

M·D·S

THE
MICROBICIDE
DEVELOPMENT
STRATEGY

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Acknowledgments

The Microbicide Development Strategy (MDS) is the product of consultative meetings and working group discussions held over the course of nearly a year in 2005 and 2006. Its content reflects the input of more than 100 experts in the microbicide, HIV/AIDS, and reproductive health fields. (Further description of this process is contained in Chapter 2.3 and in the Appendices.)

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M·D·S

THE MICROBICIDE DEVELOPMENT STRATEGY

Worldwide, women now account for nearly half of all new HIV infections each year. For many women, abstinence, sexual fidelity, or condom use are not sufficient strategies for reducing exposure to HIV and sexually transmitted infections (STIs). These facts highlight the overriding need for HIV prevention methods that protect women.

Microbicides are a new category of health products, formulated for topical use to prevent the sexual transmission of HIV and other pathogens.

The Microbicide Development Strategy proposes specific actions to accelerate the development and distribution of safe, effective, acceptable, and affordable products that women can use to reduce their risk of acquiring HIV through sexual transmission.

Key Terms

In the MDS, the term **microbicide development** encompasses both the basic science and product development activities that will be necessary to design safe, effective, acceptable, and affordable microbicides, manufacture them on an industrial scale, turn them into commercial products, and ensure that they are widely and easily accessible.

The MDS was developed through a “gap analysis”, in which teams of experts identified and agreed on the crucial **gaps and obstacles** in activity, leadership, physical infrastructure, human capital, coordination, networks, policies, funding, or other resources where limits are hindering progress in microbicide development. The MDS teams also identified and discussed obstacles to action, including specific logistical or knowledge deficiencies that are difficult to resolve. The MDS teams then designated some gaps as **priority gaps** that should be addressed urgently—either because they are the biggest impediments to progress and/or because of the time required to fill them. This analysis then produced recommended actions. Both the analysis and proposed actions are included in this report.

This document also discusses the **rational development** of microbicides. This term refers to the process of developing a new medicine by gathering sufficient detailed scientific information and understanding of a compound’s structure and characteristics, potential cellular targets, potential delivery pathways, and probable function, such that the drug can (sometimes) be “designed” rather than found solely by empirical testing. One of the first (and best known) rationally designed drugs are the non-nucleotide HIV reverse transcription inhibitors (NNRTIs), which were developed by engineering molecules with very precise size, shape, and binding characteristics. The result: Drugs that find the active site of the reverse transcriptase enzyme and bind tightly and irreversibly, completely inactivating the enzyme and stopping HIV replication.

The **actions and recommendations** listed in the MDS are proposed activities that, if carried out successfully, should help to overcome the identified obstacles, resolve the gaps, and thereby help to accelerate progress in microbicide development. In some cases, the MDS teams identified certain actions as **priority actions** that should be implemented urgently, for the same reasons mentioned above.

Table of Contents

06	1. EXECUTIVE SUMMARY
14	Priority Gaps in Microbicide Development
15	Priority Actions for Microbicide Development
18	Microbicides Candidates in Clinical Development
19	Microbicides Candidates in Pre-Clinical Development
20	2. INTRODUCTION
28	3. BASIC SCIENCES AND PRE-CLINICAL DEVELOPMENT
48	4. CLINICAL RESEARCH
70	5. MANUFACTURING AND FORMULATION
94	6. COMMERCIALISATION AND ACCESS
114	7. CROSS-CUTTING TERMS, ISSUES, AND THEMES
122	8. LOOKING AHEAD
124	9. REFERENCES
125	Appendix 1: MDS Steering Committee
126	Appendix 2: MDS Working Groups and Experts Consulted

Acronyms and Definitions

Active agent: the compound, drug, or ingredient with anti-microbial properties

Advocacy: support or argument for a cause, policy, or programme

AMD: Alliance for Microbicide Development

API: active product ingredient; active agent

ARV: antiretroviral drug

Biomarker: a biological signal or measurement which can be used as a surrogate indicator

CDC: Centers for Disease Control and Prevention (US government agency)

Coital dependence: the need for microbicide insertion shortly before sexual intercourse

Combination product: a microbicide with two or more active agents or delivery systems

CONRAD: Contraceptive Research and Development Program

Delivery system: applicator, diaphragm, ring, suppository, or other formulation for delivering microbicides

Distribution system: public and private systems to ensure availability to the consumer

DFID: Department for International Development (UK government agency)

Dosage form: the microbicide formulation, which includes both active agent dose and delivery system

DSMB: Data and Safety Monitoring Board

EC: European Community

EDCTP: European and Developing Countries Clinical Trials Partnership

Effectiveness: level of protection against HIV infection in non-controlled 'real world' conditions

Efficacy: level of protection against HIV infection under ideal, controlled conditions

EMA: European Medicines Agency

EMPRO: European Microbicides Project

EU: European Union

FDA: Food and Drug Administration (US government agency)

Gap: any type of deficit in future microbicide development activities

GCM: Global Campaign for Microbicides

GCP: Good Clinical Practice

GLP: Good Laboratory Practice

GMP: Good Manufacturing Practice

GFATM: Global Fund to Fight AIDS, Tuberculosis and Malaria

HPTN: NIH-sponsored HIV Prevention Trials Network

HPV: human papilloma virus

HSV: herpes simplex virus

In silico: in virtual data environments, such as in computer modelling

In vitro: in laboratory environments, such as in a test-tube

In vivo: in living organisms, such as in animal models or human volunteers

IND: investigational new drug

IPM: International Partnership for Microbicides

IP: intellectual property

Marker: indicator used in place of, or to bolster, direct measurements of behaviour, safety, efficacy

MDC: Microbicide Donors Committee

MDP: Microbicides Development Programme

MHRA: Medicines and Healthcare Products Regulatory Agency, United Kingdom

MRC/ZA: Medical Research Council, South Africa

MRC/UK: Medical Research Council, United Kingdom

MSM: men who have sex with men

NDA: new drug application

NGO: non-governmental organisation

NIH: National Institutes of Health (US government agency)

NRA: national regulatory agency

Phase 1 study: small controlled clinical trial testing a product's safety and side effects

Phase 2 study: clinical trial collecting further safety data and assessment of dose levels and schedules

Phase 2B study: proof-of-concept clinical trial designed to capture preliminary evidence of efficacy

Phase 3 study: large controlled clinical trial to determine efficacy with sufficient data for licensure

pH: measure of acidity or alkalinity

Q/CTWG: "Quick" Clinical Trials Working Group

STI: sexually transmitted infection

UNAIDS: Joint United Nations Programme on HIV/AIDS

USAID: US Agency for International Development (U.S. government agency)

WHO: World Health Organisation

Chapter 1

EXECUTIVE SUMMARY

This Microbicide Development Strategy (MDS) is the product of consultative meetings and working group discussions held over the course of nearly a year in 2005 and 2006. Initiated on the recommendation of donors, clinical researchers, and other stakeholders at a meeting in 2004, the strategy reflects input from more than 100 experts in the microbicide, HIV/AIDS, and reproductive health fields.

The goals of the MDS were to identify and prioritise the important gaps in global efforts to develop and deliver microbicides, identify the chief obstacles to resolution of these gaps, and suggest priority actions for overcoming each gap. To this end, the core of the MDS is a list of high-priority actions aimed at accelerating the development and distribution of safe, effective, acceptable, and affordable microbicides.

The MDS takes as its starting point the status of the field in early 2006. Many of the recommended actions in the MDS are neither new nor surprising. Most target long-standing issues, such as our incomplete understanding of how the sexual transmission of HIV occurs, the lack of sufficient capacity in clinical trials, and the need for further research on consumer preferences. Indeed, in 2002, the Rockefeller Foundation produced a comprehensive set of monographs addressing many of these issues and providing a useful framework and a set of priorities for the field.

What is new in 2006, however, is that the global microbicide endeavour has reached a point where many key issues can now be resolved, given the right strategies and the necessary support. The MDS reviews these issues and describes priority actions to initiate effective strategies and support.

Important recent scientific and infrastructural developments include the following:

- **Microbicide science is advancing considerably, including the knowledge base that informs the design of new candidates.** Until recently, there was relatively little detailed information about the cellular and molecular mechanisms of HIV sexual transmission. Consequently, the first microbicide products that entered clinical evaluation were those found empirically to prevent HIV infection *in vitro* and in animal models, and those that also seemed to have acceptable safety characteristics. The field now has a better, albeit incomplete, understanding of the diverse mechanisms of sexual transmission, including relevant aspects of vaginal physiology and mucosal immunology, and the relative importance of R5 and X4

viral strains (Moore et al., 2004; Haase, 2005). This expanded knowledge, in turn, is helping researchers design novel molecules that interfere with specific steps during the infection process (for example, by inhibiting HIV reverse transcriptase or by blocking the molecules that mediate viral access to co-receptors on the cell surface). An equally important development is an increasing attention to clinical study design and standards of care (Stone, 2003; Global Campaign for Microbicides, 2005).

- **A few pharmaceutical companies have recently begun contributing to the microbicide effort and are taking initial steps toward direct involvement in product development.** For the most part, the pharmaceutical industry has not actively invested in microbicides because most companies are deterred by uncertainties about the science, the regulatory situation, and unknown potential for profit. However, several large companies have now reached agreements with academic laboratories and/or public-private partnerships, authorizing them to evaluate company-owned drugs as potential microbicides.
- **Growing numbers of public and philanthropic donors are investing in microbicide research and development,** which has led to higher levels of funding. In 1997, available funding for microbicide research, development, and policy advocacy totalled slightly over US \$28 million (Alliance for Microbicide Development, 2004); by 2000 it was US \$65 million, and in 2005 reached \$163 million (HIV Resource Tracking Working Group, 2006).
- **An increasing number of players in the field has led to the need for a new level of strategic communication, coordination, and allocation of resources.** Today's larger, more diverse effort—while laudable—requires new initiative to prevent unnecessary duplication of work and encourage shared learning across the field. A larger research and development effort also brings increasing competition for highly skilled scientists, funding, laboratory space, manufacturing capacity, and clinical study capacity. This pressure, combined with rapidly expanding scientific knowledge about HIV and its mucosal transmission, has highlighted the need for a comprehensive strategy to accommodate the accelerating pace of microbicide development.
- **Advocates continue to bring greatly increased attention to the microbicide agenda.** Advancements in science, private sector interest, and funding have generated new momentum for microbicides. Furthermore, the global public

health community has gained new interest in the potential of microbicides as crucial prevention products in the fight against HIV/AIDS. As these forces build, advocates are becoming increasingly involved in catalysing and monitoring ongoing changes in policy and programmes.

The main analyses and recommendations of the MDS are organized into four chapters, covering four key areas: (1) basic science and pre-clinical development; (2) clinical research; (3) manufacturing and formulation; and (4) commercialisation and access.

The following briefly summarises each chapter's content.

The **BASIC SCIENCES AND PRE-CLINICAL DEVELOPMENT** chapter recommends five priority actions to target research areas relevant to microbicides, and to strengthen links between basic science and product development so that each area better informs the other. The proposed actions should result in an expansion of the knowledge base that fuels the design, selection, and evaluation of new microbicides.

Several areas are singled out as under-studied but crucially important to this knowledge base. One is a more complete understanding of how HIV is transmitted sexually to women. Another is a fuller characterisation of the normal physiology, immunology, and microbial environment of the vaginal tract. Studies so far have shown that sexual infection with HIV can occur via multiple pathways, collectively involving a variety of target cells and co-receptors, and probably involving both cell-free and cell-associated virus. Although the early events of HIV infection are known to be influenced by (and to influence) the vaginal environment and its immune defences, a deeper understanding of these dynamics is needed in order to identify specific steps and molecules with potential as microbicide targets. This strategy of designing drugs rationally to interact with a particular molecular target offers a potential path to developing microbicides that block the sexual transmission of HIV without perturbing normal vaginal physiology or ecology.

To fill these gaps in understanding, researchers need a robust, reliable, and validated set of model systems and surrogate markers. In fact, the inadequacy of currently available tools is mentioned frequently throughout the MDS as a key obstacle not only to designing candidates but also to their pre-clinical and clinical evaluation. The crucial task ahead is therefore to develop models and biomarkers to the point where specific biomarkers in defined models can accurately predict a product's safety, and eventually its efficacy, in humans.

To achieve this goal, the key proposal is to establish one or a few centralised microbicide development laboratories that can devote significant effort to identifying, analysing, standardising, and validating these valuable tools for the field, hopefully to a standard acceptable to regulators. Success on this front would greatly improve the basis for deciding which concepts, products, formulations, and delivery methods should be advanced through pre-clinical and clinical evaluation. It could also help scientists to further rationalise the pipeline—that is, to review the wide diversity of microbicide approaches and select only the products that seem most promising.

Another area where more research is urgently needed is that of formulations—the form in which the microbicide is delivered into the body (e.g., in a gel, vaginal ring or diaphragm). Although the five most advanced candidates are all gels, little is known about how their various physical properties might affect safety and/or efficacy. For example, would a more viscous gel cover less area within the vaginal tract? And if so, is that necessarily bad, as long as certain areas are covered? And how important is it that a gel should be readily miscible with incoming semen? Answers to these questions should help put the development of formulations—like that of the product’s active agent itself—on a more rational basis. Research on physical properties of these and other delivery methods (as well as research on consumer preferences for various types of formulations, as discussed in Chapter 5) should therefore be supported and expanded.

Further dialogue among researchers and regulatory authorities is also recommended, as a way to catalyse the establishment of clear regulatory requirements for both single and combination microbicides at each stage of development.

The **CLINICAL RESEARCH** chapter recommends actions to advance clinical research capacity and investment, standards of medical care for participants and local communities, and behavioural research relevant to microbicide testing. The chapter also recommends a variety of activities to support the planning and preparation of microbicide research, from collecting information on actual clinical research costs to expanding dialogue with regulatory agencies and participating communities.

The clinical evaluation of microbicides requires that sites are able to recruit and retain participants, and can accurately estimate HIV and STI incidence, pregnancy rates, and normal ranges for clinical laboratory measures of health in participating populations. Given the pace at which new microbicides are now advancing through product development, study designs, training, and communications should be adapted to newer types of microbicides, such as ARV-containing products, vaginal

rings, and diaphragms. Forging strong partnerships with local health providers and communities is another key component of expanding clinical research site capacity.

Shortages of trained health professionals and limited clinical infrastructure pose serious challenges to clinical research in many of the countries where microbicide studies are planned or underway. Investment is therefore needed in human resources, physical infrastructure, preparation of clinical research sites, engagement with communities at those sites, and initial recruitment of study cohorts.

Another strategic focus is the need to define and ensure a standard of health care for study participants and other community members, including family members of participants, prospective participants who are found ineligible, and participants who become infected with HIV through unsafe sex during the study. While microbicide development is primarily an endeavour to improve health outcomes, choices, and equity for women, the services provided in the course of conducting clinical research can also be a valuable health resource in high-need, resource-poor settings. If organised and run properly and ethically, clinical research sites can engage communities and stakeholders in important dialogue about standards of care, contribute to global consensus about standards and obligations for health, and measurably improve people's lives.

Behavioural research is also identified as an utterly critical priority in clinical research. Greater understanding of women's (and men's) sexual behaviours, their risks for HIV and STI infections, and their preferences when it comes to methods of HIV prevention can help researchers interpret clinical trial results, and can also support improved design, use, and effectiveness of microbicides.

Development and validation of standardised surrogate markers is also identified as a priority. Although the validation of surrogate markers of efficacy can be done only once a microbicide first demonstrates at least some degree of protection against HIV infection, important research can be expanded now to identify potential surrogate markers of behavioural risk, HIV exposure, microbicide use, and product safety.

The **MANUFACTURING AND FORMULATION** chapter recommends involving formulation experts at an earlier stage in the product development process than is now common practice. It also recommends greater communication and information-sharing among product developers, resolution of logistic and regulatory hurdles to supplying product for clinical studies, the development of commercialisation plans for products now in clinical efficacy studies, and the clarification of regulatory pathways.

Microbicide development is focusing on an expanding range of possible formulations—besides gels, researchers are now evaluating suppositories, films, tablets, diaphragms, and vaginal rings. Each of these formulations can include various kinds, combinations, and levels of active agents, and each has various manufacturing, packaging, and labelling possibilities. Effective selection, design, and evaluation of these formulations should be guided by two questions: What is preferable (that is, what formulations do users in different settings prefer) and what is feasible (how can formulations be manufactured on a commercial scale at affordable prices?)

Consumer preferences are essential to microbicide development. Given the range of products now in clinical evaluation, there is an urgent need for improved knowledge about how the attributes of a product might influence women's adherence and use. For example, some women might prefer microbicides that are inserted immediately prior to sexual intercourse, while others might prefer products that are less time-dependent. Applicators used for microbicide gels could be designed for multiple or single use, and with disposability as a key attribute. Emerging and existing data on whether, when, and how women might use microbicides should inform all product design choices.

Feasibility is also a core consideration for microbicide formulations. For each product in development, manufacturing processes, infrastructure, and supply-chain management systems are needed to support timely distribution of experimental candidates for clinical studies, and also systematically prevent logistical and regulatory barriers to the manufacture and supply of product for clinical trials. Industrialisation—the processes for turning laboratory concepts into well-defined, consistent, and mass-produced medical product—is therefore a priority for each of the major categories of microbicides in development. Increased capacity is needed for microbicide design, characterisation, manufacturing scale-up, and quality control of microbicide production.

For products now in efficacy studies, commercialisation planning is an urgent need. Once a product proves to be protective, the speed at which hundreds of millions of doses can be made available globally will depend on manufacturing processes, capacity, time, and cost. To minimise the delay between identifying a protective microbicide and distributing it globally, the field must take inventory of existing manufacturing capacity throughout the world, and then evaluate it against the current and predicted roster of candidate products. Low-cost, large-scale commercial production of future microbicides may also depend on resolution of non-technical issues such as intellectual property rights, the existence of manufacturing contracts and technology transfer arrangements in low-cost regions, and the capacity and

speed of regulatory review. Early attention to these formulation and manufacturing considerations could save significant time and effort by increasing the likelihood of eventual microbicide acceptance, commercialisation, and access.

The **COMMERCIALISATION AND ACCESS** chapter suggests actions to address the challenges of transitioning protective products from clinical evaluation to commercialisation and widespread use, emphasizing the speed with which they are made available and accessible.

Microbicides are needed most urgently in resource-poor settings. Because there is no established market for microbicides in these (or other) settings, it is unlikely that normal market forces will drive the transition of the first microbicides from research products to viable, self-financing public health products. Rather, this process will have to be actively and jointly managed by sponsors, product developers, industry partners, and donors. Microbicide commercialisation requires engaging new partners from the pharmaceutical industry and from the public and social marketing sectors.

Improved cost and demand forecasting models are also essential. Sound cost and demand estimates are crucial tools in planning for manufacturing scale-up, and for financing for product procurement and distribution. Since microbicides are a new type of product, initial estimates of costs and demand will be informed by distribution systems used for other public-sector goods. These initial estimates can then be refined as data emerge on microbicide product characteristics, local health system capacity, price, and other determinants of demand.

Identifying and strengthening distribution systems for future microbicides is yet another priority. Depending on the setting, it may be possible to build on existing distribution systems for other products, including women's health products, female condoms, vaccines, and high-volume over-the-counter commodities. Decisions about the most appropriate distribution systems will require forward-thinking analysis of the costs, challenges, and benefits of these different systems. Pilot programmes should also be developed to demonstrate effective introduction and use of women-initiated HIV prevention products such as female condoms or diaphragms. But ultimately, donor support is essential to ensuring product access. The first products are unlikely to be commercially viable or to generate large private sector sales, and public subsidy will be necessary to ensure product availability in developing countries over the first five to ten years.

Greater clarity is also needed with respect to intellectual property arrangements and to potential pathways for regulatory review and licensure, particularly for newer microbicide formulations and combinations. Clarifying intellectual property arrangements is central to determining the options for pricing, manufacturing,

and availability of products. This may involve greater guidance and communication among the US Food and Drug Administration (FDA), the European Medicines Evaluation Agency (EMA), and the national and regional regulatory agencies where microbicides are now being evaluated.

IN CONCLUSION

The MDS offers a set of recommended actions for accelerating and optimising microbicide development. It is not intended as a comprehensive blueprint, but instead focuses on notable gaps and priorities identified by experts.

Taken individually, each of the four chapters of the MDS provides a strategic framework for action by identifying the priority gaps where action is urgently needed and by proposing ways to move forward. Taken as a whole, the MDS also highlights several cross-cutting themes and related recommendations for microbicide development and future microbicide access and use. These themes include consumer research, development of surrogate markers, industrialisation, regulatory issues, and funding. Each MDS chapter implicitly recommends monitoring of policies and practices, the recruitment and mobilisation of new constituencies, the initiation of new work, and advocacy for a stronger effort.

More than one hundred experts have provided input into this document. Further review is anticipated, particularly from high-need countries where large-scale clinical research is being implemented. It is likely that the MDS will modify its framework incrementally to incorporate and better emphasise creative new concepts and cross-cutting themes, and to adapt to changes in the field. It is also expected that the value of the MDS will be maintained by this broad review and by periodic updates based on global consultation and incorporation of new findings, technical developments, and evolving concepts. A complementary “Mapping Exercise” is also underway, in which experts are working to match ongoing and planned activities in the field to the perceived priority gaps. This process will also look at the level of effort within each activity. The result will be a brief document that describes current efforts to advance the field.

In combination, the MDS and the complementary Mapping Exercise will facilitate monitoring of progress in microbicide development by posing five simple questions:

- Which actions have been completed?
- Which gaps persist as priorities?
- What have we learned?
- What actions need to be added?
- What remains to be done?

PRIORITY GAPS IN MICROBICIDE DEVELOPMENT

Currently, a number of components that are essential to the successful development and distribution of microbicides are lacking, missing entirely, or generally overlooked. These gaps are listed below (*numbered for easy reference but not in priority order*).

