2. Background: How Microbicides Are Developed and Tested

As with any new health technology or drug, candidate microbicides must pass through a series of rigorous tests to determine their safety and efficacy. These tests start in the laboratory, where researchers determine whether a compound fights HIV and sexually transmitted disease (STD) pathogens, first in test tubes and then in animals. If the data from these trials show that the product is potentially effective and relatively safe (non-irritating) in animals, then clinical (human) trials can begin.

Determining safety and effectiveness through clinical trials

There are three phases of clinical trials. Phase 1 trials determine the safety of the product when used by a small number of healthy, low-risk women over a few weeks. Phase 2 trials also test for safety of the product, but over a longer time and with a larger number of women, some of whom may have higher risk factors. Some preliminary data about efficacy and acceptability of the product may also be collected. Phase 3 trials enroll thousands of people in several sites. The trials measure effectiveness—that is, whether or not the microbicide actually works to prevent HIV and STDs.

Microbicide candidates generally proceed through a series of Phase 1 safety trials for different user groups before moving on to effectiveness testing. If a candidate appears safe for low-risk women, additional Phase 1 trials are conducted to establish safety in heterosexual men, for HIV positive women and men, and sometimes for rectal use.

If safety is *not* demonstrated in early human trials, research on that candidate is stopped and the product is dropped from consideration as a potential microbicide. (See Box 2 for definitions of safety, efficacy, and effectiveness.)

Sixteen products with various targets and mechanisms of action are currently in

BOX 2: Safety, Efficacy, and Effectiveness in Clinical Trials

Safety refers to the absence of significant adverse events related to gel use in the study population. *Safety* does not mean "keeping participants *safe* from infection."

Efficacy is the maximum ability of a drug or treatment to produce a result. It represents the protection achieved if the drug is delivered and used correctly every time.

Effectiveness is the real life ability of a drug or treatment to produce a result under conditions of "real use." It is measured as reduction in infections averaged across all users.

Note: Because not all trial participants in the active arm will use the microbicide every time, Phase 3 microbicide trials measure the effectiveness of a candidate microbicide, not its efficacy.

clinical trials in the United States and globally. It is crucial that several products with different mechanisms of action be tested simultaneously. This increases the probability and speed of finding a successful microbicide.

The differences between and among different kinds of products will greatly affect how they might be used and by whom. For example, some product concepts are based exclusively on enhancing the ecology of the vagina; others could potentially offer protection from rectal transmission as well.

Randomized clinical trials are the most reliable method of determining whether a new drug or intervention can be used safely by a large cross section of a population and whether it actually works. As shown in Figure 1, it normally takes about 10 years to move from a laboratory lead to a fully tested product that regulators deem safe and effective for human use.

How Phase 3 effectiveness trials are carried out

The critical Phase 3 effectiveness trials work by comparing two groups—those who receive the microbicide plus a standard prevention package (e.g., condoms, counseling, and STD treatment) and those who receive the standard prevention package plus a placebo gel. The placebo looks identical to the drug being studied but does not contain the active ingredient. Researchers randomly assign participants to one of the two groups, termed "arms." Randomization ensures that women in each arm are similar in every respect except the matter under study—the use of a test product versus a placebo. It should be emphasized that women are *never* deliberately exposed to HIV to see if the microbicide protects them. Instead, researchers compare the two groups to see whether the rate of HIV infection is lower among those who received the candidate microbicide with condoms compared with those who received condoms and a placebo. The difference is considered to be a measure of the candidate microbicide's effectiveness.

All trial participants receive intensive condom counseling; free, high quality condoms; and regular treatment for STDs. Women are actively encouraged to use condoms whether or not they are given the active microbicide candidate. As shown in Table 1, several thousand women must participate in a Phase 3 trial in order to determine whether a reduced HIV infection rate can be attributed to the microbicide.

