIOPHARMACEUTICAL COMPANIES AND PRIVATE SECTOR CLINICAL AND POLICY RESEARCH COMPANIES**

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Ablynx  
Advanced BioSciences Laboratories  
BioStat Solutions, Inc. (BSS)  
Carbohydrate Synthesis Ltd.  
DakoCytomation  
EMD Biosciences  
Farmovs-Parexel  
Fisher BioServices Corporation  
Gilead Life Sciences, Inc.  
Glycores 2000  
HLSP  
HTI Plastics  
Idenix Pharmaceuticals  
ImQuest BioSciences  
Indevus Pharmaceuticals, Inc.  
Instead, Inc.  
I.T.I., Inc.  
Lekoko PMC  
LIFElab  
Lionex Diagnostics and Therapeutics

Mapp Biopharmaceutical  
MatTek Corporation  
Medivir  
Novaflux Technologies  
Novartis (Siena)  
Osel, Inc.  
Paradigm Pharmaceuticals  
Pepscan Systems  
Polydex Pharmaceuticals Ltd.  
Progenics  
Renaissance Scientific, LLC  
RNA-TEC  
ReProtect, Inc.  
SGS Biopharma  
Social & Scientific Systems, Inc. (SSS)  
Starpharma Holdings Ltd.  
Tibotec BVBA  
Vision7 GmbH  
VivoMetrics  
Voxiva

## RESEARCH CONSORTIA/COLLABORATIONS/NETWORKS

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*Supported by the European Commission*

### **ALLOMICROVAC**

*Coordinator:* King's College London

*Partners:*

DakoCytomation

Karolinska Institutet

Lionex Diagnostics and Therapeutics

Swedish Institute for Infectious Disease Control

### **EMPRO (European Microbicide Project)**

*Coordinators:* King's College London,

St. George's Hospital Medical School

*Partners:*

Ablynx N.V.

Carbohydrate Synthesis, Ltd.

Centre International de Recherches Médicales

Franceville (CIRMF)

Commissariat à l'Énergie Atomique (CEA)

Consejo Superior de Investigaciones Científicas (CSIC)

Glycores2000 SRL

Institut Cochin

Institut Biomédical des Cordeliers

Istituto Superiore di Sanità (ISS)

Leuven Catholic University

Pepscan Systems BV

Institute of Tropical Medicine/Belgium (ITM)

Queen's University Belfast

Rega Institute for Medical Research

San Raffaele Scientific Institute

Tibotec BVBA

University College London

University of Basel

University of Milan

University of Munich

University of Oxford

University of Reading

University of Siena

University of Stellenbosch

University of York

### **EUROPRISE (European HIV Enterprise)**

*Coordinators:* Karolinska Institutet; Novartis  
(Siena), St. George's Hospital Medical School

*Countries involved:*

Austria, Belgium, France, Germany, Netherlands

Russia, Spain

### **SHIVA (Selection/Development of Microbicides for Mucosal Use to Prevent Sexual HIV Transmission/Acquisition)**

*Coordinator:* Università di Cagliari

*Partners:*

Centre International de Recherches Médicales

Franceville (CIRMF)

Centre National de la Recherche Scientifique

(CNRS-AMFB)

German Primate Center (DPZ)

Hôpital de la Salpêtrière

Idenix Pharmaceuticals (Montpellier)

Research Institute for Development- Montpellier (IRD)

Università di Roma La Sapienza

Université de la Méditerranée Aix-Marseille II

(ESIL-CNRS-AFMB)

Università di Cagliari

University of Milan

University of Patras

University of Southern Denmark

### **VIRAPT**

Institut Pasteur

University of Leeds

Vision7 GmbH

*Supported by the US Agency for International Development (USAID)*

AIM Project (Analysis, Information Management and Communications)

Centers for Disease Control and Prevention (CDC)

CONRAD

Family Health International (FHI)

Global Campaign for Microbicides (GCM)

PATH

Population Council

World Health Organization (WHO)

*Supported by the UK Department for International Development (DFID)*

**Microbicide Development Programme (MDP)**

*Partners:*

Africa Centre for Health and Population Studies (ACHPS)

AMREF/NIMR

Imperial College London

LSHTM

Manhiça/National Institute of Health/Mozambique

(INS)/Foundation for Community Development (FDC)

MRC Clinical Trials Unit

MRC Social and Health Public Services Unit,

University of Glasgow

MRC UK/Uganda Virus Research Institute (UVRI)

MRC/ZA

Population Services International (PSI)

St. George's Hospital Medical School

University of Barcelona

University of Oxford

University of Southampton

University Teaching Hospital (UTH)/Zambia

University of the Witwatersrand, Reproductive

Health and HIV Research Unit (RHRU)

University of York

*Supported by the US National Institutes of Health (NIH)*

**NIH Integrated Preclinical-Clinical Program for HIV Topical Microbicides (IPCP-HTM)**

Brown University

Case Western Reserve University

Harvard Medical School

Mount Sinai Medical School

New York Blood Center

Novaflex Technologies

Osel, Inc.

Population Council

Starpharma

University of California, Los Angeles (UCLA)

University of Pittsburgh/Magee-Womens Research

Institute and Foundation

Weill Cornell Medical College

**STI-TM Cooperative Research Centers (CRC)**

BioDesign Institute at Arizona State University

Indiana University

Louisiana State University

University of North Carolina

University of Texas Health Science Center

at Houston

University of Washington

**NIH Microbicide Innovation Program (MIP)**

Aaron Diamond AIDS Research Center

Boston University

Case Western Reserve University

Drexel University

Georgetown University

ImQuest BioSciences

Northwestern University

Scripps Research Institute

University of Minnesota

University of Texas Health Science Center

University of Texas Southwestern, Dallas

University of Wisconsin

Weill Cornell Medical College

**Partnerships for Topical Microbicides**

Johns Hopkins University

Osel, Inc.

Population Council

University of California, Los Angeles (UCLA)

University of Illinois, Chicago/College of Dentistry

## ENDNOTES

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## **THE ALLIANCE FOR MICROBICIDE DEVELOPMENT**

The Alliance for Microbicide Development is a global, multidisciplinary, multisectoral coalition of scientists, product developers, advocates, and public health experts. The Alliance was founded in 1998 to accelerate development of safe, effective, and affordable microbicides to prevent the ongoing spread of HIV and other sexually transmitted infections. The Alliance works through advocacy, communication, convening, monitoring progress, addressing critical problems in practice and policy, and providing a neutral platform for dialogue on key issues.

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