BASIC SCIENCE AND PRE-CLINICAL DEVELOPMENT

- 01 An in-depth understanding of vaginal physiology and ecology
- 02 Comprehensive knowledge about the biological and physiological nature of transmitting viruses
- 03 An understanding of microbicide-induced changes in genital tract immunity and transmission
- 04 Validated markers/models of genital tract immune response and inflammation
- 05 Pipeline enhancement through rational development and acquisition of chemical entities and targets
- 06 A clear strategy for the optimal selection of actives for combination microbicides with multiple mechanisms of action
- 07 A means of determining delivery method properties required for efficacy, safety and acceptability

CLINICAL RESEARCH

- 01 Appropriate study site capacity and study populations for effectiveness research
- 02 The recruitment and retention of suitably trained staff at clinical research sites
- 03 HIV treatment programmes that provide care for those who become infected during a study
- 04 Consensus about how to measure sexual behaviour and condom and product use
- 05 Accurate system of estimating study costs and timelines
- 06 Information on surrogate markers for efficacy and safety to assist the selection of products for Phase 2/3 trials

MANUFACTURING AND FORMULATION

- 01 Free and efficient information exchange among product developers at public meetings
- 02 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
- 03 Optimal methods to formulate different classes of microbicide actives for product safety and effectiveness

- 04 Creative and practical package designs that will enhance consumer acceptance at low production cost
- 05 Information on product preferences for different groups of users
- 06 A Commercial Business Plan to base commercial production planning

COMMERCIALISATION AND ACCESS

- 01 Consolidated information for experts in the field to create marketing strategies for topical microbicides
- 02 An accurate assessment of the capacity of drug and health commodity supply and distribution systems
- 03 Comprehensive information on cost and financing issues
- 04 A clear pathway to regulatory approval
- 05 A clear pathway for the transition of microbicide from research product to available and accessible public health product
- 06 Clarity about how IP issues affect private and public sector pricing
- 07 A policy awareness and commitment to microbicides, especially at a national level

PRIORITY ACTIONS FOR MICROBICIDE DEVELOPMENT

BASIC SCIENCE AND PRE-CLINICAL DEVELOPMENT

- 01 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
- 02 Identify, develop, and validate biomarkers that correlate with relevant *in vivo* properties
- 03 Build and certify 2-3 Good Manufacturing Practise (GMP) reference labs
- 04 Establish mechanisms for bringing expertise from other scientific areas and settings into the microbicide field
- 05 Establish expert task forces that work collaboratively on key issues

CLINICAL RESEARCH

- 06 Develop an inventory of potential research sites and an assessment of their “readiness”, to be shared among product developers and research sponsors working in microbicide development and in other areas of HIV and STI research
- 07 Increase the capacity of clinical research sites to recruit, train, and retain staff, using mechanisms such as increased core funding, network support, and centres of excellence
- 08 Document the full costs of ongoing clinical studies, as an aid to investigators, funders, and sponsors in planning for future studies

- 09 Develop transparent processes whereby clinical research sites can seek to implement studies with different sponsors and investigators
- 10 Develop new local and international consensus statements for responsibilities and standards of care in the context of HIV prevention research, including microbicide, vaccine, pre-exposure prophylaxis, and behavioural studies, including consensus on key arrangements such as the duration of study sponsors' commitment to provide care; elements of the care package to offer to research participants, their family members, and those found ineligible to participate; study sponsors' commitments to treating research-related injury or illness; study sponsors' role in contributing to health in the community; and study investigators' roles and limits of responsibility
- 11 Expand ongoing efforts to document and evaluate research methods for measuring sexual behaviour, condom use, and candidate microbicide use, including efforts to identify best practices across different studies and sites, and to develop consensus about when to use standardised behavioural measures versus a tailored or supplementary approach
- 12 Create an international database containing safety and other data from all microbicide products and studies that will be organised to foster cross-comparison and detailed analysis of completed, ongoing, and future studies
- 13 Establish ongoing dialogue between trial investigators and regulators to identify the most efficient strategies for evaluating microbicide products, including the use of potential surrogate markers and alternative study designs

MANUFACTURING AND FORMULATION

- 14 Form a manufacturing, formulation, and supply logistics information exchange forum
- 15 Expand consumer research to better understand consumer preferences, demand, and 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 the lowest common denominator, and speed commercial industrialisation
- 21 Fund process development and scale-up of drug substances and product

- 22 Develop a strategic and tactical product development and marketing plan that would provide 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 the studies—in order to achieve commercial license in those countries, even prior to FDA or EMEA approval, thereby rewarding countries that participate in clinical evaluation and provide product faster where it is needed the most

COMMERCIALISATION AND ACCESS

- 25 Work with product developers to create a useful and accessible new pool of expertise that includes areas of social, private sector, end-user, and community marketing as well as advocacy to craft strategies for marketing, product positioning, and creation of consumer demand
- 26 Fund demonstration projects that introduce and scale up access by issuing a request for proposals (RFP) for demonstrating introduction and access to existing and emerging technologies such as the female condom and the diaphragm in approximately five to seven potential “early adopter” settings
- 27 Develop plans, protocols, and budgets for continuing to make products available in study site communities after Phase 3 studies have been completed
- 28 Develop initial demand, cost forecasting, and impact models to inform manufacturing scale-up, procurement, and decision-making
- 29 Determine how existing financing mechanisms for public goods can be applied and adapted to support microbicide manufacturing scale up, purchase, marketing, and delivery
- 30 Engage regulatory experts to map out registration and regulatory pathways, including clear strategies for over-the-counter status
- 31 Develop a commercialisation and access planning working group to define business plans and 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., an initiative may be needed to define and communicate the 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)

Microbicide candidates in clinical development

MICROBICIDE CLINICAL STUDIES* (June 2006)	
PHASE	STUDIES
1	ACIDFORM™/Amphora™ gel Carraguard® Cellulose acetate 1,2-benzenedicarboxylate (cellacefate/CAP) PC 815 (Carraguard® and MIV-150) TMC120 UC-781 VivaGel™/SPL7013
1/2	Invisible Condom™ TMC120
2	Cellulose sulfate/CS (Ushercell) Praneem Polyherbal Vaginal Tablet Protected Lactobacilli in combination with BZK** Tenofovir/PMPA gel (1%)
2/2B	BufferGel™ and PRO 2000 (0.5%) Tenofovir/PMPA gel (1%)
3	Carraguard® Cellulose sulfate/CS (Ushercell) PRO 2000 (0.5% and 2%) Savvy™ (C31G)
<p>© Alliance for Microbicide Development</p> <p>* This table is an attempt to give a picture that is as accurate as possible of the microbicide candidates that have reached the clinical stages of testing. Some of these products are being tested in more than one phase of clinical trials. The trials that appear in this table may be (1) in the active planning stage, (2) ongoing, or (3) recently completed but with published analysis pending. For any modifications, please contact Carolyn Plescia, email cplescia@microbicide.org, tel. 301-587-3302.</p> <p>** Continuation of trial pending.</p>	

Microbicide candidates in pre-clinical development

MICROBICIDE PRE-CLINICAL CANDIDATES* (June 2006)	
MECHANISM OF ACTION	CANDIDATE COMPOUND/PRODUCT
Vaginal defence enhancers (5)	Genetically engineered probiotics Lactobacillus-delivered Cyanovirin-N MucoCept HIV RANTES peptide Single chain anti-ICAM antibodies
Surfactants (2)	Alkyl sulfates Polybiguanides
Entry/fusion inhibitors (21)	Antibodies and fusion proteins (HIV, HSV, HPV), tobacco-derived Betacyclodextrin bKLA BMS-38806 CMPD 167 Cyanovirin-N Flavinoids K5-N, OS(H) Lactoferrin/DC SIGN Mandelic acid condensation polymer (SAMMA) Novaflex proprietary product Optimized dendrimers Pomegranate juice Porphyrins PSC-RANTES Recombinant lactic acid bacteria (LAB) Retrocyclin siRNA Soluble DC-SIGN TAK779 TatCD
Replication inhibitors (1)	MC1220 (as lead compound in dihydroxy alkyl benzyl oxopyrimidine series)
Combination (2 or more actives or 2 or more mechanisms of action) (6)	BufferGel™ with dendrimers (SPL7013 and optimised dendrimers) CAP with NCp7 nucleocapsid inhibitors M167, BMS, polyanion PC 710 (Carraguard® and Zn) PC 815 (Carraguard® and MIV-150) SJ3366
Uncharacterised mechanism (1)	CO (ciclopiroxolamine)
*This chart includes only those candidate microbicides about which researchers and developers have provided information, and therefore is not exhaustive.	

Chapter 2

INTRODUCTION

2.1 Microbicides: a new opportunity for HIV prevention

The latest reports from UNAIDS and WHO make it clear that, despite promising news from a few countries, the global HIV/AIDS epidemic shows no sign of abating. The estimated number of people living with HIV continues to increase every year, and will continue to outstrip the availability of HIV therapies unless there is a rapid, effective, and sustained expansion of HIV prevention. As the epidemic continues, it is infecting more and more women; roughly 2/3 of all infected 15-24 year-olds worldwide are young women. In addition to its tragic humanitarian impact, the fact that HIV/AIDS afflicts the most economically productive members of society means that many hard-hit regions are seeing the reversal of decades-long progress in increased life expectancy and the numbers of young children (especially girls) who attend school.

TABLE 1 An overview of the HIV/AIDS epidemic as of December 2005
(UNAIDS, 2006)

Category	Total estimated number people (in millions)	Total estimated number women (in millions)
Adults (15+) newly infected in 2005 (global)	4.1	NA
Newly infected in 2005 (sub-Saharan Africa)	3.1	NA
Living with HIV/AIDS (global)	40.3	17.5
Living with HIV/AIDS (sub-Saharan Africa)	24.5	13.2 (59%)

The great majority of adult infections in the developing world are acquired through unprotected heterosexual intercourse. Women—especially adolescents and young women—tend to be more vulnerable than men to sexual transmission of HIV, for a combination of both biological and socio-economic reasons. Yet, despite intensive

efforts in many parts of the world to reduce sexual transmission of HIV and STIs, unprotected sex remains widespread. There are roughly 340 million cases of STIs annually and STIs collectively remain one of the twenty leading global causes of years of life lost to disability and death (World Bank DCP2, 2006).

There is extensive evidence that condoms, if used correctly and consistently, can provide a high level of protection from HIV (UNAIDS/UNFPA/WHO, 2004). However, rates of sexual transmission of HIV and STIs remain stubbornly high throughout the world. One factor is that male condoms and female condoms are not always available or affordable. Even where condoms are accessible, use may be influenced by a myriad of factors such as a desire to have children, or desire for sexual spontaneity, intimacy, and trust. Because men often decide whether or not to use a condom during intercourse, it can be difficult or impossible for women (especially if they are young, married, and dependent on their spouse) to ensure consistent condom use.

This context makes clear the need for new options to prevent the sexual transmission of HIV and STIs that do not require women to negotiate use with their partners. In this respect, microbicides potentially offer many attractive features. For example, most microbicides now being developed are designed to be self-administered prior to sex; others, such as the microbicide-impregnated intravaginal ring, are designed to remain in place for several weeks and provide continuous protection. None of these types of products would interfere with intimacy or spontaneity, thereby eliminating a frequently-voiced concern about user friendliness of microbicides. And while many of the first commercially available microbicides are also likely to be contraceptive, future microbicide development should provide women with a choice between contraceptive and non-contraceptive products.

Further strengthening the rationale for microbicides as an important prevention technology, mathematical models have shown that even a moderately effective product used only some of the time could have a substantial impact on curbing the HIV/AIDS epidemic (see Table 2 below). In combination with other HIV and STI prevention strategies, microbicide development is therefore a core part of global efforts to slow the spread of HIV/AIDS.

TABLE 2 Impact of a microbicide with 60% efficacy

IF USED...
in 50% of sexual encounters without condoms by 20% of people reachable through existing health services (as of 2002)
WITHIN THREE YEARS, WOULD
prevent 2.5 million new infections save US\$2.7 billion in care and treatment of HIV/AIDS patients and their families save US\$1 billion reduction in productivity losses due to AIDS

These figures come from a 2001 study that assessed the impact of microbicides with different levels of efficacy and use. The study, cited in the 2002 Rockefeller Foundation reports, used a mathematical model to analyse data from 73 countries (Watts and Vickerman, 2001).

2.2 The rationale and background of the Microbicide Development Strategy

At the time this report was being prepared (March 2006), clinical researchers were evaluating five microbicide candidates for their protective efficacy in populations at high risk for sexual infection. These five products are all gels, including an acid-buffered vaginal defence enhancer, three HIV entry/fusion inhibitors, and a surfactant. An additional six products are in expanded Phase 2 testing and more than six others are undergoing Phase 1 studies to assess safety and acceptability in small numbers of women. Many more candidate microbicides are in pre-clinical evaluation and development. In addition to the large number of experimental products, the microbicide pipeline also includes some innovative technologies and formulations.

The outcome of the furthest-advanced clinical studies should become known in 2008 and 2009. If we are fortunate, at least one of the five microbicides may show sufficient protective capacity to merit licensure and distribution. Once a first microbicide reaches the market, future research and development will be focused on developing products that are even more effective, affordable, and acceptable—and easy to make available in a range of forms that suit different preferences. Alternatively, even if none of the products now in efficacy studies proves to be sufficiently effective, these studies will nevertheless suggest future directions for product development, such as identifying types of molecules and formulations that may be more protective than others, and approaches that maximise product acceptability and adherence. They will also render valuable data and experience for future clinical site preparation, study design, and implementation.

Since 1994, several organisational developments have helped to accelerate progress on microbicides and facilitate cooperation among scientists, research institutions, government agencies, and grassroots community leaders. They include the following:

- **The International Working Group on Microbicides (IWGM) was established in 1994 to convene and facilitate communication among several hitherto largely separate microbicide research programmes.** For the first time, the IWGM brought together senior representatives from major governmental and non-governmental organisations involved with microbicide development in the industrialised and developing world. The IWGM was also instrumental in increasing coverage of microbicide research at prestigious international scientific conferences.
- **In 1998 the Alliance for Microbicide Development, a global, multidisciplinary, multisectoral coalition, was founded to catalyse microbicide development.** As a coalition working to advance the needs and interests of scientists, small biotechnology companies, and non-profit research groups developing microbicides, the Alliance has addressed critical problems in practice and policy through advocacy, communications, and convening of all key stakeholders in microbicide development. (www.microbicide.org)
- **In the same year, the Global Campaign for Microbicides was founded as a broad-based, international effort.** The Global Campaign has built support among policymakers, opinion leaders, and the public for increased investment in microbicides and other user-controlled prevention methods. (www.global-campaign.org)
- **Experts in the field launched a regular series of international conferences devoted to microbicides.** The first conference, which took place in Washington, DC in March 2000, began what is now a biennial gathering committed to the growth and success of the field. The 2008 conference will be held in New Delhi.
- **In July 2000, the Bill & Melinda Gates Foundation awarded \$25 million to CONRAD to establish the Global Microbicide Project with a mandate to hasten the development of microbicides and provide a resource for the field.** Most of the microbicides now in late-stage clinical testing have received assistance in one form or another from GMP. (www.gmp.org)
- **In 2002, stakeholders in microbicides produced the first-ever field-wide microbicide strategy.** In June 2000, the Rockefeller Foundation sponsored an intensive consultation among leading experts in microbicide research and advocacy, together with representatives of donor agencies and the pharmaceutical industry. The Foundation's Microbicide Initiative monographs were published in 2002 as a comprehensive set of reports providing an analytic framework and a set of priorities for further work in microbicide science, public health, pharmaco-economics, advocacy, and access.

- **That same year, the International Partnership for Microbicides (IPM) was created as a new public-private partnership.** As is a non-profit product development partnership dedicated to accelerating the development and accessibility of microbicides to prevent the transmission of HIV in women in developing countries, the IPM is now working to screen compounds, design optimal formulations, establish new manufacturing capacity, develop clinical trial sites, and conduct large scale efficacy trials. (www.ipm-microbicides.org)
- **A series of international consultations about the regulatory aspects of microbicides, held in Switzerland (2002), Botswana (2002), India (2004), and South Africa (2005), have led to substantial progress in defining a scientific basis for microbicide regulation.** Sponsored by WHO and others, these consultations also encourage the strengthening of regulatory capacity not only within individual countries but also at the regional level.
- In 2004, at a meeting convened by the Bill & Melinda Gates Foundation and the Alliance for Microbicide Development, the primary donors supporting large microbicide trials were convened to begin a dialogue about how the field might proceed more efficiently and strategically. This group of donors formed a **Microbicide Coordinating Board (later renamed the Microbicide Donors Committee)**. This group prioritised the establishment of a working group that could provide coordination, information sharing, and problem solving across the ongoing and imminent Phase 2b and Phase 3 clinical trials. Because of its rapid launch, this activity is persistently known as the “Quick Working Group” and regularly convenes senior clinical study investigators to discuss progress, challenges, ways to optimise comparability of data, and strategies for addressing any emerging problems. The group’s work has already led to significant learning, and has been valuable to the field as a whole and to articulation of the MDS.

2.3 Creating the Microbicide Development Strategy

The MDS is the product of consultative meetings and working group discussions held over the course of nearly a year in 2005 and 2006. Its content reflects the input of more than 100 experts in the microbicide, HIV/AIDS, and reproductive health fields.

The primary purpose of this process was to identify and prioritise important gaps in the global microbicide effort, to identify the main obstacles to their resolution, and to propose possible ways for overcoming them. This document contains both an analysis of the state of the current field and a prioritised list of recommended actions for continued microbicide development.

Via a strategy that focuses on addressing impediments to progress, the MDS aims to:

- consistently update the Microbicide Donors Committee (and donors more generally), thus building greater confidence that their investments contribute to a global strategy;
- assist other funding organisations in formulating or updating their own strategies, thereby facilitating their participation in the global effort;
- generate, as a result of the above two steps, enhanced funding for the microbicide field as a whole;
- encourage greater communication and coordination across the field, which should lead to better collaboration while minimizing unnecessary duplication of effort; and lastly,
- assist researchers and product developers in embedding their work creatively within a broader strategic framework.

The impetus for the MDS dates back to 2004, when a group of funders, trial planners, and other stakeholders met to discuss the need for increased coordination and information-sharing across the field. The process for generating and publishing a strategy was launched at the request of the Microbicide Donors Committee, which represents 14 funding agencies and government departments actively supporting microbicide development.

One of their early steps established a five-person Steering Committee (see list of members in Appendix 1). The Committee began by considering the entire range of microbicide research and development and deciding where the MDS should focus in order to have the most impact on controlling the global epidemic. Its second task was to define major steps of the microbicide development process that would benefit from intensive consideration by groups of experts, including specialists in each stage.

Participants in initial MDS-related meetings agreed that there were persistent gaps in the knowledge base and in the availability of specialised skills and facilities. These were impeding progress such that the pace of research and development was not commensurate with the fast-growing global need for microbicides. The notion of identifying and prioritising these gaps in a coordinated manner was seen as a benefit to stakeholders already working in the field, and to funders and donors seeking to increase support.

The Steering Committee assembled four working groups (see the list of Working Group members in Appendix 2), each of which focused on an area considered crucial for accelerating microbicide development, and each contributing a chapter to this report:

- basic science and pre-clinical development;
- clinical trials;
- manufacturing and formulation; and
- commercialisation and access.

Each group had at least seven people, including two chairpersons, who worked together through a series of meetings and conference calls. They also sought advice from experts outside the group (see Appendix 2 for a list of the 59 people consulted). The aim was to bring an evidence-based perspective to the process, together with a body of informed opinion. The process was aided by personnel from McKinsey & Company, a management consulting firm.

Each of the four working groups drafted a chapter of this MDS report. There was intensive cross-communication among the working groups at all stages and, while each group addressed different topics, the 31 working group members employed a common conceptual framework and terminology for communicating their findings. On 28-29 November 2005, the working group members and some outside experts met in London to review progress. This meeting, with approximately 60 international experts, helped synthesise information and ideas across the individual groups into a cohesive strategy document that reflected the joint thinking of the whole group.

The working groups then revised their chapters and incorporated feedback from the meeting participants. The resulting draft report was then (early 2006) circulated for comment to a wide range of relevant organisations and individuals. About 40 people provided feedback, which was taken into account in revising the document. In late March 2006, at a two-day meeting in Washington, DC, more than 100 microbicide experts discussed key gaps and existing and planned actions.

In late April 2006, at a satellite meeting of the Microbicides 2006 conference in Cape Town, South Africa, the MDS priority gaps and actions were presented. Over the next two months, the document underwent several more rounds of revision and review, with the final round culminating in June 2006.

PRIORITY ACTIONS

BASIC SCIENCES AND PRE-CLINICAL DEVELOPMENT

- 01 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.
- 02 Identify, develop, and validate biomarkers that correlate with relevant *in vivo* properties. These biomarkers offer the means for linking pre-clinical study results with clinical data.
- 03 Build and certify 2-3 Good Manufacturing Practise (GMP) reference labs. These facilities should have pre-clinical assay capabilities for developing and evaluating microbicides, and should take a lead role in work on model systems and biomarkers for use by the whole field. They should also establish/expand specimen banks that store and make available tissue explants (for *in vitro* studies) and clinical material from microbicide studies.
- 04 Establish mechanisms for bringing expertise from other scientific areas and settings into the microbicide field. Particularly important are initiatives that foster access to industrial expertise to support pipeline expansion and technology infusion and to people from areas such as gynaecology, reproductive biology, and other non-microbicide HIV/AIDS research.
- 05 Establish expert task forces that work collaboratively on key issues. For example, the “Quick” Clinical Trials Working Group is a good model for effective information-sharing among clinical researchers conducting large microbicide trials.

Chapter 3

BASIC SCIENCES AND PRE-CLINICAL DEVELOPMENT

The past few years have brought progress in several important areas of microbicide development. In particular:

- The number and diversity of products in development are increasing. Not only are there more candidates in clinical evaluation, but these candidates collectively reflect several different mechanisms of action.
- This fuller clinical pipeline—in particular, the five ongoing Phase 3 trials—has pushed the field to build capacity for manufacturing and delivering product.
- Researchers are developing new and innovative forms of microbicides. Beyond the gels used in the early products, newer technologies include vaginal rings, diaphragms, films, and suppository tablets.
- Growth of the field has expanded the use (and therefore the development) of model systems, in particular genital tissue explants as well as various animal models. This is a positive development, since the need for better model systems is acute.

Contributing to this progress, basic knowledge is improving about the sexual transmission of HIV, normal vaginal physiology and function, and mucosal immunology. This should offer an opportunity to apply the principles of rational drug development. This approach would use the extensive information gathered about HIV infection via the vaginal mucosa to design products with the potential to target (and interfere with) specific molecules and pathways that are crucial to the infection process.

Use of basic science knowledge for rational microbicide development requires closer links between basic research and product development. Encouraging rational design and product development means finding ways to funnel new basic research findings as rapidly as possible into product development. At the same time, collaboration can help researchers to correlate the desirable properties of a microbicide (including safety, potential efficacy, and aspects that relate to consumer preferences and feasibility of commercialisation) to specific pre-clinical surrogate markers.

It should be feasible to resolve many of the other challenges and obstacles that stand in the way of rational product development. Basic scientific questions about HIV

infection and related mucosal immunology can be answered. New model systems, biomarkers, and new assay technologies can be created and validated. Once any level of efficacy is demonstrated in a Phase 3 trial, surrogate markers for efficacy can be sought and applied to decide which additional microbicide candidates might be the most promising, and to design a rapid series of Phase 2B proof-of-concept studies.

Specifically, the following four activities are highly promising areas to pursue for accelerating progress. They are: (1) characterising in detail the physiology and ecology of the vaginal tract, and the identity and availability of HIV target cells; (2) characterising microbicide-induced changes in genital tract immunity and their effects on HIV transmission; (3) increasing and rationalising the number and diversity of microbicide candidates being developed, and (4) determining whether and how the physical properties of microbicide formulation influence product safety and efficacy (as well as acceptability).

Before moving on to each of these specific areas, one note: While there are many gaps in the basic and pre-clinical sciences areas, the obstacles to filling these gaps show a great deal of commonality—and consequently, so do the activities needed to overcome them. Therefore, in contrast to the three other chapters of the MDS, all of the priority actions listed on p.28 apply to all or most of the topics discussed below. These actions will not be re-listed in each section, although they will be mentioned in the context of more specific activities relevant to the area.

3.1 Characterise vaginal physiology and ecology, including the identity and availability of target cells for HIV

A sophisticated understanding of the female genital tract is critical for the success of the microbicide field. This understanding will help ensure that candidates which block sexual transmission of HIV do not also interfere with vaginal physiology or ecology. At the same time, this knowledge is central to our understanding of HIV target cells and early events in sexual transmission to women. Knowledge about vaginal physiology and ecology is, therefore, the foundation for rational product design of candidates that block specific viral pathways or cellular targets.

The human vagina is a unique and complex environment. It is lined with multi-layered stratified squamous epithelium and its associated immune system and non-immune cells, and contains a dynamic balance of bacteria, viruses, fungi, and protozoa. The epithelial wall is coated with mucin, while the vaginal fluid contains

serous transudate, microbial products, immune products (e.g., SLPI and cytokines), antimicrobial components (e.g., lactic acid and hydrogen peroxide), and antimicrobial peptides (e.g., calprotectin and lysozyme). Hormonal changes (due to age or other factors) are known to have a dramatic influence on the vaginal ecosystem, affecting pH, flora, and epithelial thickening.