FIGURE 1: Timeline to Develop and Test a Microbicide Product

Source: *Global Campaign for Microbicides*

TABLE 1: Clinical Trial Phases—Number of Participants, Length, and Purpose

	Number of participants	Length of treatment and follow up	Purpose
Phase 1	25-40	1 to 4 weeks	To assess local and systemic safety and acceptability, and to determine dose and formulation. May run into a Phase 2 trial (called Phase 1/2).
Phase 2	200-400	2 to 6 months	To assess safety and acceptability among higher-risk women over a longer time.
Phase 2b	500-3000	6 months to 2 years	To screen for products reaching a minimum level of effectiveness. Smaller, less costly than Phase 3, but numbers of participants and length of follow-up indicate whether a subsequent larger trial would be worthwhile. If so, participants sometimes continue from one trial to the next, and additional participants are recruited (such trials are called Phase 2/3).
Phase 3	3,000-10,000	2 to 4 years	To evaluate effectiveness in preventing HIV infection and other STDs and to assess long-term safety and acceptability. Some Phase 3 trials will involve multiple products, which will require more participants than those testing only one product.

Note: Phases 1/2, 2/2b, and 2/3 are variants of study designs or studies that move from one clinical trial phase to the next. The number of participants and length of treatment and follow-up vary.

Source: Table adapted from Upadhaya U. *Microbicides: New Potential for Protection*. INFO Reports No. 3. Baltimore, MD: Johns Hopkins Bloomberg School of Public Health; 2005. Available at: http://www.infoforhealth.org/inforeports/microbicides/microbicides.pdf

What microbicide products are being tested—how they work and what they do

Table 2 shows the five major microbicide products in Phase 2b or Phase 3 clinical trials as of early 2005. Their mechanisms of action and characteristics differ significantly.

Participants generally do not increase their risk of becoming HIV infected by participating in a Phase 3 microbicide trial. Rather their risk is likely to decrease because the trial actively promotes condoms and provides treatment for STDs, which otherwise increase women's vulnerability to HIV. However, some women will nonetheless become infected during the trial because they are still unable to negotiate consistent condom use with their partners. Among these cases, Phase 3 effectiveness trials measure whether the active microbicide product offers any protection over and above standard prevention.

Table 3 shows the developers and principal trial investigators for the five main microbicide candidates in effectiveness trials as of early 2005 as well as the phase and location of these trials.

TABLE 2: Microbicides Entering Effectiveness Trials

Microbicide name	Mechanism of action	Description	Potential pregnancy prevention?	Potential STD/HIV protection*
BufferGel (Carbomer 974P)	Vaginal defense/ acid buffer	Polymer gel reinforces vaginal acidity by acidifying the ejaculate.	Yes	HIV, chlamydia, herpes, HPV, gonorrhea
Carraguard (PC-515)	Attachment inhibitor	Carrageenan (derived from seaweed) binds to block viruses from attaching to and infecting healthy cells.	No	HIV, Herpes, HPV, gonorrhea
Cellulose sulfate	Attachment inhibitor	Binds to viruses and bacteria to prevent them from attaching to and infecting healthy cells.	Yes	HIV, gonorrhea, chlamydia,
PRO 2000 (Polynaphthalene sulfonate)	Entry and fusion inhibitor	Binds to viruses and bacteria to prevent them from attaching to and infecting healthy cells.	Yes	HIV, gonorrhea, herpes
Savvy(C31G)	Surfactant	Detergent disrupts viral, bacterial, and cell membranes, including those of sperm.	Yes	HIV, chlamydia, herpes

*As demonstrated in animal models.

Source for potential STD/HIV protection: Zeitlin L. and Whaley K.J. Microbicides for preventing transmission of genital herpes. Herpes. 2002;9(1):4-9.

(For more information on these and other candidate products, see the Alliance for Microbicide Development's website www.microbicide.org or the Global Campaign's Trials Watch, Factsheet #13, at www.global-campaign.org/download.htm.)