There are several under-studied research questions which, if answered, could make a major contribution to microbicide development. Some of the primary areas for investigation are defined in the following discussion.

3.1.1 Analysing the influence of physiological and pathological changes on HIV infection

Limited understanding of genital tract physiology and ecology hampers rational product design and the evaluation of products, especially in terms of safety. Advances in this area can be directly translated into new pipeline approaches.

In contrast to the relative wealth of knowledge about the physiology of the vaginal tract, the influence of the various physiological and pathological changes in relation to HIV infection is under-studied and poorly understood. This lack of attention is largely due to the lack of validated animal models and intact human tissue models for studying the course of HIV infection.

In addition to looking at the role of individual target cells, it is also important to expand understanding of the protection provided by the physiological barriers in the female genital tract (e.g., vaginal mucosa and cervical tissue). Furthermore, distribution of cell types throughout the female genital tract is heterogeneous, and it is not yet known whether the risk for infection is equally distributed throughout the vaginal tract or if sites of greater susceptibility for infection (i.e., “hotspots”) exist.

As studies reveal the course of infection in healthy vaginal tissue, it is also important to examine the factors (such as inflammation caused by other STIs, vaginal douching or washing, tampons, or the microbicide itself) which can affect the quantity, distribution, and activation state of CD4+ T-cells in the genital tract, since these cells are the primary targets of HIV infection regardless of the pathway used to establish initial infection.

ACTIVITIES RELATED TO PRIORITY ACTIONS

- Develop appropriate models—e.g., non-invasive human or animal models for the study of vaginal ecology, as well as new small animal models, such as transgenic rodent models
- Involve centralised reference labs in providing access to vaginal and cervical tissue biopsies from HIV-positive and -negative individuals, which are useful experimental systems for studying these issues
- Develop imaging tools and cell labelling technologies for studying the vaginal ecosystem and HIV infection in the human genital tract

3.1.2 Characterising HIV infection

The last few years have brought marked progress in understanding the basic biology of mucosal transmission. An especially important finding is that HIV infection across the mucosa can involve at least five mechanisms:

- direct infection of epithelial cells;
- transcytosis through epithelial cells and/or specialised microfold cells;
- epithelial transmigration of infected donor cells;
- uptake by intraepithelial Langerhans cells; and
- circumvention of the epithelial barrier through physical breaches.

The extent to which each of these mechanisms contributes to HIV infection across the mucosa is not yet known, and continues to be studied *in vitro* and in animal models. While any of these initial events may predominate under different circumstances, all of them lead to the infection of CD4+ T-cells whose distribution and activation state are of paramount importance.

Our understanding of target cell identity, distribution, and involvement in HIV is incomplete because of several important gaps, including poor understanding of:

- Details of HIV transmission via the genital mucosa. For example, the precise portals of viral entry are not known, nor are the roles and interactions of various cell surface receptors (i.e., CD4, CCR5, CXCR4, DC-SIGN, and other yet-to-be identified receptors) in the vaginal tract.

- The role played by different potential target cells in the vaginal tract during each step of transmission. Obstacles in identifying the type and availability of these target cells arise since the multiplicity and activation state of target cells are poorly understood. The vaginal epithelium changes during the menstrual cycle, with age, in response to hormones, and after exposure to pathogens and/or mechanical disruption, all of which could affect target cells—for example, inflammation can increase the number and activation status of CD4-positive T-cells. Although it is reported that the frequency of sexual intercourse affects the composition of the cell layers targeted by HIV, quantitative studies have not been conducted.
- The role of receptors other than CD4 and chemokine receptors (such as DC-SIGN). It is not clear whether mucosal HIV infection invariably requires the CD4 receptor for entry or under which circumstances co-receptors other than CCR5 are used. There is also the possibility of non-specific viral entry into epithelial cells and monocyte/macrophages by cell-to-cell fusion, large vesicles, or Fc-receptors, which has not sufficiently been explored. Moreover, antigen-presenting cells, which efficiently transmit HIV to CD4 cells, could play a role in harbouring infectious virus and providing a reservoir protected from chemical intervention. Understanding the role and relative importance of these receptors will help guide product development, and can also inform the design of animal challenge studies, since some challenge strains are CCR5-tropic while others are CXCR4-tropic.
- Focal (or localised) infections and their role in virus dissemination throughout the body. In addition, the possibility of self-limiting infection (the “threshold” effect) needs to be investigated.
- Lack of clarity about appropriate models for studying target cell availability and identity. The complex environment of the vaginal tract is not easy to mimic *in vitro*. Nevertheless, cell culture assays are often utilised to mimic the pH transition that occurs during coitus, and vaginal and seminal simulants have been developed for use *in vitro*. Alternatively, HIV can infect cervical explant tissues (obtained from hysterectomies), which are a useful *ex vivo* system. There are also a number of animal models that mimic various aspects of HIV infection in humans, including the SIV/SHIV/maaque model and several highly contrived small animal systems. Synthetic tissue systems designed to represent human vaginal ectocervical (VEC) epithelial cells have also been developed, and are used to study toxicity and basal mucosal phenomena. However, all of these systems have limitations, suffer from inter- and intra-assay variability, and have not been standardised or validated.

3.1.3 Characterising the biological nature of the transmitting virus

The viruses that are transmitted during sexual infection may have distinct characteristics. Understanding the properties of transmitting strains—an important microbicide target—should help guide more rational design of candidates.

An important issue in the HIV field is whether transmitting (and transmitted) viruses are a representative sample of the overall viral population in the blood, or whether they represent a minor sub-population with a particular phenotype that confers an advantage in transmission. If the latter is true, what phenotypes are selected, and what could the molecular basis of such an advantage be?

The question arises in the present context because HIV exhibits a high degree of variability in several properties relevant to microbicide product development. It is therefore important to know whether transmitting strains differ from the overall viral population with respect to any of these specific properties. Some possibilities and issues to examine include:

- co-receptor usage. While there is evidence that CCR5-tropic virus is responsible for infecting cervical tissue, it is not known whether human sexual transmission of HIV can also occur via CXCR4-tropic strains.
- the roles of cell-free and cell-associated virus in infection. Both forms are capable of infecting tissue culture cells.
- the potential for subtype differences in the efficiency of mucosal transmission.
- the minimum viral load in ejaculate needed to establish productive infection.
- the fitness and phenotype of viruses in the ejaculate.
- the initial cell targets in vaginal infection, and the speed and mechanisms by which HIV progresses from a localised infection to a systemic infection, which determine where and how quickly microbicides need to act.
- the role of seminal fluid and other proteins in enhancing viral transmission. There is some evidence that seminal fluid and other proteins appear to enhance transmission, but this phenomenon is poorly studied.
- identifying the most appropriate animal models to use to study viral transmission.

The limitations in available *in vitro*, *ex vivo*, and animal model systems were addressed above, while our capacity to study transmission in humans is very limited.

ACTIVITIES RELATED TO PRIORITY ACTIONS

- Develop model systems suitable for these studies
- Identify source, such as a specimen bank, for vaginal and cervical tissue biopsies from HIV-positive and -negative people, and vaginal fluids from HIV-positive patients
- Establish contract reference laboratories that can meet the needs for *in vitro* and explant systems, and for animal models

3.2 Build understanding of genital tract immunity and the effects of HIV infection and microbicides

Far too little is known about the interrelationship among mucosal immunity, microbicides, and HIV and other STI pathogens—despite the fact that local immune changes caused by a microbicide product could have strong effects on safety and efficacy. Understanding these changes is crucial to developing both safe products and accurate product profiles.

There is an urgent need for information on how microbicides affect genital tract innate and adaptive immunity and, by extension, HIV transmission. One key question is whether repeated applications of microbicides might trigger an inflammatory response or interfere with protective mediators of mucosal immunity and thus paradoxically promote transmission or acquisition of HIV and/or other sexually-transmitted pathogens. STIs, in turn, can influence innate and adaptive immunity in the genital tract and thereby potentially modify microbicide efficacy.

However, despite the critical importance of being able to determine the proinflammatory potential of microbicide candidates, both at the pre-clinical level and in early clinical trials, research in this area and the related gap of biomarkers (see section 3.4) is scarce and underfunded. Most of the efforts are geared toward assessing the cytotoxicity and proinflammatory potential of microbicide candidates on epithelial cells and tissue explants derived from the reproductive tract. Progress has also been made in characterising potentially relevant biomarkers (e.g., cytokines, chemokines, and inflammatory mediators) in model systems. For example, studies are underway to validate the use of cytokines in cervicovaginal lavages as biomarkers of genital inflammation. But few published reports address the impact of microbicides on

the innate mucosal and adaptive immune responses to microbial and other foreign antigens, or analyse how these immune alterations affect HIV acquisition and transmission.

The main obstacle to such studies is, once again, the paucity of well-characterised and validated pre-clinical models. The need for very specific models that can adequately represent the properties of the genital mucosal immune system stems from several factors: (1) the constitutional uniqueness of the genital tract, which precludes applying knowledge gained from respiratory or gastrointestinal tracts directly; (2) the distinct influence of reproductive hormones; and (3) the influence of human-specific microflora and semen. Scarcity of suitable human tissue and non-human primates further hampers the development of appropriate model systems, as does the lack of solid clinical or epidemiological data linking genital tract immune changes with HIV transmission. Approaches to resolving the lack of models are discussed below in section 3.3.

Several other obstacles add to the difficulties in carrying out this research. One is the relative lack of interest among immunologists and most microbicide researchers studying innate and adaptive immune responses in genital tissues, perhaps arising from the difficulty in obtaining these tissues or in gaining access to appropriate models. Another obstacle is the paucity of clinical studies focused on cervicovaginal inflammation and immunity, especially those correlating biomarkers with signs of inflammation and immune dysfunction. In developing and validating new biomarkers of inflammation and immune disruption, the main obstacle is the scarcity of adequate model systems to elucidate microbicide mechanisms of action from which to derive such biomarkers. This problem is compounded by the many different platforms and methodologies for measuring new biomarkers, the lack of standardisation and normative values for existing biomarkers, and the presence of interfering factors in the cervicovaginal environment. Last, too few studies correlate data from *in vitro*, animal, and clinical studies to support validation of currently-used markers.

These efforts will only succeed if there is a high degree of communication among scientists working in different disciplines. Fostering interdisciplinary collaborations among immunologists, microbiologists, reproductive biologists, and gynaecologists would bring existing expertise into the microbicide field and reduce duplication of efforts.

ACTIVITIES RELATED TO PRIORITY ACTIONS

- Develop and characterise new model systems (based on cell lines, explants and small animals) suitable for studying the immune system of the lower and upper genital tract and for assessing the impact of microbicides, reproductive hormones, semen, and microflora
- Develop *in vitro* and *in vivo* models to study interrelations between epithelial and immune cells from the upper and lower reproductive tract, and between these cells and commensal and pathologic microorganisms
- Increase access to nonhuman primates for microbicide safety research

OTHER RECOMMENDATIONS

- Conduct more epidemiological and clinical studies to confirm the association between genital mucosal inflammation and HIV/STI acquisition, and to establish correlations between human and pre-clinical/model data
- Fund research that addresses the genital mucosal immune system and its interaction with microbicides, perhaps through programs that support studies in targeted areas
- Foster interdisciplinary collaborations among immunologists, microbiologists, reproductive biologists, and gynaecologists, which will bring existing expertise into the microbicide field and minimise duplication of effort

3.3 Develop, standardise, and validate key research tools for microbicide studies

The lack of appropriate model systems severely impedes progress on key scientific issues. Development and validation of models suitable for resolving these questions should open the door to rapid progress, hastening the field's evolution towards more rational microbicide development. The development and validation of biomarkers represents another rich opportunity to accelerate progress, by providing links between pre-clinical properties of microbicides and their clinical effects. Given the significant cost and efforts associated with large safety and efficacy trials, development of properly validated biomarkers for use in pre-clinical and early-stage clinical studies is an imperative.

The lack of appropriate tools and technologies represents perhaps the biggest obstacle to answering the crucial scientific questions facing the microbicide field, and are raised throughout this chapter.

Model systems represent the best way—and often the only way—to approach many questions experimentally. Systems in use by the microbicide field include:

- cell cultures;
- epithelial cells or tissue explants from the reproductive tract;
- synthetic tissue systems designed to represent human vaginal ectocervical epithelia;
- small animal models (e.g., mice infected with HSV or retroviruses, or rabbits); and
- nonhuman primates, especially macaques.

However, all of these models suffer from one or more limitations, usually including a high variability and poor reproducibility. None of them is validated or rigorously standardised, making it difficult to compare data from different laboratories, or in some cases even between different experiments in the same laboratory.

ACTIVITIES RELATED TO PRIORITY ACTIONS

- Standardise and validate the more promising models among those presently in use
- Develop new, more innovative model systems, such as transgenic rodent and rabbit models, optimised *ex vivo* systems, and alternative retrovirus models (e.g., FIV/cat or mouse retroviral models)

Since no single model will be suitable for all purposes, it is critical to pursue the development of several different systems. The availability of multiple diverse model systems would allow for selective and combined development of leading microbicides from the array of concepts currently in pre-clinical evaluation. Improved model systems would also enhance the prospects for defining surrogate markers once clinical data become available. Validation should allow data generated with these systems to be used for regulatory purposes.

Turning to surrogate markers, their importance lies in the fact that they can link the properties of a product *in vitro* with its behaviour in people and vastly simplify

the tasks of developing and evaluating microbicide candidates. Finding a surrogate marker for efficacy will not be possible as long as there is no candidate which shows even partial efficacy in humans; however, markers for safety, other biological properties (such as exposure to HIV) and perhaps microbicide use and sexual behaviour, can potentially be identified.

The main approach to resolving the gap around the discovery and validation of novel biomarkers and assay methodologies is to foster focused research on these areas, trying to integrate pre-clinical and clinical studies aimed at selecting and validating markers with good predictive value.

ACTIVITIES RELATED TO PRIORITY ACTIONS

- Establish a centralised specimen bank containing clinical samples and associated data from past, current, and future safety trials (e.g., cervicovaginal lavages, sera, biopsies, and colposcopic data)
- Establish centralised facilities with Good Laboratory Practices (GLP) certification, to provide microbicide researchers with standardised analytical tools such as biomarkers, reagents, technologies and assays, and biomarker determination for clinical studies

3.4 Develop, broaden, and rationalise the pipeline

A shared rational plan for expanding and managing the number and diversity of microbicides in development would contribute to rapid progress and efficient use of resources across the field.

An optimal microbicide pipeline must support not only highly promising candidates, but also novel approaches with potentially higher risk of failure. The selection and progression of candidates should be organised in an iterative manner, utilising assessment algorithms that continue to evolve with our expanding knowledge base. In contrast, today's pipeline, although it continues to grow, remains narrow. A critical task for the field is therefore to expand the pipeline rationally so it includes a wider array of candidates that act on a variety of different targets.

TABLE 3 Properties used to assess microbicide candidates

PIPELINE MANAGEMENT What compounds should be advanced into clinical trials?	
Mucosal infection	mechanism of action; vaginal compatibility; range of action
Immunology	impact on innate and adaptive immunity; inflammatory response; relevance to transmission
Pipeline	potency/activity; toxicity; stability; cost
Formulation	potency; toxicity; stability; acceptability

3.4.1 Rationalising product selection and development

A key challenge in rationalising the pipeline is the lack of criteria that definitively identify the most promising products. For example, compounds that are effective therapeutics, or that show potent in vitro inhibition of HIV infection, are not necessarily strong microbicide candidates. (Table 3 lists the properties that are usually considered in decisions about which products to advance into clinical evaluation.) A collection of better defined criteria should come from a more complete understanding of mucosal infection and the genital tract immune system, so that a more rational design of microbicides, and a more rationalised pipeline, can be achieved.

To achieve a greater diversity of microbicide candidates, including multiple conceptual approaches, targets, and formulations, researchers should seek to:

- incorporate the use of biophysical and *in silico* tools of medicinal chemistry and rational drug design for the selection of new microbicide targets and molecules;
- gain access to private academic and government screened and unscreened libraries to enhance chemical diversity;
- secure intellectual property for acquired compounds and processes;
- accelerate the incorporation of high-throughput screening methods and resources into microbicide development; and
- identify candidates that cannot be readily scaled beyond initial assessments, to avoid their consideration as primary leads.

Candidate microbicides with similar profiles should also be directly compared, so that true innovations and/or drawbacks to a given design can be identified.

Although many investigators in private, NGO, and government facilities are developing microbicides, cross-comparisons of relative microbicide safety, efficacy, and acceptability are not the norm for these efforts. This is not true for industry, which classically works toward leads using a pre-identified product profile incorporating go/no-go criteria. At least four factors contribute to the current situation: (1) lack of a proof-of-concept for an efficacious microbicide; (2) lack of correlates for safety and efficacy; (3) reluctant industry participation in microbicide development; and (4) failure to develop consensus guidelines for selection within the pipeline.

The ability to identify and acquire existing government and private compound libraries while maintaining intellectual property was also identified as critical to enhancing the pipeline. Underlying these proposed interactions is the need to refine and develop guidelines, standards, and validated approaches to be used as a selection sieve to identify leads. Importantly, the International Working Group on Microbicides has assembled some criteria for selecting leads, in terms of both obligatory and desirable criteria, and has linked these to recommendations for the pre-clinical development of microbicides. (Lard-Whiteford et al., 2004)

Achieving a robust microbicide pipeline will depend heavily upon communication and coordination among microbicide developers and funders, and on development of a consensus approach to pipeline management. This management should also rely on sources outside the microbicide field (e.g., the Center for HIV and Vaccine Immunology (CHAVI), the National Institute of Health Director's Road Map Initiatives, the development initiatives currently underway at FDA, and other established or *ad hoc* panels from around the world). Whenever possible, experts from the pharmaceutical industry should be incorporated into this process.

ACTIVITIES RELATED TO PRIORITY ACTIONS

- Bring in outside expertise through increased coordination and communication between resources with medicinal and combinatorial chemistry expertise, and those groups studying genital tract infection and immunity. Integrate high-throughput technologies and manufacturing expertise into the pipeline for both compound and target development
- Focus efforts to identify, acquire, and facilitate the association of new types of expertise and capability (which are largely outside the field) with the microbicide pipeline development effort
- Develop centralised resources that can confirm and validate microbicide candidate profiles, providing developers with cross-platform standardised data

3.4.2 Developing combination microbicides with multiple mechanisms of action

The field's current understanding of mucosal transmission, especially the finding that HIV can utilise multiple pathways to infect cells in the genital mucosa, suggests that candidate microbicides that combine multiple mechanisms of antiviral action may be the most effective at blocking HIV and STI transmission.

The microbicide strategies of several private and government funders acknowledge the need to develop combination strategies, and several individual researchers are identifying potential combinations. However, efforts to develop combination microbicides lack focus, cohesiveness, and direction, and developers are not yet assured that combination products will be able to pass regulatory review. In particular, five obstacles are slowing the development of combination microbicides:

- the perception that regulatory requirements for complex combinations will require all components of a combination to be developed singly, and that an efficacy trial must show greater protection by the combination than by any of the component microbicides used separately;
- lack of focused approaches to identify workable microbicide combinations consisting of: (1) multiple discrete candidates; (2) formulary elements as active components; and (3) multi-target combination strategies that may involve interaction with multiple anti-transmission targets and/or STIs associated with HIV acquisition;
- the inappropriate use of therapeutic discovery assays and paradigms to identify microbicide candidates;
- IP conflicts arising from combining products; and
- a lack of validated analytical assessment methods specifically derived for prevention combinations. For example, it is unknown how concentrations of active agents in microbicides shown to have *in vitro* activity will translate to required concentrations of active agents in microbicides for use by people. Data from recent nonhuman primate microbicide studies suggest that combination microbicides might have to contain active agents at concentrations that are potentially orders of magnitude higher than the concentration used *in vitro*.

ACTIVITIES RELATED TO PRIORITY ACTIONS

- Define a regulatory path for microbicide combinations
- Develop assays that address the development of combinations in the context of their probable usage concentrations rather than in antiviral therapeutic concentrations
- Standardise, validate, and incorporate the assays into the development pipeline, once combination assays are being performed in the proper context

In addition, resources are needed to define both the *in vitro* and *in vivo* constructs needed for identify promising microbicide combinations and then transition them into the pipeline. This effort should be complemented by dialogue with regulatory authorities to identify the most efficient developmental pathway for approving clinical studies and licensure of both single and combination candidates (see section 3.5.2). Additional tools to address this gap include the funding of focused efforts to develop relevant models.

3.4.3 Clarifying and simplifying regulatory requirements

Progress on rationalising the pipeline is dependent on establishing clear regulatory requirements for the advancement of candidates through development and commercialisation. There are several obstacles to achieving this clarity, in particular:

- regulatory requirements are often unclear when applied to microbicides, and can be overly restrictive;
- consideration of regulatory requirements is not always integrated into the process of early pre-clinical microbicide design and formulation; and
- there are no current guidelines for microbicides composed of complementary and alternative medicine formularies, RNA- or DNA-based approaches, and vaccine/microbicide combinations.

It should be acknowledged that regulatory guidance is critical to determining the resource and technical requirements of conforming to the regulations. The available guidelines can be adapted to microbicides, but this less-than-optimal approach may increase the risk of regulatory failure for developers, a prospect that reduces their willingness to continue development.

There are also potential challenges arising from continued advancement through pre-clinical toxicology and clinical studies. Developers may see a challenge as a disincentive, causing them to deprioritise a particular approach before pre-clinical studies can even establish the potential value of a given microbicide.

The recent FDA guidance for antivirals (www.fda.gov/cder/guidance/6568dft.pdf) does not address any of the unique problems associated with pre-clinical development of microbicides or combinations of microbicides. And, in the microbicide field, regulatory challenges are often noted but placed at a lower priority than pushing a microbicide through discovery and feasibility assessment for clinical evaluation. This points to a specific and as-yet unmet need for focused interactions between product developers and regulatory authorities, with the aim of beginning to establish regulatory pathways and guidelines for both single and combination microbicides.

Because most regulatory decisions are evidence-based, it is crucial to have experimental approaches designed to generate the necessary data. Currently, a few funders (e.g., NIH, IPM, and CONRAD) are supporting basic science and clinical studies that can provide the sort of evidence needed to address regulatory concerns. However, these studies frequently arise from investigator-initiated efforts and lack any direct coordination with regulatory sources. Thus, there remains an urgent need for the coordinated support and funding of critical microbicide studies designed to provide the kind of evidence that can be used to develop microbicide regulatory guidelines.

Two approaches were identified for overcoming regulatory obstacles. The first is to recruit expertise to assist and empower microbicide developers in working more intensively with regulatory authorities. Second is to define and implement specific pre-clinical and clinical studies to generate data that supports or disproves the value of specific regulatory requirements or strategies. Thus, support should go into efforts such as those of WHO and others that stress the scientific basis of microbicide regulation, as well as efforts that bring regional coherence to regulation.

3.5 Identify and characterise the properties of microbicide formulation that affect safety and efficacy

Addressing requirements for physical formulation properties will improve existing formulations and delivery strategies and speed the development of novel approaches for future delivery systems.

There is an urgent need for a more sophisticated understanding of the physical properties required to rationally design formulations or delivery technologies that

are stable and maximise safety, efficacy, acceptability, and adherence. Steps taken to address this gap would improve existing formulations and delivery strategies and help develop novel approaches for future delivery systems.

Four key issues need to be addressed: (1) characterisation of formulation physical properties (such as viscosity, adherence, deployment, distribution, release, and retention); (2) pre-clinical assessment of formulation safety and potency; (3) acceptability and adherence; and (4) alternative delivery technologies. This section will discuss the first two; the latter two are covered extensively in chapter 5.

3.5.1 Characterise advantageous physical properties

There are few data available to clarify what physical properties a formulation should have to be safe and efficacious. The physical properties relevant to acceptability and adherence have not yet been validated in the appropriate populations. Each of the four key issues listed above represents a considerable deficiency in knowledge, capability, technology, or resources, and a primary obstacle to the development and subsequent use of a microbicide.

Several obstacles contribute to this poor understanding. One is that the field has not yet completed the current round of Phase 2B and Phase 3 trials, so there are no safety or efficacy data sets available to correlate with physical properties. Another is that retention, miscibility, absorption, and deployment have yet to be systematically studied. There is, for example, insufficient understanding of the significance of vaginal distribution of microbicide gels. Studies using MRIs to assess vaginal coating have shown that gels can provide broad epithelial coverage, but it is unclear whether broad coverage is an ideal characteristic. While 100% coverage seems desirable in theory, it may be that effectiveness is enhanced if the gel is retained near the cervix or transition zone. To achieve 100% coverage, developers may trade off other properties (such as vaginal retention), and it is vital to assess the effect of these properties on safety and efficacy.

Another factor contributing to the continued uncertainty about ideal physical properties stems from insufficient understanding of mucosal infection—an example of how formulation gaps are strongly linked to other basic science and pre-clinical development gaps and to the specific mechanism(s) of action of the individual candidate microbicide.

ACTIVITIES RELATED TO PRIORITY ACTIONS

- Conduct deployment trials utilizing MRI or another suitable technique to assess multiple formulations in terms of appropriate volume and physical formulation properties
- Conduct appropriately powered clinical trials comparing vaginal formulations, with the aim of developing a compendium of formulation components and their corresponding spreadability, retention properties, and acceptability
- Link physical characterisation data of these formulations to the *in vivo* MRI studies

3.5.2 Conduct pre-clinical assessment of safety and potency

The field must increase efforts to identify *in vitro* tests that are predictive of *in vivo* outcomes. Traditional pre-clinical formulation tests, including Franz-type diffusion, mechanical, muco-adhesive, texture testing, and others, may not be adequate predictors of clinical experience. In addition, existing explant models may yield varying results for a single formulation. There are no marketed microbicides, and therefore no clear comparators through which to evaluate investigational products. There is also a need to establish methodologies to assess novel delivery methods, and a lack of regulatory guidance on a range of associated issues.

ACTIVITIES RELATED TO PRIORITY ACTIONS

- Standardise *in vitro* tests utilised during formulation development to allow comparison among microbicide products
- Continue to develop explant model systems and establish a standard approach for formulation development in all available explant models
- Integrate cross-cutting expertise from relevant fields early in the development process, including industrialisation and commercialisation expertise, and expertise in developing products with both cosmetic and pharmaceutical benefits

PRIORITY ACTIONS

CLINICAL RESEARCH

- 06 Develop an inventory of potential research sites and an assessment of their “readiness”, to be shared among product developers and research sponsors working in microbicide development and in other areas of HIV and STI research
- 07 Increase the capacity of clinical research sites to recruit, train, and retain staff, using mechanisms such as increased core funding, network support, and centres of excellence
- 08 Document the full costs of ongoing trials, as an aid to investigators, funders, and sponsors in planning for future studies
- 09 Develop transparent processes whereby clinical research sites can seek to implement trials with different sponsors and investigators
- 10 Develop new local and international consensus statements for responsibilities and standards of care in the context of HIV prevention research, including microbicide, vaccine, pre-exposure prophylaxis, and behavioural studies. These statements should represent consensus on key arrangements such as the duration of trial sponsors’ commitment to provide care; elements of the care package to offer to research participants, their family members, and those found ineligible to participate; trial sponsors’ commitments to treating trial-related injury or illness; trial sponsors’ role in contributing to health in the community; and trial investigators’ roles and limits of responsibility
- 11 Expand ongoing efforts to document and evaluate research methods for measuring sexual behaviour, condom use, and candidate microbicide use, including efforts to identify best practices across different trials and sites, and to develop consensus about when to use standardised behavioural measures versus a tailored or supplementary approach
- 12 Create an international database containing safety and other data from all microbicide products and studies that will be organised to foster cross-comparison and detailed analysis of completed, ongoing, and future trials.
- 13 Establish ongoing dialogue between trial investigators and regulators to identify the most efficient strategies for evaluating microbicide products, including the use of potential surrogate markers and alternative trial designs.

Chapter 4

CLINICAL RESEARCH

Around the world, a growing number of microbicide candidates is entering into, and progressing through, clinical evaluation. These studies are attracting considerable attention, investment, and community support. As of mid-2006, five candidate microbicides are being tested (at more than 35 clinical sites in 17 countries) for their ability to prevent HIV infection. More than a half dozen other products are being assessed in Phase 1 and Phase 2 studies.

Preparing for and carrying out these large, complicated studies is a mammoth undertaking in any setting, but especially in resource-poor regions. Together, this research involves tens of thousands of women participating as volunteers, engagement of trial site staff with dozens of local communities and community leaders, and the training, support, and retention of hundreds of trained HIV counsellors and clinicians. To reach this point, substantial investments have already been made in building up clinical facilities, laboratories, and logistical operations at dozens of sites in Africa, Asia, and Latin America.

To the collective benefit of global microbicides development, clinical investigators are demonstrating an unprecedented enthusiasm to share information and experiences across the organisational boundaries of study sites, networks, and sponsoring agencies. For example, beginning in 2004, an international working group began to meet regularly to share information among clinical researchers conducting large microbicide trials. Persistently named the “Quick” Clinical Trials Working Group, this group has also promoted the use of common approaches in areas such as study protocol design, data collection instruments, and specimen collection protocols. The goal is to make it easier to compare data from different studies and to optimise the information gathered from each study. So far, specific discussions have included:

- identifying optimal methods for assessing HIV incidence;
- designing protocols to assess the impact of pregnancies among study volunteers on retention rates (and, in turn, on research outcomes);
- integrating relevant social science questions into efficacy trials; and
- defining the standard of care for research participants and communities.

However, despite this progress, many challenges remain. Furthermore, these challenges are being brought into sharper focus by expansion of the overall microbicide development effort, by increased research investment into other potential HIV

prevention technologies (such as vaccines and pre-exposure prophylaxis), and by the urgent needs of millions of people around the world who still lack adequate health care, HIV treatment, and access to preventive measures against the virus.

One of the biggest challenges is to ensure that substantial investment, coordination, and planning are available over a sustained period. A series of large trials will be necessary to identify an effective candidate microbicide, vaccine, or other new prevention technology. Without substantial and sustained support, there will not be enough clinical sites with well-trained staff, sufficient community support, and robust incidence and prevalence data to conduct the needed research.

Behind the analysis and recommendations presented here are several key assumptions. They are:

- Clinical research site development should optimally be linked to preparation for a specific study. Experience has shown the difficulties in developing and sustaining trial site capacity if there is no early prospect of a candidate product being studied at those sites.
- Community input at the local, national, and international levels is a critical part of all prevention research. The success of clinical research depends not only on meeting the scientific and logistical challenges of clinical trials, but also on developing and maintaining open, collaborative relationships with community groups and advocates.
- It is likely to take several years and a series of efficacy trials to identify a highly protective microbicide, even if the early microbicide candidates, several of which are now in Phase 3 testing, demonstrate strong efficacy.
- New and innovative trial designs may be needed to answer questions about microbicide safety, efficacy, and acceptability, particularly for newer microbicide formulations and for combination products.
- If and as efficacy is demonstrated of newer HIV prevention approaches (such as of the candidate microbicides, vaccines, use of diaphragms and other barrier methods, PrEP, STI treatment, or male circumcision), these approaches will need to be immediately integrated as standard ‘control’ interventions for all clinical research participants. This might change the design and cost of clinical evaluation of future microbicides.

Based on these assumptions, recommendations for raising the effectiveness of clinical research on microbicides focus on ways to:

- develop and sustain clinical research site infrastructure and personnel to prepare for new clinical studies;
- increase investment in clinical research and development;
- ensure good standards of care;
- expand behavioural research; and
- identify and validate surrogate markers of clinically important outcomes.

Each of these high-priority activities is discussed in detail below.

4.1 Develop research site capacity

Building clinical research site capacity is a long process that involves major effort not only at the sites themselves, but also at the national and international levels. To ensure that there will be sufficient capacity for conducting trials for the coming years when many new products should be ready for efficacy testing, multi-front site preparedness activity should be underway now. At the same time, stakeholders in the global microbicide effort need to help mobilise new investment for this very expensive task.

At the local level, investment is needed to build, equip, and maintain clinical and laboratory facilities. Investment is also needed to recruit, train, and retain qualified staff. Site staff also need to work at building trust with potential trial cohorts and communities, local and national civil society groups, local and national government (especially health ministries), and other stakeholders. At a local level, community engagement can guide clinical research design and implementation in ways that maximise research outcomes while also maximising health outcomes and social benefits. At the national and international levels, an environment supportive of clinical research also means that regulatory capacity should be expanded and requirements further defined so that that regulatory review, monitoring, and approval of clinical research plans and data are timely and effective. Stakeholders also need to improve international coordination of activity and information across the microbicide field.

4.1.1 Engaging multiple research sites and populations

The series of iterative studies anticipated for microbicides (and for HIV/AIDS vaccines and other prevention strategies) will require multiple sites and many thousands of research participants. Anticipated shortages in sites and in well-characterised cohorts present a major obstacle to rapid progress in the field.

The fact that 35 research sites in 17 countries are now conducting microbicide efficacy studies is a major achievement. Yet despite this impressive build-up, many more sites and much greater overall capacity will be needed to meet future research needs. More than a dozen candidate microbicides may be considered for large Phase 2b and Phase 3 research studies during the coming decade, with each requiring thousands of participants. If any product in these studies proves to be protective, additional clinical research—such as confirmatory studies, bridging studies, and/or post-marketing research—are also likely to be needed. At the same time, other prevention interventions such as HIV/AIDS vaccines and pre-exposure prophylaxis are also advancing through proof-of-concept and large efficacy trials, with more to follow.

Study site preparation requires attention to an extensive range of issues, often down to the last detail. Experience shows that enrolment into a microbicide study can be prematurely stopped at any study site for one of many reasons; examples include inadequate recruitment of research participants, poor quality of data collection or laboratory work, a low number of expected endpoints (due to lower than anticipated participant retention or HIV incidence), or lack of community support. All of these factors can seriously impair a site's ability to contribute its share of data to answer the trial's primary research questions about HIV prevention. An overall strategy for site development should therefore aim to build some redundancy in clinical research site capacity, while being cognizant of costs, since this could avoid major delays in completing large multi-site microbicide trials.

Therefore, over the coming decade, many more well-prepared clinical research sites are needed. Core requirements include having a capacity to recruit and retain research participants at high risk for HIV, being able to provide high-quality prevention, care, and treatment services, and generating high-quality laboratory samples and data.

Standards for clinical site preparation have ranged between a 'minimalist' approach (rapid site assessment and training, limited scientific questions, and lower trial cost) and a 'maximalist' approach (extensive multi-year preparatory studies, pre-trial assessment of incidence and retention, multiple protocol reviews, and higher trial costs). Both of these extremes have had relative successes and some disadvantages. However, given that not all clinical study sites will be capable of implementing every research protocol, creation of sufficient contingent and competitive capacity for each protocol among research sites is essential.

In addition to physical infrastructure, human resources, and scientific preparation, clinical site preparedness also includes accessing and understanding the political, social, and behavioural landscape of a potential cohort. Preparatory community mapping and engagement can provide valuable experience in learning how to reach members of a community, how to best inform and educate the population about research goals, risks, and benefits, and how to evaluate and improve local standards of care. Preparedness research can also map patterns of sexual behaviour and fertility, identify high-risk sub-groups, develop research-related recruitment strategies and protocols with community input and ‘buy-in’, and provide an opportunity to orient and train staff.

Community support and ‘buy-in’ is also critical to the success of clinical research sites, the conduct of specific studies, and the long-term microbicide research endeavour. Researchers, trial sponsors, and product developers must develop supportive, trusting relationships with local stakeholders in each place where clinical studies are conducted. These stakeholders include potential research participants, study site community leaders, individuals in the local media, and regional and national political leaders. Such relationships require time, investment, and considerable attention. Failure to invest in them can result in problems later on, such as the inability of trial staff to respond adequately to concerns, which in turn can lead to confusion, controversy, and even cessation of the study. On the more positive side, relationship-building by microbicide researchers can be complicated (or complemented) by the presence of other research projects taking different approaches to the various ethical and human rights issues raised by clinical studies; therefore, research projects working in the same country or region should develop harmonised approaches to critical cross-cutting issues.

PRIORITY ACTIONS

- 06 Develop an inventory of potential research sites and an assessment of their ‘readiness’, to be shared among product developers and research sponsors working on microbicide development and other areas of HIV and STI research
- 09 Develop transparent processes whereby clinical research sites can seek to implement trials by multiple sponsors and investigators

OTHER RECOMMENDATIONS

- Define what constitutes adequate site preparation to run registrational-level clinical studies, developing criteria for a hybrid approach between the “minimalist” approach (rapid site assessment and training, limited scientific questions, lower trial cost) and “maximalist” approach (extensive multi-year preparatory studies, pre-trial assessment of incidence and retention, multiple protocol reviews, high trial costs) to achieve cost-effective trial preparation
- Invest in developing new sites with potential to recruit and retain large cohorts of high HIV-incidence populations for HIV prevention studies and that can develop reliable estimates of a population’s likely HIV or STI incidence over time, project levels of reported risk behaviours and risk factors, predict population mobility, define methods to attain study recruitment and retention rates, and identify laboratory reference ranges for the research population
- Explore tools to determine cohort-based HIV incidence more accurately, particularly in the context of regular study visits, quality prevention interventions, condom provision, STI treatment, and access to medical and social services
- Establish ways to create or contract for technical assistance and capacity development at clinical trial sites and to identify one or more providers that could collaborate with existing entities and/or centralise some aspects of site development across the field
- Work with clinical research sites to create and support local public forums for dialogue and consultation about research goals and community priorities, as well as encouraging research sponsors and product developers to support complementary discussions at regional and national levels
- Engage community advocates and community advisory boards and groups to document, disseminate, and seek funding for innovative approaches
- Regularly brief local press and brief activists in-country and internationally, as a way of building advocacy and support for prevention research and to ensure that potentially contentious issues, both current and emerging, have been addressed and adequately discussed prior to the launch of the study

4.1.2 Investing in human resources

Studies cannot be conducted without sufficient appropriately skilled human resources to staff both the study sites and the general health care systems which serve research participants, families, and communities.

The recruitment and retention of sufficient numbers of trained, experienced health care professionals—physicians, nurses, lab technicians, social workers, counsellors, community educators, and others—is essential for conducting clinical research and for the functioning of local health care and public health systems. A shortage of these human resources remains one of the most significant obstacles to improved public health and health research.

For clinical research sites and other health facilities in resource-poor settings, the shortage of health care workers stems from a variety of factors, including lack of training institutions, poor financing of national health programs, and structural adjustment policies that affect national hiring and salary levels in health care. Beyond low pay, trained health workers who work in resource-poor nations also usually face under-resourced health facilities and are overwhelmed by the high level of need for health services.

In addition to the challenge of recruiting skilled staff, many clinical research sites also report difficulties in staff retention. For small research sites, ensuring continuity of staff positions can be a challenge when transitioning between clinical study protocols and associated funding. Health workers can often find better paid and more stable employment in wealthier countries, which target health workers with active recruitment and specific visa and hiring programs. The advent of new international AIDS funding and scale-up of ARV treatment programs has exacerbated this, with health care professionals in HIV/AIDS treatment and care facilities finding themselves in an ‘employees’ market’ with many attractive opportunities to relocate. This mobility of health professionals is fuelled by the lack of structured advancement opportunities and low pay scales in local employment.

Microbicide clinical research sites around the world report struggles to find individuals with certain skill sets such as training in good clinical research practice, good laboratory practice, site management, and community education. Beyond this, even when research sites have managed to attract and retain qualified staff, there is often a shortage of health care personnel in the surrounding health care and public health system. This is an urgent problem for clinical research, since clinical study sites often rely on surrounding health systems to provide general (non-study-related) health care for research participants and their families, and to provide health care for individuals who are ineligible to participate in a given study.

International funding streams for health and development—such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the US President’s Emergency Plan for AIDS Relief (PEPFAR), and the World Bank—provide significant financial support for training and hiring of health care professionals. However, to date these programs have been unable to alleviate shortages of trained qualified health care staff in most resource-poor settings.

Although those involved in microbicide research cannot entirely redress inequalities in the international labour market, specific actions can be taken to improve the ability of clinical trial sites to attract and maintain high-quality staff for microbicide trials and other prevention research.

PRIORITY ACTION

07 Increase clinical research site capacity to recruit, train, and retain staff, using mechanisms such as increased core funding, network support, and centres of excellence

OTHER RECOMMENDATIONS

- Coordinate salary scales and per diems among clinical research staff and stakeholders working within a country or a region to improve overall staff compensation and retention
- Develop and fund clinical studies protocols with some attention to clinical site capacity and continuity and retention of staffing
- Create transparent processes through which sites with skilled staff can work with multiple study and product sponsors
- Develop and fund clinical research centres of excellence to support on-site staff recruitment and training
- Support off-site education and training programs for clinical research staff at all levels, including university training programs and Institutional/Ethical Review Board member training
- Explore potential partnerships between communities and researchers to maximise the capacity of communities to take an active role in working with researchers to ensure implementation of clinical research

4.2 Create an environment that supports clinical development

The past few years have yielded a wealth of ‘real world’ insights into the costs and challenges of conducting microbicide studies in the developing world. Overall, these studies are requiring more time, money, and human resources than either sponsors or funders had anticipated or prepared for. Adjusting these expectations and developing commensurate funding commitments, as well as plans to avoid problems that delay or slow down studies, are vital for further progress in the field.

Since efforts to make microbicides began, more than a dozen studies (from Phase 1 to Phase 3) have been carried out in developing countries—experience that has highlighted the importance of some less obvious types of support needed for clinical development. For example, looking at the factors that cause delay or slow down studies, and/or increase their costs, has identified some common obstacles beyond those related to inadequate site preparation (see sections 4.1.1. and 4.1.2).

These include:

- complexities of ethics and regulatory review and approvals;
- slower-than-expected research participant recruitment and enrolment;
- lower than expected HIV and STI incidence;
- reduced participant retention rates;
- raised expectations in terms of standards of health care for research participants, their partners and families, and/or those found at screening to be ineligible to participate in the study;
- new decisions by trial sponsors about providing related services (such as a decision to require on-site family planning services, made after noting high rates of pregnancy within the cohort);
- new decisions by regulatory agencies about trial design requirements (such as requiring an additional control arm); and
- changes in the political and/or economic environment of the host country, such as rapid fluctuations in currency exchange rates or inflation and/or politically-inspired changes in host institutions, including government agencies and non-profits.

The lower than expected rate of HIV and STI incidence may be due to a lack of prior data on infection rates, or to reliance on data from preparedness studies that do not correspond closely to the enrolled population in the present study. Alternatively, it could mean that the research activity and related services have had a positive effect on changing peoples’ behaviour in terms of reducing exposure to HIV and STIs.

In addition, reduced study participation may be a result of protocols for microbicide studies that currently require volunteers who become pregnant, or who test positive for pregnancy, to withdraw from the study. Many research sites report high pregnancy rates. This requirement can therefore significantly reduce the statistical power of microbicide studies, since power decreases as the number of volunteers drops. Even if women are allowed to re-enter the study after completion or termination of a pregnancy, the number of total person-years of exposure in the study will decrease.

PRIORITY ACTION

08 Document the full costs of ongoing microbicide clinical research. These costs should include the assessed cost of establishing clinical study sites, as an aid to funders and sponsors in planning for future studies. These costs should also allow for the possibility that demonstrated efficacy of a microbicide or other new HIV prevention intervention (such as a vaccine, PrEP, STI treatment, use of diaphragms or other barriers, or male circumcision) will change the standard of prevention to be provided to all participants and could change the design and cost of further microbicide efficacy trials.

OTHER RECOMMENDATIONS

- Improve regulatory capacity for evaluating clinical study protocols and experimental products in developing countries. While some national regulatory authorities have taken big steps towards strengthening their review capacity, others still have only limited experience reviewing trial designs for HIV prevention research and candidate microbicides. Building this regulatory capacity can be accomplished by expanding and supporting initiatives such as those at WHO, which is currently working on a project to educate regulators about microbicide research, along with the African AIDS Vaccine Programme (AAVP) and others. More coordination, training, and sharing of models is needed to ensure that there is appropriate in-country regulatory capacity.
- Encourage continued guidance by regulatory agencies in developed countries (EMA, FDA) on innovative study designs to speed evaluation of HIV prevention technologies (e.g., research designs tailored to evaluate and compare newer microbicide formulations, or study designs using potential surrogate endpoints once these can be correlated with HIV exposure and product use, safety, and efficacy)

- Explore potential value of innovative HIV prevention study designs, such as those that enrol larger numbers of volunteers for shorter periods of time
- Allocate funding for segment 3 and carcinogenicity research, building suitable laboratory capacity for these experiments to be conducted as soon as possible, contracting consultants to draft the reports rapidly, and developing ancillary sub-study protocols for submission to regulatory and ethics authorities so that pregnant women can continue using microbicide gel safely
- Fund clinical research sites to improve estimates of HIV incidence before and during trial screening and study enrolment, as well as systematic data collection related to HIV and STI risk and exposure (e.g., such as circumcision status or STI incidence of male partners)
- Fund clinical research sites to learn as much as possible from participants who seroconvert during the study due to unsafe sexual behaviour (e.g., these studies should assess the effect of an ARV-containing microbicide on the natural history of HIV infection, including the response to ARV treatment and development of viral resistance)

4.3 Ensure good standards of care

Balancing an appropriate focus on primary research goals, caring for research participants, and leaving communities better off post-study is an ethical requirement for providers of both HIV-related treatment and general health care in resource-poor settings.

Sponsors of clinical research, including product developers and research agencies, have an ethical obligation to provide medical care to research participants. Providing appropriate care helps establish conditions through which the research provides an overall net benefit, limits harm, and comes as close as possible to ensuring equitable outcome for those who participate voluntarily. In HIV/AIDS prevention research, where large efficacy studies must recruit, screen, and enrol thousands of individuals at high risk for HIV, this obligation for care is an urgent and expensive mandate.

Global public debate about the standard of care in HIV prevention research has often focused only on HIV-related treatment, including ARVs, routinely provided to individuals who become HIV-infected during the course of the prevention research. However, a standard of care also refers to the general health care accessible to all research participants and their families, even for health concerns that are not related

to the research or to HIV infection. A standard of care may also refer to the level of health services offered to individuals who are found to be ineligible for research participation during the screening process for study enrolment.

Despite high variability in the background levels of health care available for communities and countries in which research takes place, most microbicide clinical research sites offer all research participants a standard array of health interventions. These include routine HIV counselling and testing, HIV risk-reduction counselling, male condoms (and at some sites, female condoms and counselling about their use), medical histories and physical exams, pelvic exams (sometimes including Pap smear, cervical screening, and colposcopy), pregnancy testing and family planning counselling, and regular screening for STIs, including chlamydia, gonorrhoea, HPV, HSV, syphilis, and trichomoniasis.