Figure 2 shows the location of all communities that have participated or are participating in clinical trials of microbicides. The map illustrates that microbicide trials are taking place in both the industrial and developing world. Most of the trials in the United States and Europe are Phase 1 safety trials rather than Phase 3 effectiveness trials. Microbicide trials must be mounted among populations at high risk of acquiring HIV who do not use injecting drugs or engage in other HIV risk behaviors besides vaginal intercourse. (If a woman uses injecting drugs, it would be impossible to know whether an infection is due to sharing of needles or a failure of the experimental products). Populations that fit this description are mostly in the developing world.

Protecting the human rights of participants during trials

Before a trial can proceed, a national and/or local ethical review board must approve the trial protocol. These boards differ across the world, but their purpose is similar everywhere: to ensure that trials are scientifically valid and conform to prevailing ethical guidelines. Once a trial begins, a data and safety monitoring board (DSMB)

TABLE 3: Developers, Investigators, and Status of Trials, by Candidate Product

Candidate product	Developer	Trial investigator	When and where trials are happening
BufferGel (Carbomer 974P)	ReProtect LLC	HIV Prevention Trials Network	• Phase 2/2B—shared with PRO 2000 (.5% formulation). • Enrollment began February 2005. • Four-arm Phase 2b trial in which BufferGel will be compared to PRO 2000/5, a placebo gel, and a condom only arm. 3,000 participants will be enrolled in Durban and Hlabisa, South Africa; Lilongwe and Blantyre, Malawi; Moshi, Tanzania; Philadelphia, USA; Lusaka, Zambia; Harare and Chitungwiza, Zimbabwe.
Carraguard (PC-515)	Population Council	Population Council	• Phase 3. • Enrollment began in March 2004. • Two-arm study, standard prevention and microbicide compared to standard prevention and placebo gel. • Four sites in 3 centers: Pretoria, Cape Town, and Durban (South Africa). • 6,639 women will be recruited and followed at quarterly clinic visits for two years.
Cellulose sulfate	Global Microbicide Project	Family Health International CONRAD	• Phase 3. • Two separate trials, each is a 2-arm study, compared to placebo gel. • FHI is running a trial with 2,160 participants in Nigeria. Enrollment began in January 2005. • CONRAD is running a trial with 2,574 participants in Benin, Burkina Faso, India, South Africa, Uganda. Enrollment anticipated to begin in June 2005.
PRO 2000 0.5% formulation (Naphthalene sulfonate polymer)	Indevus Pharmaceutical, Inc.	HIV Prevention Trials Network	• Phase 2/2B-shared with BufferGel. • Enrollment began in February 2005. • Four-arm Phase 2b trial, in which PRO 2000 will be compared to BufferGel, a placebo gel, and a condom only arm. • 3,000 participants will be enrolled in Durban and Hlabisa, South Africa; Lilongwe and Blantyre, Malawi; Moshi, Tanzania; Philadelphia, USA; Lusaka, Zambia; Harare and Chitungwiza, Zimbabwe.

Table 3 continued on next page

TABLE 3: Developers, Investigators, and Status of Trials, by Candidate Product *(Continued)*

Candidate product	Developer	Trial investigator	When and where trials are happening
PRO 2000 0.5% and 2% formulation (Naphthalene sulfonate polymer)	Indevus Pharmaceutical, Inc.	Microbicide Development Programme	• Phase 3. • Three-arm study for two formulations (.5% and 2%) of PRO 2000. • Enrollment anticipated to begin in 2005 for 11,920 participants in South Africa, Tanzania, Uganda, Zambia. • This trial originally included dextrin-2-sulphate (Emmelle) but this product was excluded from the final design of the phase 3 trial.
Savvy(C31G)	Biosyn, Inc.	Family Health International	• Phase 3. • Enrollment began September 2004. • Two-arm study, compared to placebo gel. • A trial to assess its efficacy against HIV, supported by USAID and Family Health International. • 4,284 volunteers in Accra and Kumasi, Ghana; and Lagos and Ibadan, Nigeria.