Some of the potential gaps in this standard care include interventions needed by non-participants, treatment interventions such as adult and perinatal HIV treatment, and consistent provision of prevention interventions known to be effective. For example, some sites provide female condoms, cervical screening, or harm-reduction interventions to reduce unsafe drug use. Others may use newer prevention interventions if and as they are proven, such as community-level STI treatment, HIV and STI vaccines, pre-exposure prophylaxis (PrEP), and/or circumcision.

Another limiting factor is that in many clinical research settings with high HIV incidence, HIV is only one of many endemic health concerns. Research participants and the surrounding communities are often poor and present a range of health needs and priorities alongside their risk of HIV, including needs for basic family planning, obstetric and gynaecological care, and basic primary and emergency care. They also may require treatment for malaria or tuberculosis. While clinical research sites rarely have the funding or a mandate to provide this full spectrum of health services, even to enrolled research participants, they are ethically obligated to ensure that these services are accessible at some level.

In recent years, the standard for HIV treatment in many resource-poor settings has rapidly improved due to development of inexpensive treatment options, demonstration of feasibility in many countries, and increased global funding and expectations. This has focused attention on the standard of care provided in the context of HIV prevention research to research participants, to those who are found ineligible for trial participation during the enrolment process, and to members of communities surrounding the research sites.

A decade ago, provision of ARVs for study participants in many resource-poor countries was prohibitively expensive, and would have therefore been considered an undue inducement for participating in the research and a gravely inequitable, unsustainable intervention in the study site community. Now, through international and national funders, many countries are preparing for broad community access to ARVs. Against this backdrop, many research sponsors and community groups have made commitments to ensure that participants who become infected in the course of an HIV prevention study will receive HIV care, including ARVs when required. In some cases these commitments involve direct assistance from the research entity, although many entities have expressed a preference for referring patients to a national HIV treatment program.

These commitments are relatively affordable if they are made solely to research participants who become infected during the study. However, for studies in high-prevalence areas, sites face a major challenge in linking individuals diagnosed with HIV during screening to appropriate care and treatment facilities. The sites themselves lack financing and infrastructure to treat large numbers of HIV-infected individuals. Fortunately, in some instances, national programs may be able to meet these needs. But there are still only a limited number of facilities with the capacity and expertise to provide this care, and those that do exist usually have limited slots for new enrollees. Addressing the needs of people found to be infected during the screening process is one of the major issues confronting study sites that are attempting to implement high standard-of-care policies while at the same time implementing a demanding research protocol.

Another care-related issue now emerging is the lack of information about the potential risk of viral ARV resistance in women who use microbicides containing ARVs but nevertheless become infected with HIV. It will be critical to assess whether prior use of an ARV-containing microbicide affects their response to systemic ARV treatment initiated several years later. A related concern is whether any of the ARVs used in microbicides are also on the formulary of the national ARV treatment program in the host country. In at least one country that halted an ongoing PrEP trial (to test the drug tenofovir as a pre-exposure prophylactic), one reason the health ministry cited for this action was that tenofovir would also be used in ARV treatment for its population.

At present, standard of care, provision of ARV treatment, and research into ARV resistance are three issues being addressed in a fragmented way. Locally appropriate solutions are now often developed on a case-by-case, site-by-site, and study-by-study basis, an approach that provides valuable local autonomy and adaptability. But the

microbicide effort also needs greater documentation and sharing of these solutions, a stronger consensus on standards, and more coordinated planning and communications for global action.

Global communications are particularly important. Given the likelihood that local health care standards will continue to diverge and change, even within the same country and multi-site study, the microbicide research effort will need to position itself to communicate about how it plans to address this issue of standards amid real-world disparities.

PRIORITY ACTIONS

- 10 Develop new local and international consensus statements for responsibilities and standards of care in the context of HIV prevention research, including microbicide, vaccine, pre-exposure prophylaxis, and other prevention research initiatives
 - Develop consensus on the duration of study sponsors' commitment to provide care; elements of the care package to offer to research participants, their family members, and those found ineligible to participate; study sponsors' commitments to treating study-related injury or illness; study sponsors' role in contributing to health in the community; and the role and limits of responsibility of study investigators

OTHER RECOMMENDATIONS

- Document and disseminate case studies of good standard of care policies and practices at microbicide research sites that focus on managing community expectations regarding the mandate and capacity of clinical research sites in supporting local standards of care; supporting basic equity (so that health care options are similar among research participants, those screened out of participation, and those in the community who are not eligible or choose not to participate); and arranging continued access to health services (establishing systems for accessible health care after a trial ends)
- Support active involvement by local stakeholders in developing, documenting, and communicating about standards of care in the earliest possible stages of clinical site development and throughout the course of clinical research

- Explore innovative mechanisms for ensuring long-term access by research participants and research communities to quality health services
- Develop a coordinated research agenda to study potential ARV resistance arising from use of ARV-containing microbicides

4.4 Expand behavioural research

Clinical research relies on accurate estimates of sexual behaviour, pregnancies, microbicide use, and condom use to evaluate data from efficacy studies. Clinical studies need strategies to evaluate the accuracy of individual (self-)reporting and data collection. Early microbicide design and development also require information about whether and how various microbicide products might be used, and some of this information might be available from participants in clinical research settings. Behavioural research is therefore needed, at a scale that can capture a variety of risk groups and social and cultural contexts, and also collect findings that are consistent across many locations.

Sexual behaviour is complex and culturally diverse. It varies from country to country, within communities, between individual women and men, and over the course of an individual's life. Furthermore, in many cultures, sexual behaviour is not easily discussed in the public sphere. The way people ask about, and report on, sexual behaviour, intentions for pregnancy, and condom and microbicide use is therefore subject to multiple types of bias. Even when human sexual behaviours are similar across cultures and communities, people often speak about sex in ambiguous terminology and in culturally specific language. As a result, investigators and research participants face the challenge of defining and standardizing the variable and imprecise terms used to report sexual behaviour.

Such variations in terminology, culture, and expectations should not be minimised or ignored. The numbers and types of sex acts, frequency of microbicide and condom use, and numbers of partners are crucial parameters for microbicide product evaluation. The efficacy of a candidate microbicide—particularly one that may have only partial efficacy—could potentially be obscured by inaccurate self-reporting of sexual behaviour and microbicide use or inaccurately reported use of a partially protective candidate microbicide. Microbicide clinical studies therefore urgently need methods for collecting reliable and valid data.

Socio-behavioural scientists have developed a range of approaches to measure sexual behaviour. In the context of microbicide studies, researchers are developing a variety of tools, including objective surrogate markers, for gathering information about the use of microbicides, condoms, and other proven or experimental prevention measures. These data have already provided many useful insights.

Further research is needed to validate and streamline measures of sexual behaviour and of condom and microbicide use. Focused sub-studies that use different approaches to collecting the same type of data within a single study may help to validate data collection methods. Resolving these questions should increase the strength of clinical research data, reduce the potential costs and burden of data collection, and obviate the need for continued, multiple, and extensive behavioural research approaches in the context of microbicide studies.

As of mid-2006, a working group of clinical researchers involved in conducting the present Phase 2B and Phase 3 studies has assembled a directory of the sexual behaviour data collection tools currently in use in large-scale efficacy studies. Although the working group has not reached consensus on which tools are most appropriate to different situations, this effort forms the basis for further work to standardise research, share approaches, and map out a research agenda that will meet the needs of multiple study sponsors.

PRIORITY ACTIONS

- 11 Expand ongoing efforts to document and evaluate research methods for measuring sexual behaviour, intentions for pregnancy, condom use, and candidate microbicide use, and identify best practices across studies and sites to develop consensus about when to use standardised behavioural measures versus a tailored or supplementary approach
 - Initial tasks to improve social science research could include:
 - documenting measures currently employed, based on review of the literature relating to researching sensitive behaviour;
 - clarifying key terminologies related to sexual behaviour and condom and microbicide use (to increase validity of these terms and to enable comparison);

- identifying similarities and differences in measures employed after data are obtained from current studies, and evaluating the utility of these different types of data;
- developing and evaluating alternative ways to measure sexual and adherence behaviour, for example, in-depth approaches or use of psychometric scales (these approaches may prove more reliable than single-item questions or questions that only assess behaviour “in the last week”);
- using alternative, more confidential interview approaches (e.g., computer-based or mobile phone-based data collection);
- evaluating alternative data collection formats for their impact on research participants, and the comparative burden of these formats on the research process;
- providing ongoing training in qualitative analysis at sites;
- continuing to search for surrogate markers that could validate self reports;
- engaging non-study participants (screened out, early end-of-study discontinuers, parallel cohorts) in qualitative research to better understand sexual and adherence behaviour within study settings; and
- building on the existing directory of materials, including data from various studies, to develop consensus on generic versus tailored methods of data collection (e.g., there may be some tools that can be used, with minor adaptation, in all studies, while others may be developed in response to a specific setting or protocol).

OTHER RECOMMENDATIONS

- Explore ways to “triangulate” data on sexual behaviour collected in different ways and in comparison with biological data (e.g., surrogate markers indicating applicator use or the presence of semen in the vagina)
- Document and critically assess behavioural measures currently employed with a focus on identifying advantages and disadvantages across studies and study sites and to evaluate other potential and innovative measures and combinations of measures

4.5 Identify and validate surrogate markers

The field's lack of an effective microbicide and of validated animal models means that decisions about advancing products are made without predictors of efficacy in different contexts. Safety is presently evaluated with the best available approaches, but the optimal biomarker would make it possible to know a candidate's likely safety profile based on laboratory measurements prior to human trials. Lack of validated biomarkers for safety and efficacy hampers efforts at every level, including clinical evaluation of candidates, candidate design, and the comparability of data from different studies.

Surrogate markers of microbicide efficacy would be perhaps the single most powerful tool for 'rationalizing' the microbicide pipeline—that is, by ensuring that promising approaches are advanced, weaker ones are dropped, and clinical research resources are invested in candidate microbicides with the greatest likelihood of success. However, surrogate markers of efficacy—if they exist—can only be identified *after* a candidate shows at least some ability to protect volunteers in large-scale studies. It is hoped that one or more of the ongoing Phase 3 studies will yield some efficacy data that can be used to identify and validate potential markers. This will depend in part on the availability of stored samples from all studies that can retrospectively be tested for a variety of such markers. Some ongoing studies are already asking women for consent to take samples that will be used for future, unspecified assays. This type of approach should ideally be standardised across the field.

Microbicide research currently uses several approaches to establish product safety, including extensive pre-clinical and Phase 1 safety testing. In March 2006, the US HIV Prevention Trials Network (HPTN) held a meeting to discuss different strategies for assessing safety in microbicide studies. However, an international system is needed to collect reports of adverse events seen in all microbicide clinical research studies. Clinical researchers need to develop greater consensus on the types of pre-clinical and early clinical safety data that should be collected, and then to create and fund a mechanism to automatically and rapidly collect safety data from completed, ongoing, and future studies.

As discussed earlier, research also needs to explore potential inflammatory markers related to safety and efficacy in both the vagina and the rectum; the safety of microbicide products in the presence of asymptomatic STIs and reproductive tract infections (including the potential of microbicides to increase susceptibility to HIV infection); the impact of microbicide use on pregnancy (including teratogenicity and pregnancy outcomes); and the potential for ARV resistance linked to use of microbicides that contain ARVs.

PRIORITY ACTIONS

- 12 Create an international database that rapidly aggregates safety data and other data from all microbicide products and studies, allowing cross-comparison and more detailed analysis of completed, ongoing, and future studies
- An expert panel should be convened with the mandate to:
 - monitor cross-trial safety;
 - assess patterns of individual events, such as minor gynaecological complaints, that could influence or confound acceptability data or product use;
 - identify gaps and conduct additional studies;
 - select the best potential markers and develop hypotheses to be tested in Phase 3 studies;
 - develop, evaluate, and validate a range of technologies to assess biomarkers; and
 - develop and invest in technologies that better measure and standardise assessment of cervical, vaginal, and rectal safety
- 13 Establish ongoing dialogue between trial investigators and regulators to identify the most efficient strategies for clinically evaluating microbicide products, including information about potential surrogate markers and alternative study designs

OTHER RECOMMENDATIONS

- Increase support for research into microbicide safety in the presence of asymptomatic STIs by:
 - working with clinical researchers, epidemiologists, and statisticians to evaluate this question in Phase 3 studies through nested sub-studies and other research methods, and
 - beginning to plan for post-licensure safety studies
- Increase support for research into microbicide safety in the context of pregnancy and teratogenicity by:
 - planning post-marketing Phase 4 studies immediately after licensing;

- using pregnancy registries and data from community randomised studies with staggered introduction of product; and
- incorporating into all large microbicide studies the systematic, standardised collection and storage of samples and associated consents to allow for future retrospective analysis of potential efficacy markers.
- Establish a long-term cohort to evaluate the potential impact of ARV-containing microbicides on women who become HIV-infected despite using a microbicide, and on those who use an ARV-containing microbicide while having an established (undiagnosed) HIV infection. If resistance is observed once these women begin ARV treatment later on, this should be evaluated not only by genotypic analyses of the virus, but also in terms of the clinical impact of resistance on response to treatment. This will involve long-term follow-up of HIV-infected individuals in study settings and in post-marketing studies. The following steps would address the current knowledge gap:
 - ensuring that resistance testing from persons who acquire HIV infection in studies of ARV-containing microbicides is routine (including circulating and genital tract HIV isolates to determine if there are site-specific differences in resistance profiles);
 - initiating studies designed to determine dose-related risks of ARV resistance development;
 - designing and initiating studies and/or post-marketing surveillance to examine the safety of ARV-containing microbicides in those who acquire infection while using the products and those with already-established HIV infection;
 - designing and initiating studies and/or post-marketing surveillance to examine the potential for HIV-infected microbicide users to transmit resistance to their sexual partners; and
 - holding discussions with regulators about data regarding resistance that would potentially be required for licensure of ARV-containing microbicides.

PRIORITY ACTIONS

MANUFACTURING AND FORMULATION

- 14 Form a manufacturing, formulation, and supply logistics information exchange forum
- 15 Expand consumer research to better understand consumer preferences, demand, and 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 the lowest common denominator, and speed process development
- 21 Fund process development and scale-up of drug substances and product
- 22 Develop a strategic and tactical product development and marketing plan that would provide 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 the studies—in order to achieve commercial license in those countries, even prior to FDA or EMEA approval, thereby rewarding countries that participate in clinical evaluation and provide product faster where needed the most.

Chapter 5

MANUFACTURING AND FORMULATION

Microbicides are a new and as yet unproven health technology. Unlike preventive health products that have been approved by regulators and subsequently have acquired new markets, both the demand and market for microbicides remain largely undefined. The full potential range of microbicide product formulations, packaging, market preferences, and market demand is therefore unknown. These uncertainties should command attention.

The microbicide field has, nevertheless, advanced, successfully finding ways to manufacture and deliver millions of doses of candidate microbicide products for clinical evaluation. As of mid-2006, five candidates are in large-scale clinical trials, the result of significant investment in product design, development, manufacturing, and packaging. Getting to this point has been difficult, indicating that even this achievement is just the beginning of what must happen in microbicide manufacturing and formulation to accommodate changes in the development landscape. For example, the five current leading candidate products are all formulated as highly water-soluble gels containing high levels of the experimental microbicide, with no significant systemic absorption. All five candidates being tested in the ongoing clinical trials are packaged in unit-dosed, pre-filled applicators—a design intended to encourage user compliance and ensure accurate dosing during research studies. Furthermore, although manufacturing capacity, in most cases with considerable difficulty, was found and proved sufficient for producing enough product for clinical testing, it is still the case that none of the five candidates was backed by a fully-developed commercialisation plan that would ensure rapid availability of hundreds of millions of doses should the candidate prove sufficiently effective for licensure. Industrialisation is a critical need for the field. The current work in microbicide manufacturing and formulation represents only a first step toward a full-scale effort.

Formulation considerations have always been important but they are particularly important for the newer microbicide candidates, combinations, and applications in development. Unlike the water-based gels now in efficacy testing, new candidate microbicides just entering clinical research have different mechanisms of action and vastly different properties, including lower water solubility, potential for local or systemic absorption, more specific forms of action and potentially greater potency against HIV and other pathogens, and much lower dosing (on the order of micrograms to several milligrams). And, at least some of the newer products may

not require application just before each sex act, as is the case for the water-based gels in unit-dosed applicators now being tested. Instead, they are being formulated as once-a-day gels, long-acting diaphragms, and vaginal rings, all permitting the timing of application to be varyingly independent of the sex act, thus potentially improving ease and therefore likelihood of use and greater protection. Combination products, which offer advantages (discussed in detail in Section 3.4.2) raise additional but highly interesting challenges for formulation for a number of reasons such as synergies and the effects of different formulations on activity and potential efficacy.

Formulation decisions are, of course, also intimately tied to consumer preferences. The most effective product in the most sophisticated formulation will fail if consumers do not or cannot choose to use it. Dosage form research should not only be linked to consumer use studies, market research, and design of delivery mechanisms and prospective packaging, but should be incorporated into the earliest phases of clinical evaluation when products are being evaluated for cervico-vaginal tissue concentrations, anti-inflammatory responses, and effects on normal microflora. Furthermore, candidates that incorporate antiretroviral drugs must have well-defined structural variants (“polymorphology”) to help define potential drug availability, pharmacokinetic profiles, systemic toxicity, and potential for the development of viral resistance development. Other newer microbicide candidates that are small molecules with traditional pharmaceutical properties will also need similar pharmaceutical definition. Sharing this type of information about formulations and related manufacturing considerations as early and widely as possible would be an important step in catalysing progress.

Even though ways were found to manufacture enough product for testing in the very large current effectiveness trials, it was not easy or efficient, and generated no strikingly good models for replication. The fact remains that, as is true for HIV vaccines (or any other public health vaccine, for that matter), the microbicides field will continue to need to anticipate manufacturing requirements for forthcoming trials. And, as will become clear later in this chapter and in the chapter on *Commercialisation and Access*, manufacturing arrangements will also be needed in advance of efficacy trial results in order to avoid excessive delay in distribution once a product is licensed.

This is far from straightforward. For both fields, lack of knowledge about how effective a given product in late-stage clinical testing is likely to be means that estimates of manufacturing volumes and demand are necessarily hypothetical, which indisputably entails some risk. Still, substantial and critical work is possible before a candidate is identified as effective. There may be, for instance, common manufacturing

processes and scale-up challenges which may in turn suggest common solutions to commercialisation and global capacity generation. There may also be lessons to be learned from large-volume manufacturers in low-cost regions who have enough experience in their own settings to be able to help with developing cost projections for future microbicide production.

At present, more than a dozen companies and product developers have a candidate microbicide in clinical evaluation, and at least two dozen others are developing products for future studies. However, there are several points that apply to all companies and developers, regardless of how advanced their microbicide candidates are in terms of research or development. For example:

- Very few have a formulator on staff; instead, they generally rely on contractual services to produce and develop formulations. One exception is the International Partnership for Microbicides (IPM), which constructed and is staffing a GMP formulation facility for Phase 1/2 clinical supply manufacturing and development. The IPM facility is an example of the approach needed across the field.
- No product developers have a fully-fledged commercialisation plan that would ensure availability of hundreds of millions of doses of an effective microbicide. If any of the products now in clinical evaluation proves effective, it is unclear how its developers would address the challenge of securing manufacturing capacity for applicators, active pharmaceutical ingredients, and the compounding drug product at a reasonable cost.

Key assumptions about the future developments and needs in microbicide formulation and manufacturing include:

- only a few of the dozens of candidate microbicides currently in pre-clinical or clinical evaluation will prove to be sufficiently feasible, safe, effective, stable, and inexpensive enough for global manufacture. The current pharmaceutical success rate in product development, across therapeutic areas, is 1 of 11 products in the clinic reach marketing approval;
- microbicide technologies and drug(s) must be properly matched to meet requirements for safety, effectiveness, industrialisation, and consumer acceptance and preference;
- formulations research should be integrated into all phases of pre-clinical and clinical evaluation;
- information exchange and public presentations of achievements in formulation and manufacturing can contribute to advances in pharmaceutical technology;

- beyond the water-soluble gels currently in large-scale clinical evaluation, newer candidates include some products containing ARVs and/or combinations of active ingredients;
- manufacturing and formulation experts are needed at an early stage to anticipate the unique challenges associated with these products;
- additional experienced pharmaceutical scientists are needed to evaluate vaginal drug delivery technologies and pharmacokinetics;
- new non-coitally dependent formulations could prove to be highly desirable and should be prioritised;
- the first few licensed microbicide products will need funding for commercial scale-up, and funding will be needed to provide a microbicide supply and social marketing at subsidised cost for more than 90% of the global market; and
- an early comprehensive commercial business plan is needed for these first products because their funding and marketing will set important precedents for the field.

Based on these assumptions, the effectiveness of microbicide manufacturing and formulation can best be achieved by focusing on ways to 1) share product development information; 2) develop a range of product designs and formulations; 3) develop package designs that match commercialisation and consumer needs; 4) clear logistics and regulatory hurdles for clinical supplies; and 5) prepare for global commercialisation and marketing. Each is discussed in detail below.

5.1 Share information about product development

Individual developers “going it alone” cannot efficiently overcome the challenges inherent in optimising microbicide formulation for safety, efficacy, and ease of manufacturing. Sharing information in a timely and transparent manner is crucial to the success of the field.

More sharing of information would help overcome many obstacles in microbicide development, particularly in product and process development, clinical supplies logistics, manufacturing, and commercialisation planning. Mechanisms should be established to encourage all microbicide development groups to exchange information and advice, even about competing products or intellectual property, such as centralised posting of scientific information and publications on password-controlled websites and weblogs.

PRIORITY ACTIONS

- 14 Form a manufacturing, formulation, and supply logistics information exchange forum that meets at least once a year to exchange information, assess progress, and catalyse industrialisation and commercialisation planning for products, including:
- absorption, distribution, metabolism, elimination, and toxicology;
 - selection of drugs and derivatives based on pharmaceutical parameters and biological activity;
 - pre-formulation and formulation design and evaluation;
 - Good Manufacturing Practice “Chemistry, Manufacturing and Controls” development;
 - paths to commercial scale-up of active pharmaceutical ingredients and delivery systems;
 - logistics of providing supplies for clinical trials; and
 - customs office and regulatory strategies.

OTHER RECOMMENDATIONS

- Form a pre-commercialisation working group to assess strategic and tactical plans and to provide guidance to product developments in technical and business areas
- Create a resource depot of potential manufacturers and a central record of facilities’ Good Manufacturing Practice (GMP) compliance audit reports.

5.2 Develop a range of product designs and formulations

Formulations and delivery methods, semi-solids (including gels), suppositories, or vaginal rings, will have effects on microbicide safety, effectiveness, and use that are independent of the active agents. At the same time, since any single dosage form is unlikely to meet all or even most consumer needs—as is the case with contraceptive products—a range of product formulations and delivery methods should be developed.

Research into consumer preferences must be closely linked with the design, safety, and efficacy testing of various candidate microbicide formulations and delivery methods using different active ingredients.

5.2.1 Developing formulations based on consumer preferences

Microbicide effectiveness is dependent on correct and consistent use. This, in turn, will depend on the acceptability of the product to the consumer. Understanding the attributes—other than safety and efficacy—that affect consumer acceptance is therefore crucial to optimising the effectiveness of future products.

Properly matching microbicide candidates, and the active agents they contain, with consumer preferences for formulations and delivery systems, is critically important, and should be addressed at the earliest stages of product development. Failure to do so could result in delays, disappointment, and a waste of financial resources. Two sample scenarios are considered below.

1. Consumer preference research could indicate that a vaginal ring formulation is highly desirable in a major market. However, if the active pharmaceutical ingredient in a promising microbicide is a highly charged molecule (as are some ARVs), it cannot be released from a silicone ring. This challenge might be overcome through the use of a derivative of the relevant compound. In this scenario, understanding consumer preferences, and then investing a few months in early development to bring forward a derivative of a lead compound better suited for the consumer-preferred delivery system, could determine the difference between a product that forever produces technical difficulties and poor efficacy and one that is commercially viable and highly effective.
2. Consumer research could determine that in certain markets, women's decisions to use a product could be highly influenced by whether or not the product must be inserted shortly before sexual intercourse, and is thus 'coitally-dependent.' In these markets, it would be highly plausible that a non-coitally dependent formulation would contribute to higher rates of use, and would therefore be more effective.

The current market for vaginal products provides other useful examples of how formulation affects consumer preference and use.

- A relatively simple cosmetic alteration to K-Y Jelly (originally marketed by Johnson & Johnson to menopausal women for lubrication) created K-Y Warming Liquid, which was then marketed by J&J as a sexual enhancer. This had a dramatic impact on consumer desire for this product in major markets such as the United States.

- In another example, Johnson & Johnson has had commercial success with a vaginal yeast infection treatment formulated as an ovule. Prior to this product, the most common formulation was a gel/cream or a suppository, both of which are prone to leak and thus are most often used at night with a sanitary napkin. The new ovule product met a consumer need for a non-leaking product and secured a new profit and consumer base.

Several studies have already explored potential factors in microbicide acceptability, possible patterns of product use, and preferences for various delivery methods. More studies are ongoing or planned. This research undoubtedly is a good beginning, but substantially greater efforts are still needed to define consumer preferences for various microbicide formulation attributes.

Clinical studies should not be the only source of data about consumer behaviour and microbicide use. Studies of this type can provide information about product use patterns in research settings in specific countries, but the behaviours noted in those settings might not be predictive of future use. Clinical study participants might use experimental microbicides more (or less) frequently than they would if these products were available commercially; among many possible outcomes, clinical study protocols and settings might enhance adherence. Conversely, women might use an experimental product less frequently and less consistently than they would use a product once proved effective, licensed, and marketed.

For this reason, it is crucial that market research be conducted about consumer preferences and criteria for microbicide acceptability and use. This research should be conducted across and within many regions of the world, defining the range of preferences between individuals and at various points in a women's lives.

PRIORITY ACTIONS

- 15 Expand consumer research to understand consumer preferences, potential demand, and use of microbicides, by examining best practices from companies already marketing women's health products, and adding consumer preference and use studies to all Phase 3 clinical studies
- 16 Support expansion of experienced and well-staffed microbicide formulation groups that are contracted to provide their services to microbicide development organisations.

- 17 Support funding for early development of formulation designs and delivery methods that includes work on probiotics, semi-solid forms, rings, tablets, and diaphragms; designs that provide extended duration of efficacy and are not coitally-dependent; and designs with attributes such as combined cosmetic and pharmaceutical benefits.
- 18 Conduct international market research in a variety of consumer markets and among major public-sector purchasers to assess the acceptability of various packaging and distribution methods at varying levels of projected efficacy and pricing

5.2.2 Developing formulations for safety and effectiveness

Certain characteristics of formulations and delivery methods can have an important impact—independent of the active agents in the microbicide—on safety and efficacy of candidate microbicides. To optimise safety and efficacy, these characteristics must be identified so that delivery methods can be matched with consumer preferences, and in turn matched with active agents.

The innate characteristics of delivery methods can have a profound impact on the safety and efficacy profiles of a microbicide candidate. Various delivery systems, such as gels, tablets, suppositories, diaphragms, or rings, have different patterns of distribution, adsorption, and retention in the vagina. This may result in different concentrations of active ingredient throughout the genital tract. Delivery systems may also have a local impact that is not related to the impact of any active agent (e.g., by increasing inflammatory responses, shifting pH, or affecting microflora). Interactions between the delivery method and the active agents may affect distribution, absorption, safety, and product efficacy (e.g., silicone ring delivery systems are best suited for releasing molecules of low water solubility). For these reasons, formulations and delivery systems need to be evaluated independently from, and in combination with, active agents.

A range of tests is available to evaluate the safety and activity of microbicide formulations and delivery methods. Microbicide safety is now evaluated through colposcopy and, more recently, through cytokine monitoring in humans and in *in vitro* cytotoxicity studies. Vaginal distribution of microbicides can be tracked using magnetic resonance imaging (MRI), gamma scintigraphy, and visual/fluorescence monitoring. Local and systemic absorption of the microbicide and its active agents can be measured through vaginal biopsies and blood collection.

However, systematic development and evaluation of microbicide formulations and delivery systems has been limited. For one thing, vaginal product development and drug delivery are new technologies, especially when compared with fully developed oral and injectable drug delivery technologies, so there is a dearth of information about potential delivery methods. There is substantial room for more effort in vaginal drug delivery, both in terms of developing more advanced techniques and in correlating findings from various assays.

PRIORITY ACTIONS

- 19 Compare various formulations and delivery systems through a systematic, coordinated research effort involving paired *in vitro* and *in vivo* studies that includes:
- Generating a dossier of pharmaceutical properties on lead compounds (and related compounds in a chemical series) as well as comprehensive data on various delivery methods. These data are essential to the process of matching the best active agents with the best formulations and delivery systems.
 - Defining critical formulation parameters to achieve optimal local drug delivery and corresponding microbicide protection. Oral and transdermal drug development have defined parameters for optimal systemic drug absorption. Unfortunately, similar parameters have not yet been defined for vaginal microbicides, where local non-systemic absorption is most desirable. Microbicide developers would benefit from characterising the active agents' physical properties in relation to local absorption, further definition of methods to control release of active agents to maximise local drug levels without systemic absorption, and strong correlation of *in vitro* and *in vivo* data about drug release for various microbicide formulations.
 - Conducting laboratory-based studies to explore how the interactions between a microbicide formulation and active agent may affect epithelial cell uptake. Cell uptake studies can provide information about drug absorption, metabolism, secretion, and physiological benefits (i.e., production of a long-lasting reservoir of drug in the cell), and toxicities at the cellular level. One method for gathering these data is the Franz diffusion cell model (an *in vitro* skin cell model) fitted with vaginal tissue, cultured tissue, and membranes.

- Linking laboratory cellular-level studies of various formulations with human evaluation. These clinical investigations could include comparisons of pharmacokinetic profiles of two or more drug derivatives, or clinical studies to obtain the pharmacokinetic profile of radiolabelled drugs. The FDA has recently issued a guidance document for “exploratory INDs”, titled *Guidance for Industry, Investigators, and Reviewers of Exploratory IND Studies*. This guidance should be used by the field to design studies that evaluate the effects of the product’s inactive ingredients. *In vitro* measurements of gel flow should be linked with vaginal distribution patterns that are measured using magnetic resonance imaging (MRI), gamma scintography (radio imaging), or visual/fluorescence monitoring. This approach can help determine whether the distribution of the active agent throughout the vaginal tissue is determined by gel spread or whether distribution may depend on drug absorption and local tissue perfusion.
- Applying computer modelling to describe and predict cell uptake and vaginal distribution of various formulations and delivery systems. The data obtained could be shared as a tool for formulation development, scale-up, and manufacturing process development and control.

OTHER RECOMMENDATIONS

- Research and define biological variability among women (such as differences in vaginal shape, physiology, microflora, and pH) and how this variability affects drug release and drug absorption from a given formulation
- Expand the list of ingredients used in vaginal formulations, with ophthalmic and injectable products considered as a simple first step
- Characterise each of these potential ingredients (particularly preservatives) and their potential impact on vaginal tissue toxicity, as measured by inflammatory response, epithelial disruption, and other measures
- Improve animal models currently used for microbicide evaluation, and systematically correlate data from animal studies with human and *in vitro* research (e.g., the rabbit vaginal model has neutral pH and is sensitive to weakly acidic pH gel formulations used for humans; the monkey vagina, meanwhile, is closer to human parameters of microflora and pH, but digital cleaning by the primates complicates evaluation of formulations)
- Support further work by the Manufacturing and Formulation Working Group, to expand it in size and expertise to promote innovative thinking in formulation designs, drug combinations, and evaluation.

5.3 Develop package designs to match commercialisation and consumer needs

The package (applicator or digital insertion, number of doses, box size, label appearance, portability) used for microbicides will have an important impact on consumer preference for and acceptance of a product. It will also affect the ultimate cost to private sector and public-sector providers.

5.3.1 Designing appropriate packaging to ensure low production cost and, by extension, widespread availability

The packaging for a viable product must fit within manufacturers' budgets, consumers' cost requirements (or cost requirements of purchasing entity, i.e., health ministry or international agency), and consumer needs and preferences.

The microbicide effort currently faces questions about how to best package and market products that require applicators. Consumers may have strong preferences about the appearance or disposability of applicators. The field must also develop cost-effective manufacturing plans for products with different delivery and packaging requirements, such as tablets, rings, or diaphragms, as they advance through future efficacy studies.

All of the candidate microbicides now in efficacy studies require some form of applicator. Product developers and study sponsors have selected and procured various types of plastic applicators for these products, and have data about the costs associated with manufacturing, shipping, storing, and disposal of these applicators. Therefore, some data exist to assist in calculations of commercial-scale distribution budgets for products that require applicators.

However, some parameters may change as a product moves forward to commercial use. For example, a multi-use applicator is cheaper and faster to produce than unit-dose packaging. Below is an example of prices obtained from one North American contractor:

Assuming a 4,000 litre volume of gel, filling product into 100-gram tubes could cost US\$0.92, or 3.7 cents per 4mL dose in each multi-use tube. Cost of drug substance and applicators would be additional. A similar-sized batch filled into unit-dose applicators would cost US\$0.60 each (applicator component cost of US\$0.13) plus the cost of drug substance.

If consumers accept multiple-use tubes with re-usable applicators, the multi-dose tube could be an inexpensive option. However a multi-dose tube would also raise issues around portability, discreteness, storage, cleaning requirements, and disposal.

Other low-cost options include blow-fill-seal applicators, which are manufactured at low cost in India and other countries, unit-dose sachets that can be used with a re-usable applicator, and intra-vaginal cervical barriers such as diaphragms.

Understanding the production costs, available manufacturing capacity, and projected capacity needs of various formulations is critical. This expertise must be coupled with a firm grasp of consumer preferences and a consideration of the target price that purchasers will be willing to pay for public sector or socially-marketed products. Finally, given that different dosage forms are likely to be preferred in different settings, a variety of scenarios should be costed and considered.

RECOMMENDATIONS

- Funds are needed to assess packaging options for public-sector production and purchasing. Therefore as candidate microbicides proceed through Phase 3 clinical studies, microbicide developers should:
 - assess packaging components and options for their per-unit-dose costs;
 - evaluate cost differences of package components and product production in the United States, Europe, and other settings;
 - identify low-cost producers in multiple settings with GMP-compliant facilities;
 - assess available large-volume manufacturers in low-cost regions, and generate cost-of-goods (COG) projections; and
 - design and cost package types for a variety of consumer-desired delivery methods.

5.3.2 Research consumer acceptance of and preference for package designs

An effective product packaged in a way that does not appeal to users will not be widely or appropriately used, and the potential benefits of the product will be lost.

Packaging decisions can affect the potential individual and public health impact of an effective microbicide. As discussed in the previous section, multi-use applicators may be a more cost-effective packaging form for delivering an effective microbicide gel. If, however, multi-use tubes have an adverse effect on proper usage—and in comparison, unit-filled applicators ensure more accurate delivery and do not require cleaning—then the cost savings would be offset by a reduction in efficacy.

It is likely that multiple packaging options will be required to meet the needs of a variety of markets and purchasers. However, at present there are scant data on consumer package preferences in different cultures. There is also a lack of information from public sector service providers as to their preferred package types for different settings. And there is a lack of understanding of the thresholds which maximise or hinder package and market positioning.

RECOMMENDATIONS

- A multi-disciplinary and multi-organisational working group that includes commercial company expertise and academic and government representatives should be formed to investigate consumer preferences, commodity positioning, and distribution strategies in the public sector
- Commercial market researchers should be involved in creating marketing strategies for the public sector.
- Funding should be made available for:
 - consumer research studies to investigate analogous product marketing in developing countries (vaginal yeast infection, feminine hygiene, hormonal contraceptive rings, and douches);
 - consumer studies to be conducted by consumer research organisations;
 - studies that explore whether differentiation of product appearance between public and private sector markets influences the success of the product in each market
 - community and mission studies to be conducted to assess promotional marketing strategies

5.4 Clear logistics and regulatory hurdles for product supplies for clinical trials

Clinical trials can involve tens of thousands of volunteers and millions of applicators or other packaging elements, all of which must be delivered at the right time, in the right condition, and in the right quantities. Experience from current trials is revealing significant obstacles in meeting these basic requirements, particularly at new clinical centers. Supply-chain expertise is needed to address these gaps, which are discussed below.

5.4.1 Ensuring timely, reliable, and adequate clinical supplies

Clinical trials of microbicides cannot succeed without reliable and adequate supplies of the candidate, its packaging, and related commodities such as HIV test kits. Failure to address supply-chain issues can put the entire research effort in jeopardy.

Difficulties ensuring timely distribution of necessary supplies are arising at trial sites in resource-poor settings. Much of this is due to the same myriad of obstacles that can complicate provision of basic health care services—anything from poor roads and transport infrastructure, unreliable power for refrigeration and maintenance of the cold chain, to insufficient human resources for managing stores, tracking deliveries, and maintaining quality control. Addressing these issues in the research setting is not only important for the success of studies, but will also provide important information for eventual public sector product distribution to clinics.

RECOMMENDATIONS

- Initiate discussion within the field on methods currently used to deliver supplies at a reasonable price in ways that do not jeopardise product stability, and exchange information on models used to estimate product demand and production schedule
- Contact partners engaged in large-scale commodity distribution, such as the US President's Emergency Plan for AIDS Relief (PEPFAR), faith-based health networks, and government health systems
- Study and learn how supply systems work in pilot programs such as those proposed in the chapter 6

5.4.2 Clearing regulatory and customs hurdles for clinical supplies for trials

The field is constrained by various kinds of government-associated delays, including those related to regulatory approval and customs. These delays complicate efforts to initiate Phase 2b/3 studies in a timely and expedited fashion.

Many national regulatory agencies in developing countries suggest or require prior clinical protocol approval by the FDA or the EMEA before granting study approval in their country. This can lead to unnecessary delays in initiating studies. The length of time required for customs office approval of imported clinical supplies varies from days to months.

RECOMMENDATIONS

- Work with national regulatory authorities to build technical familiarity and expertise for potential review of microbicides
- Obtain a universal WHO drug number for microbicide clinical supplies to assist with import/export of microbicides

5.5 Plan for commercial scale-up

Current thinking in the field is that the first few microbicide products on the market will need to be provided by the public sector or social marketing programs at subsidised cost. Contract services for commercial scale-up are available, but they require public sector investment. The financial and technical requirements for scale-up to commercial production of lead candidates should be assessed and incorporated into business plans for individual products.

5.5.1 Funding scale-up of the processes for drug substance manufacturing

The process used to manufacture compounds for clinical studies is frequently different from the process used for commercial-scale production. Failure to invest in commercial-scale process development while clinical studies are ongoing can result in delays in availability of a licensed product, and can even derail development entirely if it turns out that commercial-scale processes cannot be developed.

The microbicide field faces significant challenges in meeting production requirements for clinical studies and commercial scale distribution. These challenges include the costs of clinical- and commercial-scale manufacturing; reluctance of the US NIH to provide funds for drug synthesis for clinical studies; concentration of process

development expertise in the private sector; and lack of commercial partners to share skills and resources with academic and small business product developers.

Microbicide developers also need to address unique and often complicated issues related to the manufacture of the active pharmaceutical ingredient (API). These issues vary depending on the drug in question. With ARVs, on the one hand, there are substantial expertise and capacity that can be harnessed with appropriate investments of time and money. Other APIs, however, may require development of specialised production capacity at substantial expense. These issues need to be addressed through process scale-up studies, few of which have taken place in the field to date.

PRIORITY ACTIONS

20 Assess products in development, using an expert team to identify commonalities and commercialisation issues, reduce processes to the lowest common denominator, and speed process development

21 Fund process development and scale-up of drug substances and product

- These actions can be accomplished by organizing and funding a pre-commercialisation team of consultants charged with:
 - assessing current drug synthetic pathways for commercial feasibility and costs;
 - facilitating collaboration between groups working with similar drug products and processes; and
 - helping to develop a tactical plan for new drug applications (NDAs) and commercial product preparation.

OTHER RECOMMENDATIONS

- Funding agencies, including foundations and government agencies, should consider funding synthesis optimisation work during Phase 2/3 clinical studies
- Commercial partners should share skills and resources for process development and production so that funders do not have to absorb all costs
- Specialised teams for developing large-scale pre-NDA batches of the active product ingredient and drug product, which are costly but required for product licensure by regulatory agencies, should be funded

5.5.2 Planning for commercial production

It can take anywhere from 18 months to three years to develop commercial-scale production capacity for a new microbicide (including process development, optimisation, securing of manufacturing facilities, new equipment installation, trial and validation runs, and stability testing). Failure to plan adequately during clinical studies can result in significant delays in availability of an effective product, with the potential cost of tens of thousands of lives.

As in the AIDS vaccine field, microbicide developers face questions of timing, including when to start process development for commercial-scale production and when to start investing in adapting existing plants (or building new ones) for commercial production. For both fields, the answers to these questions depend to some extent on a product's characteristics and efficacy data. Also for both fields, there is a financial risk involved in investing in a candidate without proven efficacy. The converse risk of delaying investment is slowing of product availability if a candidate does show efficacy.

For the microbicide fields, some of the time parameters are known and can be factored into strategic plans. For example, there are enough contractors currently operating that can make semi-solid formulations (such as the gels now in efficacy trials); therefore, new facilities would not necessarily have to be built should a semi-solid formulation be approved. However, new machinery and equipment still might need to be purchased. In addition, GMP compliance is likely to be an issue for semi-solid contract manufacturers in developing countries because these are primarily cosmetic product manufacturers.

Facilities to produce ovules, capsules, and tablets are available almost anywhere. Production preparation for a capsule or tablet product could probably be performed within a year. Due to sheer volume, larger facilities may be required to produce an ovule product for regional commercial introduction.

Looking ahead to other potential distribution systems, there are a few manufacturers of polyurethane vaginal sponges. Whether these companies can provide capacity for a microbicidal sponge depends on whether the sponge is pre-formed prior to adding the drug or if it is polymerised with the drug present. If the sponge is pre-formed, then production preparation timelines cannot be predicted. If it is co-formulated with the drug, production preparation would probably take 24 months for regional commercial introduction.

Global production capacity is very limited in the case of vaginal rings, although the IPM is starting to assess this capacity and ways to expand it. This type of exercise should be expanded and disseminated throughout the field.

Several other obstacles need to be addressed as well, including:

- insufficient planning on the part of developers for robust production processes with low cost-of-goods (COGs) or options for manufacturing in a low-cost region;
- insufficient resources provided to source producers;
- insufficient resources for technology transfer to low-cost manufacturers; and
- no clear regulatory pathway for switching from a high COG product form to a low COG form (e.g., from a gel to a tablet) without repeating toxicology and clinical studies.

PRIORITY ACTION

23 Identify large-volume manufacturers in low-cost regions and generate cost-of-goods projections to inventory and assess pharmaceutical and specialty chemical manufacturers in low-cost settings around the globe, and review producers' capability, GMP compliance, pharmaceutical manufacturing history, standing with regulatory agencies, and existing international distribution channels

OTHER RECOMMENDATIONS

- Fund synthesis development during clinical studies to optimise synthesis, improve commercial feasibility, and thereby reduce cost of goods

5.6 Prepare for global commercialisation and marketing

The primary goal of the microbicide field is to develop and introduce microbicide products globally through public sector distribution. Thus far, however, the field has largely neglected several major steps needed to achieve this goal because it has concentrated on developing products for evaluation in clinical trials. The field has yet to adequately address important questions about how to manufacture, distribute, and position microbicides (when proven clinically effective) to ensure public health impact and market success. The answers to these questions can only be determined by developing a forward vision for success and planning for industrialisation that anticipates obstacles and works towards solutions.

5.6.1 Developing a vision for commercial success

Without a coordinated and comprehensive commercial plan, the field will continue to experience needless delays in the introduction of an effective product. These delays could cost thousands of lives.

The five microbicide products that have moved into Phase 2b and Phase 3 studies advanced because of dedicated individual sponsors and their collaborators. However, single actors, or even small collaborations, cannot take on the task of ensuring the market success of a clinically proven microbicide. Instead, there is a need for planning that involves input from multiple disciplines and stakeholders including public and private sector actors, community groups, health ministries, regulatory agencies, and global health funders.

There are several obstacles to achieving this level of coordination and shared vision, including:

- an absence of strong pharmaceutical industry interest in microbicide development and commercialisation, due to:
 - perceived low profit potential and relatively small private sector market,
 - anticipation of preferential public sector pricing for what is perceived as a very large public sector volume,
 - significant up-front investment in pre-commercial production preparation, and
 - perceived high product liability risk;
- a lack of a scale-up strategy to ensure commercial-scale launch of public sector products;
- a lack of foundation/government vision or leadership for creating a public sector marketing strategy for microbicides;
- poor clarity on regulatory pathways in developing countries;
- a lack of capacity building to create distribution systems in developing countries; and
- the resource-intensive nature of preparing and supporting NDAs, particularly if they must be filed in multiple countries.

PRIORITY ACTION

22 Develop a strategic and tactical commercial production and marketing 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

OTHER RECOMMENDATIONS

- Fund a high-level, experienced law firm to assess the issues related to product liability
- Strengthen current advocacy efforts for legislation toward increasing funding and liability relief for newly licensed vaccines, microbicides, and other technologies to prevent infectious diseases (e.g., HIV, malaria, and tuberculosis).

5.6.2 Collecting data to anticipate required commercial volumes

Manufacturing plans cannot be developed and investments cannot be allocated without estimates of anticipated demand for an effective product.

Information on anticipated demand, distribution strategies, and distribution schedules is vital to product manufacturing plans. Yet it is quite difficult to generate this information. As discussed in detail in Chapter 6, the need for a product (the number of people who can benefit from it) can be quite different from actual demand, which is in turn influenced by advocacy, marketing strategy, consumer preferences, distribution platforms, and a host of other factors.

Manufacturers and industry partners are frequently not interested in taking on the commercial risk of investment in production for large quantities of a compound of unknown efficacy, yet production facilities may need to be built as soon as the first preliminary efficacy data become available to avoid delays in manufacturing. And, such partners are likely to be reluctant to invest in a product that may have a limited private sector market in its initial stages of introduction.

Another obstacle is lack of pharmaceutical company interest in marketing a microbicide. If industry were interested and involved, it would invest in market assessments and promotional campaigns that could, in turn, drive demand.

RECOMMENDATIONS

- Fund research to forecast the global need, demand, and potential market for microbicides
- Reduce the risk for manufacturers by enlisting funders to buy equipment and/or find other methods to make microbicide production more attractive
- Generate production forecasts to plan regional production and distribution needs
- Strengthen current advocacy efforts for legislation toward increasing funding and liability relief (e.g., TB, malaria, and HIV preventive technology)

5.6.3 Developing product marketing plans and expertise

Bringing a product to market involves regulatory agencies, marketing experts, and purchasers. The field lacks clarity on the roles and current capacity and commitment of these stakeholders and therefore risks delays in bringing an effective product forward.