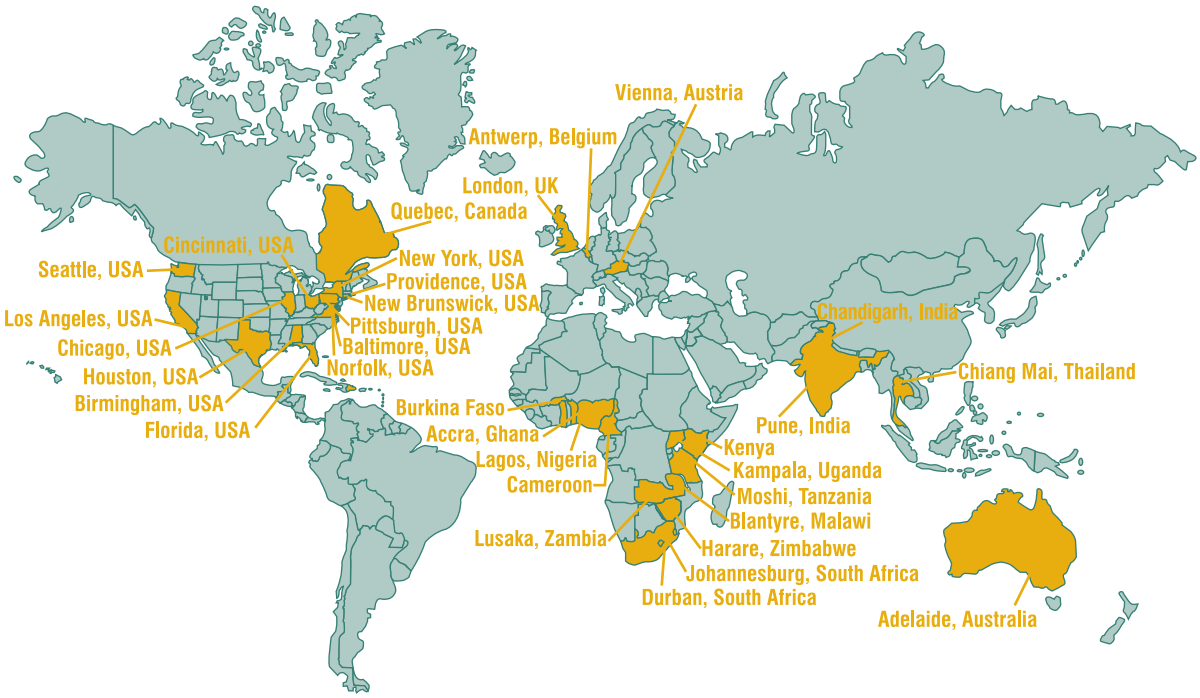
Source: Alliance for Microbicide Development

monitors the trial results in real time. This board has the authority to stop a trial if the test product appears to be definitely effective or ineffective. The "best case" scenario is for a microbicide's effectiveness to be so evident from early data that the trial can be suspended early, so that the product can be made publicly available to those who need it. This, however, has not yet occurred.

Many of the women who volunteer to participate in trials do not know their HIV status. Safety trials are conducted among both HIV-positive and HIV-negative participants, since products must be safe for both populations. However, Phase 3 trials can only enroll HIV-negative participants, because the rate of seroconversion among trial participants is the standard by which the effectiveness of the product is to be measured.

To be considered for trial enrollment, prospective participants must agree to HIV testing. Those who test positive are generally not enrolled in Phase 3 trials. Trials may exclude women for a wide variety of other reasons, including other health problems, a desire to become pregnant, or unwillingness to adhere to the trial protocol. In many communities around the world, people perceived to be HIV-positive face stigma and discrimination. For this reason,

FIGURE 2: Clinical Trial Sites (2005)



Source: Alliance for Microbicide Development

researchers and community groups must make clear that exclusion from a trial does not automatically imply that a woman is HIV-positive.

What happens to women who become infected during the trial?

The package of HIV prevention and treatment provided during the trial is referred to as the "standard of care." Within the microbicide field—and among Consultation participants in particular—everyone agrees that microbicide trials should improve upon the local standard of care—including HIV care. However, intense debate persists internationally over how the appropriate standard of care in international trials should be defined. This question is discussed in greater depth in subsequent sections of this report.