There are substantial unknowns related to bringing an effective product to market in multiple countries around the world. Many of these unknowns are also addressed in other chapters or at other points in this section. Some of the critical issues are:

- lack of clarity on regulatory pathways, including NDA approval for licensing products;
- a lack of means to forecast volumes in order to generate product procurement budgets for government and foundations;
- a lack of identified partners to commercialise and market the product; and
- a lack of clarity about what it will require to make a product successful in the public or private sector (or both).

PRIORITY ACTIONS

24 Engage with regulatory agencies where clinical studies are being conducted before, during, and after the studies in order to achieve commercial license in those countries, even prior to FDA or EMEA approval, thereby rewarding countries that participate in clinical evaluation and provide product faster where needed the most

This work may include:

- coordination with governments that have strong national drug authorities, such as India and South Africa, so that they can review a product for potential licensure without prior approval by FDA or EMEA;
- understanding regulatory requirements in several different regions as part of creating a strategy should FDA or EMEA be unable to expeditiously approve an NDA for a microbicide due to factors such as partial efficacy or lack of jurisdiction; and
- continuing to encourage pharmaceutical companies to market microbicides in the private sector, as this may be the best formula for public sector marketing success

PRIORITY ACTIONS

COMMERCIALISATION AND ACCESS

- 25 Work with product developers to create a useful and accessible new pool of expertise that includes areas of social, private sector, end-user, and community marketing as well as advocacy to craft strategies for marketing, product positioning, and creation of consumer demand
- 26 Fund and develop demonstration projects for microbicide introduction and scale-up using existing and emerging technologies. Donors should issue a request for proposals (RFP) on demonstrating introduction and access using technologies such as the female condom and the diaphragm in five to seven potential “early adopter” settings.
- 27 Develop plans, protocols, and budgets for continuing to make products available in study site communities after Phase 3 studies have been completed
- 28 Develop initial demand, cost forecasting, and impact models to inform manufacturing scale-up, procurement, and decision-making
- 29 Determine how existing financing mechanisms for public goods can be applied and adapted to support microbicide manufacturing scale up, purchase, marketing, and delivery
- 30 Engage regulatory experts to map out registration and regulatory pathways for rapid review and licensure in high-need settings, including clear strategies for over-the-counter status
- 31 Develop a commercialisation and access planning working group to define business plans and 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 Consolidate and expand research and education initiatives for key policy and communication challenges (e.g., an initiative may be needed to define and communicate the 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)

Chapter 6

COMMERCIALISATION AND ACCESS

The emphasis of the microbicide effort has been appropriately directed to developing new products and evaluating them in large-scale efficacy studies. However, as dozens of experimental microbicides move through clinical evaluation, there is an urgent need to prepare for success: once the first products show at least some efficacy and become licensed for use, they need to be introduced and marketed on a global scale, and they need to be made available and affordable to people around the world, especially those living in countries that are hard-hit by HIV/AIDS.

Many people in the field are recognising the immediate need to develop plans and capacity for commercial development and access. Several product developers are now exploring potential manufacturing partners for large-scale production. Some market research and public health impact studies have been conducted. And WHO, several national and regional regulatory bodies, and other partners are beginning to prepare for the review and possible licensure of microbicides that have demonstrated protection against HIV and STIs.

However, activity, attention, and investment in this area remain insufficient, particularly given the urgent global need for microbicides and increasing expectations for rapid access to these products once they become available.

The following discussion and recommendations about commercialisation and access are predicated on a number of assumptions:

- Planning for microbicide access is challenging without a specific product identified. However, commonalities in issues and product characteristics mean that general preparations can begin now. The products currently in efficacy trials share a number of characteristics that can be used for general planning purposes: they are gels, more likely to be partially rather than fully effective, and are expected to cost between US\$0.20-0.30 per dose.¹
- Donor support is essential to ensuring product access. The first products are unlikely to be commercially viable or to generate large private sector sales, and public subsidy will be necessary to ensure product availability in developing

¹ Clearly, this cost is approximate, and could decrease if very large production capacity brings economies of scale in manufacture. This is unlikely to happen quickly, as the processes of scaling up manufacturing, and increasing actual demand and use are complex.

countries over the first 5-10 years. The costs of *programs* to deliver and promote the product must be factored into the total costs, in addition to the cost of the *product* itself.

- Given that microbicides are needed most urgently in resource-poor settings and that there is no established market, it is unlikely that normal market forces will drive the transition of the first microbicide(s) from a research product to a viable or self-financing public health product. The process will need to be actively and jointly managed by sponsors, product developers, industry partners, and donors.
- As an entirely new product class, both demand and identity for microbicides will need to be created. The introduction of the first microbicide is critical, since it will largely define the entire product class; as such, it must be carefully managed with appropriate resources and expertise.
- Managing commercialisation and access requires expertise new to the microbicide field, and which must be actively recruited to work on microbicides.
- Over-the-counter (OTC) regulatory designation is critical to widespread access. Unnecessary barriers such as requiring a physician's prescription could compromise access and blunt the potential impact of an effective product.
- Long-term, widespread access will be built on careful, strategic, phased product introduction and scale-up, beginning in select settings: clinical trial sites; “innovator” countries, communities, and populations; and settings with high HIV incidence, to demonstrate impact.
- Expectations for rapid roll-out and uptake of microbicides need to be managed. Sponsors need to develop specific plans for continued access in trial settings after the study is complete and while awaiting marketing authorisation.
- Working closely with community and civil society organisations is critical to microbicide distribution and use.

Commercial development and global access to future microbicides will be a huge endeavour. Seven priorities for attention and action are: 1) develop strategies to introduce, position, and market microbicides; 2) improve the capacity of supply and distribution systems; 3) develop detailed cost forecasts and financing plans; 4) clarify potential pathways for regulatory review and licensure; 5) identify strategies to facilitate and speed the transition of microbicides into widely-used health products; 6) introduce greater clarity, transparency, and innovation in intellectual property arrangements; and 7) increase commitment by policy makers.

6.1 Develop strategies to introduce, position, and market microbicides

As clinical efficacy studies move forward and bring the field closer to the prospect of one or more licensed microbicide, there is a need for new marketing expertise and consolidated market information to introduce these new products in ways that might appeal to different potential user groups. To avoid delays in getting the product out and widely used, it is critical to use strategies devised specifically to define where and how microbicides will be distributed and how they should best be promoted.

Because microbicides are a new product category, there are significant opportunities to create positive associations in the public mind. Successful introduction of the first microbicides will depend on the field's grasp of and investment in marketing efforts to create demand and develop approaches that will appeal to diverse users.

To date, given the early stage of product development and clinical evaluation, the field has not yet recruited extensive marketing expertise, funding, or systems to ensure commercialisation and access. Few among the current actors in the microbicide field have expertise or experience with marketing, and among donors or developers it is unclear who will lead marketing efforts for the field or for individual products.

It is now appropriate and necessary to invest resources in activities that will facilitate bringing a product to market. Since this is a new area of activity, it is important to consider non-traditional channels and to involve advocacy, community, and service delivery networks in strategising about creating demand and crafting specific marketing strategies.

PRIORITY ACTION

- 25 Work with product developers to create a useful and accessible new pool of expertise that includes areas of social, private sector, end-user, and community marketing as well as advocacy to craft strategies for marketing, product positioning, and creation of consumer demand

Marketing information can also be collected among different sponsors, researchers, and disciplines, and expanded to create a sufficient basis from which to develop marketing strategies and identify areas where additional market research is needed.

OTHER RECOMMENDATIONS

- Collect marketing data from other public sector and socially-marketed goods—for example, female and male condoms, hormonal contraceptives, artemisinin-containing malaria treatments, and insecticide-impregnated bed nets
- Compile and compare marketing strategies for fast-moving consumer goods—especially those like soap, toothpaste, or other personal care products that are successfully targeted to women in low-resource settings
- Collate and expand microbicide product acceptability studies and social science research to collect perspectives of users, providers, and other key constituencies
- Add consumer acceptability and information sub-studies to large-scale clinical research
- Prioritise research on potential marketing strategies specifically to “early adopter” countries and settings
- Develop models and timelines for product introduction programmes with several scenarios, and adapt models for product introduction from other public sector commodities

6.2 Improve the capacity of supply and distribution systems

Many regions with a significant need and potential market for microbicides have weak supply and distribution systems, particularly for public sector goods and commodities. This could limit microbicide accessibility and, by extension, dilute the individual and public health impact of effective products. Strategies to strengthen these systems require clear definition of potential product launch processes and associated costs.

The generally poor capacity of supply and distribution systems for public sector goods in high-need settings will be a significant challenge in making microbicides accessible. Experience from other commodities, including condoms, HIV test kits, and ARVs, has shown the inherent weakness of many national and local public sector distribution systems, and the possibility in many systems of stock-outs, shortages, or insufficient supplies at distribution points.

Microbicides will be distributed through a mix of public, private, and social marketing distribution systems. Because microbicides are a new product class, the optimal mix for distribution among these systems is not known. In the high-need settings where

microbicides are likely to be first introduced, each of these systems has strengths and weaknesses. It is important to anticipate which systems need to be strengthened in which settings to reach a range of users. But for microbicides, much of this hinges on as-yet unknown product characteristics, marketing strategies, and consumer demand, as well as local health system capacity. Since anticipated demand has direct impact on investment into and scale-up of delivery systems, these unknowns make it difficult to plan for robust investment in and scale-up of health delivery systems.

Yet there are lessons to learn from other arenas. Initial demand forecasts for many new public health drugs and products—especially those that address urgent needs—tend to be highly optimistic and driven by estimated need, rather than by realistic projected uptake tempered by the public health or social marketing system’s actual capacity to introduce and distribute a new product. For example, in many settings the initial demand for anti-retroviral treatment has been far lower than anticipated, due partly to limited capacity of local health systems and to people’s reluctance to be tested for HIV.

Forward-thinking exploration of the costs, challenges, and benefits of various distribution systems should help offset some of these unknowns. Specific systems for distribution of public sector goods should be examined, and distribution models with a combination of public, private, and social marketing should be developed in selected priority districts and countries.

Finally, resources are limited for scaling up delivery of HIV prevention products and services. This will likely constrain capacity to introduce and distribute microbicides, especially given that introduction of an entirely new product category will require building trust and confidence among users and providers through careful promotion and education.

PRIORITY ACTIONS

- 26 Fund and develop demonstration projects for microbicide introduction and scale-up using existing and emerging technologies. Donors should issue a request for proposals (RFP) on demonstrating introduction and access using technologies such as the female condom and the diaphragm in five to seven potential “early adopter” settings.

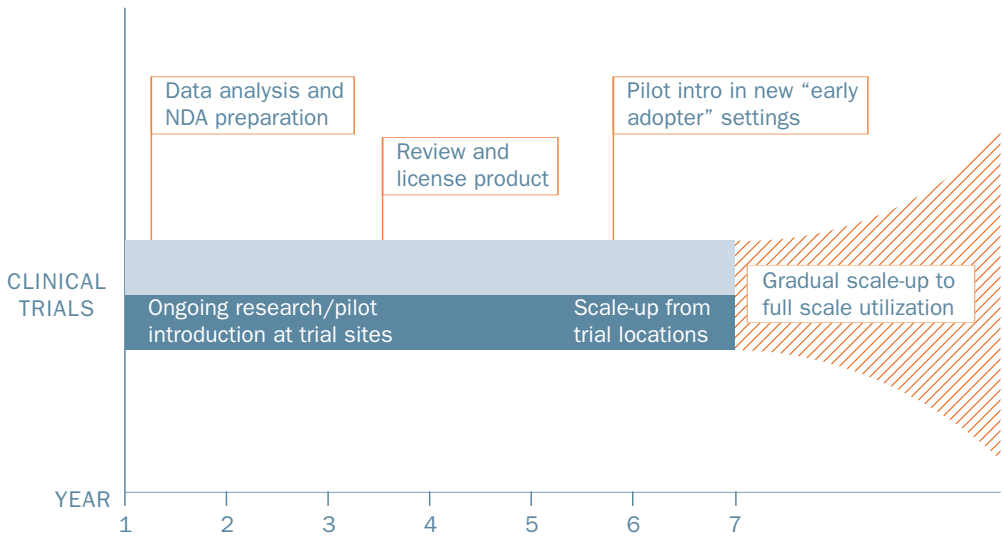
27 Develop plans, protocols, and budgets for continuing to make effective products available in study site communities after Phase 3 studies have been completed

One efficient way to plan for future microbicide introduction is to identify and strengthen existing health system and social marketing capabilities through model programs in select settings. Such model programs could introduce and market HIV prevention products targeted to women (e.g., female condoms and diaphragms). This effort would provide women with additional resources to prevent HIV infections now, and would also build capacity and experience in key settings where microbicides can be added to these systems once they are licensed.

Sites in five to seven countries should be selected for such a process (based on proximity to clinical trial settings) to facilitate eventual microbicide introduction and to ensure that study communities have access to proven products after studies end. Institutions and settings for this effort should be selected based on their ability to experiment and innovate, critically review and draw lessons from their work, and demonstrate success (see Table 4). Some of these programs may also provide opportunities for collaborating with other stakeholders who invest in distribution and supply systems, such as sponsors and implementers of ARV roll-out. Experience from these pilot projects can inform strategies mobilizing resources for broader infrastructure development, including capacity for social marketing, through both public and non-traditional sectors.

Developing precise demand and cost forecasting for manufacturing scale-up, procurement, and distribution of a new product will be challenging. However, it is critical to begin developing forecasting models. These can be informed by models used for other public sector goods, and refined as more precise and robust data emerge on product characteristics, health system capacity, risk assessment, and other determinants of demand. More generally, advocacy for adequate investment in HIV prevention interventions and research, and in women's health in general, must be sustained and expanded at both national and global levels. A final approach is to ensure adequate investment for infrastructure and support to improve capacity across the board.

TABLE 4 Illustrative product introduction timeline



- Ensure continued product supply for Phase 3 clinical trial volunteers and Phase 3 trial volunteer communities
- Implement pilot introduction plan with phased expansion through public health system in Phase 3 trial districts and countries pending approval for licensure
- Develop plan for introduction with phased product launch and expansion after licensure obtained
- Implement phased product launch and marketing plan

Note: In some high-need regions, local initiatives could compress the time required for product introduction.

6.3 Develop detailed cost forecasts and financing plans

Information on product and program costs and financing options is critical for involvement of manufacturers, donors, ministries, and marketers, all of whom are crucial to making microbicides widely available. There is as yet limited detailed information or knowledge about the range of costs for microbicide commercialisation and access. These cost forecasts will be important for helping to ensure that products

are available and affordable, and for attracting investment from commercial partners. The microbicide field must also develop greater clarity about how best to adapt or employ existing and emerging mechanisms for public sector financing, and about what financing strategies will maximise the public health impact of a microbicide product.

In the area of cost and financing, microbicide donors, developers, and advocates lack detailed knowledge about a range of costs critical for informed planning to ensure that an effective microbicide will be both affordable and sustainable. At this time, little is known about the costs of the finished product itself, the costs associated with product distribution (including educating providers and users), and what price users in different settings and circumstances would be willing to bear. Microbicides will likely require donor subsidy, especially early on until a market is established. However, it is not clear how the microbicide field can best adapt or employ existing and emerging mechanisms for public sector financing, such as the mechanisms needed to encourage consolidated public sector purchase, and how these purchase commitments would influence the balance of price and volume of a product. Finally, it is not clear what financing strategies will maximise the public health impact of a microbicide product.

The challenges associated with developing appropriate forecasting to anticipate demand also have significant implications for cost and financing issues. Especially in the initial period, there will be many uncertainties associated with projecting manufacturers' return on investment, and the rate at which demand is likely to increase. Some of this uncertainty could potentially be mitigated by the existence of reliable public sector funding to purchase products. Although there are no firm commitments by national governments to purchase microbicides, or specific proposed mechanisms for doing so, leaders at both UNAIDS and the World Bank have publicly committed to providing purchase funds for microbicides that are proven effective. A range of innovative financing mechanisms to support manufacturing scale-up, purchase, and distribution needs to be explored.

PRIORITY ACTIONS

28 Develop initial demand, cost forecasting, and impact models to inform manufacturing scale-up, procurement, and decision-making. Evidence to inform cost projections and financing needs can be generated through developing demand forecasting models for manufacturing scale-up and procurement. These models can draw on those used for other public sector goods (for example,

the “Reproductive Health Exchange” model used by UNFPA and partners to forecast supply needs for reproductive health commodities worldwide). They should be continually refined as more precise and robust data on product characteristics, health system capacity, risk assessment, and other determinants of demand emerge. These data will provide critical evidence to inform cost projections and financing needs. Demand forecasting should go hand-in-hand with efforts to identify low-cost manufacturing processes and sites, and assessing options for technology transfer to high-need countries, as these steps can all potentially contribute to lower costs of manufacture and transport.

- 29 Determine how existing financing mechanisms for public goods can be applied and adapted to support microbicide manufacturing scale-up, purchase, marketing, and delivery. The microbicide field should explore adapting or joining with existing purchasing mechanisms and suppliers for other public sector goods such as male and female condoms, vaccines, contraceptives, and ARVs. Specific models for purchasing and financing should be developed concurrently with clinical testing so that such commitments can be firmed up rapidly when clinical trials are completed. Finally, to ensure that microbicides are given appropriate priority among competing public health needs, it is critically important to continue to advocate for adequate overall investment in HIV prevention and women’s health at the national and global levels.

6.4 Clarify potential pathways for regulatory review and licensure

Thorough and rapid regulatory review and licensure are critical to ensuring access in countries of high need. The differential risks and benefits of introducing a microbicide in different epidemiological contexts may mean that a product will undergo first regulatory review in a country with a higher incidence than that found in the US or Europe. However, while some work has started to familiarise key regulatory authorities in high-need countries about microbicides, there is still a lack of clarity about the best pathways to regulatory review and licensure in most countries, including how to facilitate over-the-counter (OTC) availability. This uncertainty could lead to significant delays in introducing these new products.

The need for careful, technically sound, and expedient regulatory review is a common challenge across microbicide development, clinical testing, and access. Identifying a clear path to licensure is critical to ensuring rapid access to microbicides in countries where they are most urgently needed. However, as a new

product class needed primarily in settings where regulatory capacity may be limited, there are numerous uncertainties surrounding regulatory review and licensure for microbicides. One is that approval by the US FDA is perceived as essential by many product developers, and indeed all developers of products currently in Phase 3 trials are implementing the trials within the framework of the FDA Investigational New Drug application (IND). However, given the differences in the HIV/AIDS epidemic between the US and many other settings, it is not clear whether FDA review will reflect the risk and benefit associated with new prevention technologies in settings with a high incidence and/or prevalence of HIV and where condom use has remained low. Another is uncertainty over whether all regulatory agencies in developing countries will perceive FDA approval as a crucial prerequisite, or the degree to which FDA opinion will affect their own review processes. FDA review is also perceived as increasingly politicised, which may further blur how products associated with HIV/AIDS and women's health are reviewed. Last, few regulatory agencies in high-need countries are experienced with "first" product review. Therefore, developing alternatives to regulatory review in Europe or the US, such as initial product review and approval in an African country where an efficacy trial has been conducted, will likely present both technical and political challenges.

These are not the only obstacles related to regulatory review and licensure, and with implications for rapid commercialisation and access. In some settings, over-the-counter (OTC) status will be a major determinant of how accessible a product is in practice, and thus the impact it can have. Many countries have differing and at times inconsistent regulatory requirements; the expense and time associated with filing numerous applications may deter developers from seeking licensure in all countries where women could benefit from a microbicide. It will not be technically, financially, or ethically feasible to repeat large-scale efficacy trials in different countries, so it will not be possible to meet requirements for country-specific trial data on product effectiveness. Finally, many national regulatory agencies require that a product is approved in its country of origin and/or manufacture as a way of ensuring the quality of the finished product.

PRIORITY ACTION

- 30 Engage regulatory experts to map out registration and regulatory pathways for rapid review and licensure in high-need settings, including clear strategies for over-the-counter status

Much of the needed work in this area can build on WHO's ongoing efforts to develop regulatory capacity and technical familiarity with microbicides in countries that need them. It will also be important to engage WHO in other regulatory policy work, given its unique status as a neutral, authoritative institution.

OTHER RECOMMENDATIONS

- Continue to develop and maintain an overall “mapping” of regulatory challenges and capacities in key countries to help developers, donors, advocates, and others develop appropriate strategies for licensure and access
- Specify strategies for over-the-counter designation as a key element of this “mapping”
- Promote an existing mechanism within WHO that facilitates “twinning” of national regulatory agencies to share expertise and build capacity, and promote less formal dialogue between developing and developed country regulatory agencies
- Broker the provision of independent technical advice (in partnership with WHO) for national regulatory agencies that request support with review of protocols and licensure

Several strategies could also be employed to mitigate the disincentives created by multiple diverse application formats.

OTHER RECOMMENDATIONS

- WHO could commission and champion the development and adoption of a common application format for microbicide approval, one that would be accepted by a wide range of national regulatory agencies
- Regional review structures, such as the regional medicines regulatory efforts in the Southern African Development Community (SADC), could facilitate such a process of common applications, and also propose and develop other review strategies and mechanisms

- National regulatory agencies could be encouraged to build on and formalise exchange of information through mutual recognition of reviews (e.g., once a product is licensed and manufacturing systems are established, the existing WHO pre-qualification system implemented for ARV medications and being expanded to reproductive health commodities could be employed to certify product quality)

Several approaches could address the need for locally generated data.

OTHER RECOMMENDATIONS

- Develop models to inform risk-benefit assessments using local epidemiological and behavioural data that can predict how closely existing clinical study data would mirror actual conditions in that setting
- Encourage national regulatory agencies to consider and specify requirements for relevant bridging studies of acceptability or safety that could help ensure the safety and appropriateness of a product in a given setting without having to repeat an entire clinical trial

Finally, it is important for sponsors and developers to consider issues around eventual licensure in countries even as part of assessing feasibility for establishing trial sites.

OTHER RECOMMENDATIONS

- Continue to prepare for licensure application in all countries where trials are underway, to ensure that trial communities will have access to products that they helped to prove effective

6.5 Identify strategies to facilitate and speed the transition of microbicides into widely-used health products

Even if product developers are able to develop and license effective microbicides, it is unlikely that market forces will transform these first microbicides into widely-used, commercially viable products. Few if any product developers have the capacity to commercialise or broadly market their microbicides, particularly in high-need settings. It is therefore critical to identify specific strategies to facilitate and speed this transition and to begin specifying what roles donors, governments, developers, and other business partners will play.

Taking a product from clinical trials to widespread use involves a myriad of steps that are often complex and expensive. The product must be registered, manufactured, packaged, shipped, marketed, and distributed. A number of characteristics of the microbicide field make it unlikely that normal market forces will drive the transition from a research product to a viable public health product. First, microbicides are a new product category to be used mainly by people in resource-poor settings, and relatively little work has been done to assess likely demand from either institutional or individual consumers. In addition, their profit potential is uncertain and will likely only be realised over time, as a market is established. As such, microbicides are unlikely to have a significant commercial return. This is particularly true for first-generation products which are introduced while a market is being established, and may remain true for some time as the size and characteristics of this market will probably vary widely depending on product pricing and level of efficacy. Preferential pricing agreements and donor subsidy, critical to making products affordable, also contribute to uncertainty around profit.

Under these circumstances, it may prove difficult to draw in commercial partners or even public sector actors. Furthermore, the entities with product development expertise that brought the product through clinical trials will not be able to spearhead this transitional process themselves. Microbicide developers and sponsors are generally not-for-profit entities, public sector organisations, or relatively small biotechnology companies without the capacity to produce or market such a product on a wide scale.

It is therefore unclear what entity or entities would take the lead in driving this transition from a research product to a product in wide use, but it is likely that some external public sector entity or investment will be needed to create appropriate incentives. Such an effort will require collaboration, active management, and possibly a new model of commercialisation among donors, developers, and sponsors.

PRIORITY ACTION

- 31** Develop a commercialisation and access planning working group to define business plans and roles for moving products from research to widespread use. This working group could:
- develop or define forecasting models to anticipate demand, and identify financing options and commitments for commercialisation and access
 - work with microbicide donors, developers, sponsors, and advocates to explore models used in commercializing other public goods, specify how these models might be applied to commercialisation of microbicides, and describe the roles that various actors should play in this process
 - in conjunction with product developers, develop a template for a “business plan” to provide guidance for product-specific business plans that specify projected pathways, partners, plans, and costs for commercializing products and ensuring access
 - develop and maintain a cadre of technical experts that developers can consult. This pool would include experts in intellectual property, regulatory submissions, marketing support, and business plan development, among other areas
 - as a condition of continued funding, encourage public or philanthropic funds to require a preliminary but forward-looking business and access plans that aim beyond clinical research to commercialisation and access

6.6 Introduce greater clarity, transparency, and innovation in intellectual property arrangements

Intellectual property (IP) arrangements are central to determining pricing, manufacturing, and availability of a product. IP issues have a direct impact on the price of a microbicide for individual and institutional purchasers. Implications for pricing and affordability in turn should be factored into determining whether a product is eligible for public and philanthropic support.

Since most microbicide products are being developed and tested by entities supported largely with public or philanthropic funds, it is reasonable to expect that these products should be made available at a price which individuals and health systems in high-need

settings can afford. Yet it is not clear how IP agreements related to products in development will affect private and public sector pricing.

IP arrangements among donors, sponsors, and developers can be complex, and there is little transparency. Addressing IP issues will be particularly complex and important for emerging combination products. While some donors have policies requiring IP arrangements that will ensure public or preferential pricing for certain markets, the policies and their enforceability can be uneven. Some microbicide products are encumbered by complex IP arrangements and developers and sponsors tend to consider this information proprietary—so it can be difficult to obtain information or encourage accountability and transparency in this process.

The dynamics of intellectual property in the context of development of public health technologies are rapidly evolving. However, despite new ideas and innovations, further action is needed to develop IP arrangements that are capable of both stimulating innovation and ensuring access for public health goods.

PRIORITY ACTION

32 Clarify intellectual property arrangements for Phase 3 products, and determine implications for preferential pricing. One possible approach is to assemble an IP expert group that could bring needed expertise to the microbicide field. This group would examine the IP approaches of other public goods such as ongoing work of the Global HIV Vaccine Enterprise and key public-private partnerships. This group's initial mandate would be to review and document the following key areas:

- Classify IP arrangements for microbicide products currently under development (see Table 5). This classification would be included in the Alliance for Microbicide Development database on products in clinical evaluation
- Specify potential IP arrangements through development, manufacturing, and marketing to stimulate innovation and maximise access and public sector pricing in a working paper
- Survey donor and sponsor requirements for IP arrangements in order to ensure preferential public sector pricing
- Examine implications and develop templates for combination products

TABLE 5 Proposed classification of IP arrangements for products under development

A: Firm commitment for preferential public sector pricing based on ‘cost plus’ approach
B: Declared intentions for preferential public sector pricing though no firm commitments in place
C: No preferential public sector pricing arrangements
C1: possibility for negotiation
C2: no possibility for negotiation

6.7 Increase commitment by policy makers

National governments and policy makers will ultimately play a critical role in determining whether microbicides are accessible to women. It is important to cultivate political commitments and supportive policies to facilitate microbicide availability.

A range of national policy makers will play crucial roles in making or influencing decisions about whether microbicides are accessible to women. Regulatory authorities will decide whether or not to license microbicides; ministries of health will decide whether and how to incorporate them into programs; finance ministries will decide on funding allocations; health providers will deliver and communicate about microbicides to consumers; and politicians, advocates, and opinion leaders will decide whether to support and champion microbicides, and how to address consumer concerns and ensure accountability of public sector and private health providers.

There is increasing global attention to and interest in microbicides as microbicide science has gained momentum and as the devastating impact of the HIV epidemic, especially for women, is more widely recognised. These two factors—the increasing promise of the science and the increasing cost of inaction—are strong arguments for support by national policy makers. However, among policy makers in many countries, there is still insufficient awareness and commitment to microbicides.

In countries where microbicides are being researched and are likely to be introduced, policy makers need to hear not only about the positive potential of these products,

but they should also be informed and educated about potentially confusing or controversial issues. Any uncertainty or controversy about microbicides could otherwise deter public health experts and advocates at national and regional levels from enacting policies which would speed microbicide introduction.

For example, policy makers and providers often express concern about what the impact of introducing a partially effective microbicide will be on individual risk-taking behaviours or on population-level HIV and STI incidence. Concerns also need to be addressed about whether people will be able to understand and apply somewhat complex messages around risk reduction and partial effectiveness. These initiatives should be focused on carefully selected issues, messages, intended outcomes, and specific policy audiences such as regulatory agencies, ministries of health, finance ministries, health providers, and politicians, advocates, and other community opinion leaders.

In addition, advocacy is needed in most countries to increase the priority placed on health promotion and HIV/STI prevention, particularly for women. Many settings lack strong, organised constituencies for these issues, and there is limited investment in national and regional policy and advocacy within the field. This is especially a challenge where national and international policies often create a difficult environment for the issues raised by microbicides, such as gender, power, sexuality, and sexual behaviour.

PRIORITY ACTION

33 Consolidate and expand research and education initiatives for key policy and communication challenges such as the public health impact of partially effective microbicides, and approaches to conveying partial efficacy, hierarchy, and risk reduction to users. For example, questions and concerns about the impact of partially effective products can begin to be addressed through research: refining existing models for assessing the potential impact and risk/benefit of microbicides, applying those models to diverse settings, and presenting results targeted to policy makers and health providers. Similarly, key questions about individual comprehension and decision-making about risk reduction can be addressed through research and developing model education materials.

A brainstorming meeting could help identify other key topics. Research that is conceptualised and supported under this initiative should be required to include a clear policy-relevant presentation and dissemination strategy. Drawing in other public health product developers could encourage developing common approaches and best practices in this area.

OTHER RECOMMENDATIONS

- Support and fund local advocacy networks to present these messages and hold governments, donors and others accountable
- Formalise policy commitments by including HIV prevention research and microbicide access in policy frameworks and national plans

Chapter 7

CROSS-CUTTING TERMS, ISSUES, AND THEMES

During the MDS consultative processes, stakeholders and experts from many disciplines addressed dozens of complex issues relevant to the four different working group areas. As expected, there were not only many recommendations specific to each area, but also themes, terms, and proposed action items that were common to two or more chapters. Here we introduce these cross-cutting issues in their broader context, and leave discussion of their relevance within the different areas to the individual chapters.

7.1 Advocacy, education, and policy

Moving beyond entrenched systems and ways of working requires both independent, informed critique and changes in people's knowledge and norms. This, in turn, requires concerted and consistent education and advocacy. As stated by a US civil rights activist in the mid-19th century, "Power concedes nothing without a demand".

Advocacy, education, and policy are related areas that can bring the values, perspectives, and voices of stakeholders into the process of microbicide development.

Looking ahead, those involved in the MDS development affirm a commitment to participating in or helping to convene groups that address these topics and to ensure that the advocacy linkages essential to the field are undertaken in a sustained and systematic fashion.

RECOMMENDATIONS RELATED TO ADVOCACY, EDUCATION, AND POLICY

- Involve local press and brief activists in-country and internationally to foster both independent critique and support for prevention research. This will help ensure that potentially contentious issues have been adequately discussed prior to launching clinical trials. It will also ensure that basic knowledge and relationships exist to address emerging issues after clinical trials are underway. (Section 4.1.1)
- Address policies related to poor financing of national health programmes, national economic structural adjustment, and lack of funding for clinical training institutions. All of these issues deeply affect national hiring and salary levels in health care. (Section 4.1.2)

- Document and disseminate policies and practices demonstrating good standards of care at microbicide research sites. (Section 4.3)
- Strengthen current advocacy efforts for legislation. A stronger legislative push will increase funding and liability relief for newly licensed vaccines, microbicides, and other technologies to prevent infectious diseases (e.g., HIV, malaria, and tuberculosis). (Section 5.5.1)
- Support the introduction of existing and emerging technologies such as the female condom and the diaphragm in approximately five to seven potential “early adopter” settings. These projects help to identify potential strategies for microbicide introduction and scale-up, and to build trust among potential users and providers. (Section 6.2)
- Work with donors, product developers, and research sponsors to facilitate intellectual property arrangements that ensure public or preferential pricing for certain markets. (Section 6.6)
- Cultivate supportive policies and educational efforts that will help make microbicides widely available. For example, a broad educational and policy effort is needed to prepare for the complex task of introducing a new product that might be only partially effective. (Section 6.7)

7.2 Consumer preferences, demand, and potential use of microbicides

The MDS focuses on strategies to develop vaginal microbicides to protect women against HIV. Two facts—that women now comprise nearly half of all HIV-infected adults worldwide and that they often find it difficult or impossible to negotiate condom use—imply that microbicides have great potential to protect women’s health and well-being.

The interests of women, especially those who live in poor countries heavily impacted by HIV, should therefore remain at the centre of any microbicide development strategy. Use of microbicides is predicated on product supply, distribution, availability, affordability, and other aspects of access. However, even the most effective and accessible products will fail if consumers choose not to use them. Therefore, understanding of likely consumer preferences, demand, and potential use is crucial to the effective design and evaluation of microbicides.

There are also other important uses for microbicides. Some microbicides are already being developed and tested for their contraceptive efficacy, both as stand-alone products and in conjunction with physical barrier methods such as diaphragms and cervical caps, and as condom coatings. Some microbicides are being evaluated for their protection against STIs such as chlamydia, gonorrhoea, human papilloma virus, herpes simplex virus, or syphilis. This is important not only because STIs cause considerable health problems in themselves, but also because some of them increase the risk of HIV infection. Microbicides are also being evaluated for safety in HIV-infected women and men, and for safety in rectal use. With these safety data, further evaluation could test whether a microbicide protects HIV-infected women from re-infection, from transmitting HIV to their sexual partners, and/or protects men and/or women against infection through anal sex.

RECOMMENDATIONS RELATED TO CONSUMERS AND MICROBICIDES

- Expand behavioural research to understand whether, how, and how often women might use various microbicide products. This research should be conducted in many settings and should seek to define the range of preferences among individuals and at various points in a woman's life. (Section 4.4)
- Build and use knowledge of consumer preferences, potential demand, and potential use to develop new microbicide formulations. As with contraceptive products, any single form of a microbicide is unlikely to meet all, or even most consumer needs. Therefore, a range of product formulations will be needed. With a variety of formulations already in clinical evaluation, there is an urgent need to know more about how a product's attributes might influence microbicide use. (Section 5.2.1)
- Develop packaging based on consumer preferences. An effective product packaged in a way that does not appeal to users will not be widely or appropriately used, and the potential benefits of the product will be lost. For example, the microbicide effort currently faces questions about how to best package and market products that require applicators. (Section 5.3)
- Fund research to forecast the global need, demand, and potential market for microbicides. (Sections 5.5.2 and 6.3)
- Collect consumer marketing data from other public sector and socially marketed goods. Information from the male and female condoms, hormonal contraceptives, artemisinin-containing malaria treatments, and insecticide-impregnated bed nets should provide useful lessons for marketing future microbicides (Section 6.1)

- Add acceptability and information sub-studies to large-scale clinical research. Clinical research environments differ substantially from the service delivery or consumer contexts where products will first be introduced and used. However, research participants have unique experience with actual product use, and their experience may be invaluable to inform product marketing and positioning. (Section 6.1)

7.3 Surrogate markers of HIV exposure and microbicide use, safety, and efficacy

Reliable markers for HIV exposure, and microbicide use, safety, and efficacy, validated across *in vitro*, animal, and clinical studies, could greatly improve decision-making through all stages of microbicide development. Without such markers, it can be very difficult to answer some of the most crucial questions about a product (at least not without studies in humans): Is this formulation safe? Does it block HIV better than another product? Will it work in people? Surrogate markers are therefore discussed throughout the MDS as a crucial tool to rationalise the clinical pipeline and to make decisions about which products should move forward, especially in an environment of constrained resources.

The MDS recommends information exchange across basic science, pre-clinical, and clinical research to help identify correlates of HIV and STI exposure, and product use, safety, and efficacy. This should help facilitate decision-making about microbicide development by ensuring that product information is gathered, shared, and discussed in a timely manner and that promising research on correlates is pursued with urgency. With microbicide development now receiving substantial investments in financial and human terms, this strategic evaluation of candidates should help identify and most aggressively develop those with the highest likelihood of success.

RECOMMENDATIONS RELATED TO SURROGATE MARKERS

- Increase basic knowledge about the detailed mechanisms of mucosal infection, genital tract physiology and ecology, and immunology, and identify and analyse potential markers of safety, activity, and efficacy. (Sections 3.1 and 3.2)
- Conduct research using both *in vitro* studies and animal models to identify, develop, and validate surrogate markers. As data from ongoing efficacy studies become available, stored blood and other samples from these studies could be used to identify and validate biomarkers of safety (e.g., cytokines,

chemokines, and inflammatory mediators), and eventually (when the first product shows at least modest protection) of efficacy. (Section 3.3)

- Identify and validate surrogate markers for safety in humans. Selecting the best potential markers, developing hypotheses about them that can be tested in Phase 3 studies, and finally developing, evaluating, and validating a range of technologies to assess the most useful biomarkers will lead to surrogate markers for humans. (Section 4.5)
- Continue to analyze surrogate markers that could validate self-reports of behaviour, HIV risk, and microbicide use. Explore ways to “triangulate” data on sexual behaviour collected in different ways and in comparison with biological data (e.g., biomarkers indicating applicator use or the presence of semen in the vagina). (Section 4.4)
- Allow for future retrospective analysis of potential efficacy markers. Incorporating into future large microbicide studies the task of collecting and storing a standardised set of biological samples (and associated informed consents) will allow for future retrospective analysis of potential efficacy markers. If the study later finds even partial protective efficacy, some of these samples could be used for surrogate marker studies—for example, to see whether efficacy positively correlates with biological markers such as prevention of other STI infections, or negatively correlates with increased levels of cytokines and markers of inflammation. (Section 4.5)

7.4 Industrialisation

Many microbicide concepts have been evaluated only in small quantities in laboratory-based studies and small animal models. Industrialisation is the process of transforming these microbicide concepts into well-characterised, consistently-produced, and mass-produced products. The components of industrialisation occur in all stages of microbicide development, and include physical design and formulation, characterisation, manufacturing scale-up, and quality control in production processes.

Although the pharmaceutical industry has useful experience, ‘industrialisation’ is not equivalent to real industry involvement. All microbicide developers, including not-for-profit and public-private partnerships, are confronted by this challenge. Furthermore, for a new technology such as microbicides, the processes and standard assessment tools for industrialisation are largely undefined even for the pharmaceutical sector. (US FDA, 2004)

The need for industrialisation efforts is particularly urgent given the current array of microbicide candidates. Many microbicides now in early development are biologically-produced proteins and peptides, such as the entry/fusion inhibitors Cyanovirin-N or PSC-RANTES. Low-cost large-scale manufacturing processes for biologics like these are complicated, and corresponding global manufacturing expertise and infrastructure are extremely limited.

RECOMMENDATIONS RELATED TO INDUSTRIALISATION

- To strengthen and streamline processes that demonstrate product safety, biodistribution, and bioabsorption, build central GLP laboratory capacity and develop standardised assays and validated *in vitro* and animal models. (Sections 3.1, 3.3, and 3.4)
- Form working groups focused on manufacturing and formulation, and commercialisation and access, to catalyse industrialisation and commercialisation planning for products, define industrialisation plans and roles, monitor progress, and exchange information. (Sections 5.1, 5.2, and 6.4)
- Assess products in development, using an expert team to identify commonalities and commercialisation issues, reduce processes to the lowest common denominator, and then fund process development and scale-up of drug substances and product (Section 5.5)
- Develop a strategic and tactical product development and marketing plan for microbicides that would provide 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 (Section 5.6)

7.5 Regulatory review

Throughout the MDS, there are numerous regulatory challenges identified with advancing candidate microbicides from pre-clinical to clinical evaluation, from clinical evaluation to approval and licensure, and from licensure to widespread distribution and use. One is the perceived lack of clarity about the requirements for regulatory review, approval, and licensure of microbicides, particularly outside the United States and Europe. Even in major markets, pharmaceutical companies frequently identify the lack of clear regulatory pathways as a major barrier to involvement in microbicide development.

Regulatory guidelines, pathways, and capacity may vary widely across countries, especially in resource-poor regions, and within a context of many different microbicide product types and distribution methods. The regulatory challenges could become even more complex as an increasingly diverse array of candidate microbicides moves towards clinical evaluation, including products that combine two or more active ingredients.

However, premature or piecemeal attempts to clarify regulatory expectations in a narrow sense could fail to improve the overall regulatory environment for microbicide development. Therefore, coordinated efforts are needed on multiple fronts.

RECOMMENDATIONS RELATED TO REGULATORY REVIEW

- Develop a list of regulatory questions that remain unanswered, and then work towards a systematic, field-wide strategy for resolving these issues. Where needed, build the capacity to do so. This work would meaningfully contribute to the overall goal of a business plan to ensure that products shown to be efficacious are made available as rapidly as possible.
- Engage regulatory experts to map out registration and regulatory pathways, including clear strategies for over-the-counter status. OTC designation is critical since requiring a prescription could greatly compromise widespread access and thereby lower the potential impact of an effective product. (Section 6.4)
- Clarify regulatory concerns, requirements, and potential ancillary sub-study protocols for addressing important issues with current candidate microbicide products. These issues include the requirement of a condom-only control arm in efficacy studies, the safety of microbicides for pregnant women and the current prohibition on pregnant women participating in microbicide clinical studies, and potential ARV resistance related to the use of ARV-containing microbicides. (Sections 4.2 and 4.5)
- Encourage continued guidance by regulatory agencies in developed countries (notably EMEA and FDA) to advance innovative trial designs. These could include research designs tailored to evaluate and compare newer microbicide formulations, or research that tests different product designs and compares potential common surrogate endpoints. Another is finding ways to fast-track

approval if a study makes minor changes to a product—such as changing some formulation attributes (e.g., from a gel to a tablet)—without having to repeat the product’s pre-trial toxicology and clinical studies. (Section 4.5)

- Establish ongoing dialogue between trial investigators and regulators to exchange information about potential surrogate markers and alternative trial designs. (Section 4.5)
- Work with customs offices and regulatory agencies in countries with clinical research sites to clear logistics and regulatory hurdles for importing and exporting clinical supplies. (Sections 5.1 and 5.4)
- Improve the regulatory capacity of resource-poor countries conducting clinical trials to evaluate trial protocols and experimental products. (Section 5.5.3)

7.6 Funding

Many parts of this report identify opportunities and needs for funding. While the overall level of investment in the microbicide field has increased, it still falls well short of the total needed. Projections developed jointly by the International Partnership for Microbicides, the Alliance for Microbicide Development, and the Global Campaign for Microbicides suggest that the global annual investment must double (to a total of \$280 million per year) over the next five years and must remain at around \$260 million until satisfactory microbicides are licensed. Once a product has been licensed, substantial additional resources will be needed to manufacture, market, and deliver it.

Beyond these large numbers, the MDS proposes many actions that require only small (but strategic) investments. Each of the preceding chapters describes potential actions that could open new directions of scientific inquiry, help rationalise the clinical development pathway, pave the way for sustained governmental and private-sector investment, and create new policy and advocacy initiatives.

Chapter 8

LOOKING AHEAD

There has been impressive progress in microbicide research and development since the beginning of the endeavour two decades ago. Yet, as concluded by the MDS working groups, much more remains to be done, including additional investment and new ways of working, if safe, effective, and accessible microbicides are to become a reality.

New collaborations are particularly needed to spark new work in pre-clinical research, consumer and behavioural research, microbicide formulations, intellectual property arrangements, regulatory capacity, and commercialisation and access.

As identified in the MDS, new linkages can be forged among:

- product developers with basic scientists working on genital tract immunology and the dynamics of mucosal transmission of HIV;
- social and behavioural scientists with clinical trial design experts;
- legal experts on intellectual property issues with donors and product developers to optimise IP requirements that will promote innovation and access; and
- scientific specialists with advocates to communicate the progress and challenges in the microbicide effort.

The progress of the microbicide field also calls for immediate planning for industrialisation, commercialisation, and access. The requirement for additional strategic planning is essential to the field's evolution from a relatively small group of academic researchers and small companies to a large and well-coordinated product development enterprise. But also planning and resources are needed immediately to ensure that products can be brought from pre-clinical research through to product introduction and widespread availability.

One approach is to create a “business plan” for the field, borrowing from pharmaceutical industry models for product development. This would seek to ensure development of promising microbicide formulations, related laboratory infrastructure, and related manufacturing processes, infrastructure and supply chains. It would also aim to resolve logistical and regulatory barriers to microbicide production, and shape microbicide development to meet known consumer preferences and user-guided attributes, cost and demand forecasts, potential product distribution systems, and likely regulatory pathways.

The MDS offers a set of recommended actions for accelerating and optimising progress in the field. The MDS is *not* a comprehensive blueprint covering everything that needs to be accomplished, but instead focuses on current priority areas only.

As candidate microbicides progress through pre-clinical development and clinical evaluation, the gaps and required action items in the field will change. The MDS should therefore be regarded as a dynamic document rather than a static formula. The MDS document will be reviewed and periodically revisited as the microbicide field moves forward. Although more than 100 experts have provided input into this document, broader review is anticipated, particularly from high-need countries where large-scale clinical trials are being implemented and where microbicides will be introduced. It is likely that the MDS might modify its framework later on to incorporate and better emphasise creative new concepts and cross-cutting themes. The value of the MDS will be maintained by this broader review, by periodic updates based on broad global consultation, and by incorporating new findings, technical developments, and evolving concepts.

Its value will also be enriched by explicit expansion of the MDS dialogue. The MDS initiative focused on needs and priorities in basic science, preclinical and clinical research, manufacturing and formulation, and commercialization and access, and specific strategic efforts required in those areas. It did not seek to articulate a strategy for advocacy efforts, although its authors enthusiastically recognize the need for end-user, community, and advocacy perspectives as crucial to all phases of product development. Thus, its authors are gratified by the prospect of the establishment of an international Civil Society Working Group spearheaded by the Global Campaign for Microbicides. The Group will map out the roles, added value of, and mechanisms for engaging civil society at each level of the microbicide enterprise and the associated investment in time, commitment, funding, and other resources needed to make that engagement happen constructively. A report from this Working Group is expected in 2007 and will serve as a companion document to the Microbicide Development Strategy.

Finally, as indicated earlier, a Mapping Exercise is also underway. Using the priority gaps listed in this document, experts are now matching ongoing and planned activities in microbicide research and development to the identified gaps. This process will result in a short document that describes what is now being done to advance the field.

Priorities for the MDC and its partners are therefore to support the mapping of the microbicide effort, and help engage private sector, public-sector, community, and other stakeholders in developing collaborations and further strategic and business plans. The scientific priorities and the cross-cutting themes described in this document offer an adaptable framework to the field to measure and evaluate its progress in the near future.

Chapter 9

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NOTE: This list does not include the large number of individuals who contributed to the MDS review process and the various forums at which it was discussed.

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