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Regulatory Challenges in Microbicide Development

Paul M. Coplan,* Mark Mitchnick, Zeda F. Rosenberg

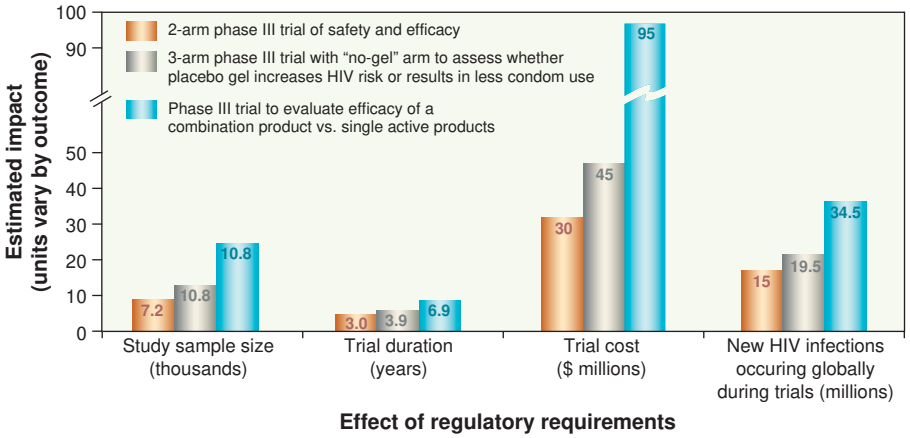
Women now account for the majority of people living with HIV, and young women bear the brunt of new infections in many parts of the world (*1*). Against this background, advances in understanding the molecular mechanisms of HIV sexual transmission are focusing new interest and resources on development of microbicides that are topical agents designed for vaginal (and possibly rectal) administration. Yet paradoxically, just as support and scientific prospects for microbicide development are improving, the regulatory obstacles to testing and licensing them are growing.

Programs to promote behavior change, condom use, and treatment of sexually transmitted infections are all crucial. But in many settings a woman's greatest risk comes from her husband or steady partner, and she may have little power to insist on condom use (*2*).

Because they provide a chemical (not physical) barrier to HIV transmission, microbicides need not interfere with physical intimacy and conception. Moreover, new formulations offer the promise of once-daily or even monthly application. Microbicides can provide a complement to existing prevention methods and to future vaccines that may control, but not prevent, infection. Mathematical modeling studies estimate that a partially effective microbicide used in half of coital acts by 20% of women at risk could prevent 2.5 million infections in 3 years (*3*).

Microbicides are designed to block HIV infection by directly inactivating the virus or interrupting its attachment, entry, or replication (*4*). Recent insights into how HIV crosses the genital mucosa, initial interactions with immune cells, and the role of dendritic cells in transporting it to the lymph nodes have suggested many potential new targets for microbicides (*5*). Safety and efficacy of more than 40 compounds are now being tested in laboratory assays and with animal models (*6*).

However, because no surrogate marker or animal model is known to reliably predict whether microbicides will work in humans, efficacy can only be assessed through large-scale clinical trials. The logistics of these studies are formidable: Thousands of HIV-uninfected, high-risk women are randomized to active or placebo microbicide groups and followed for several years to compare the rate of HIV infection in these two trial arms. Targeted efforts and significant financial investment by several organizations have established clinical sites capable of conducting these trials according to international guidelines.



Consequences of more complex clinical trial designs. Longer trials result from the time for enrolling additional volunteers. Trial costs are based on an estimated $30 million cost for two-arm phase III trials and linear increases with additional volunteers. We assume 5 million new HIV infections annually (*18*).

With six candidates currently in or about to enter phase III studies (requiring about 31,000 volunteers), both the infrastructure and the ability to recruit and retain enough volunteers will be strained. Expanding capacity for carrying out efficacy trials is therefore an important priority for all prevention interventions.

Regulatory Uncertainties

Moreover, the lack of well-defined criteria and pathways for microbicide licensure in regions with high HIV rates is a significant hurdle, because it deprives product developers of crucial guidance in terms of what will be required for licensure.

This gap is due to several factors. Except for tenofovir, all microbicides now in clinical testing are new drugs. Furthermore, chronic use of topical intravaginal drugs to prevent infection is a new concept, one with which regulators have little previous experience.

Although there are exceptions (such as South Africa and India), developing countries may not have sufficient resources to complete a multifaceted review of new drug applications within their National Regulatory Authority (NRA) and therefore often rely on product reviews by U.S. or European agencies (*7*). Many NRAs in developing countries will approve a drug or vaccine for in-country licensure with minor requirements as long as it has been licensed and widely used in the United States or Europe (*7*). The U.S. and European regulatory agencies, the Food and Drug Administration (FDA) and European Medical Evaluation Agency (EMEA), are concerned, but their mandate as defined by law is to protect their national populace. Although the requirements to demonstrate safety and efficacy are essential anywhere, risk-benefit profiles of microbicides differ enormously between developed countries and regions where HIV infection is higher by two orders of magnitude. Differential risk-benefit has historically resulted in differences in developing and developed countries, for example, for whole-cell versus acellular pertussis vaccine (*8*).

Differences in risk-benefit context came into sharp focus for the microbicide field at an FDA advisory committee meeting in August 2003 (*9*). During this meeting, the FDA raised concerns that use of microbicides could decrease condom use, resulting in a net increase in HIV infection rates. The FDA therefore recommended an efficacy trial design that departs from the standard two-arm active versus placebo trial and is unprecedented in drug regulatory requirements. It would re-

The authors are with the International Partnership for Microbicides, Silver Spring, MD 20910, USA.

*Author for correspondence. E-mail: PCoplan@ipm-microbicides.org

quire a three-arm study to compare HIV incidence rates not only in groups with active versus placebo control gels, but also in a no-gel ("condoms only") control group. Evidence of microbicide efficacy would be evaluated against both control groups (*10*).The EMEA has not provided an opinion on this issue, but the World Health Organization (WHO) concluded that a third, unblinded arm would not provide meaningful data (*11*).

This recommendation goes to the heart of the differential risk-benefit issue. FDA concerns about reduced condom use among its own citizenry have little relevance in countries where only 1% of sexually active women report condom use in the past month (*12*) and annual HIV infection rates in young women are 4 to 7% (*13*, *14*). Moreover, mathematical modeling indicates that only when condoms are used in more than 70% of coital acts can their benefit be undermined by a partially efficacious microbicide (*15*).

Because condom use is (by definition) unblinded, the proposed trial design violates the principle that randomized, controlled, double-blinded trials are the standard for determining efficacy. It is also inconsistent with other regulatory practice. For example, phase III trials of cholesterol-lowering and osteoporosis prevention medications have not been required to include third, unblinded arms to demonstrate absence of medication-associated increases in risk behavior (increased dietary cholesterol consumption or decreased exercise).

The recommendation for a third arm was also intended to address the concern that placebo gels may reduce or enhance HIV infection. Although such effects have not been detected in human or animal studies, they have not been formally excluded. However, this issue could be addressed more easily by in vitro or preclinical studies than in phase III trials. Moreover, behavior differences and condom use in an unblinded arm will be further confounding variables.

The recommendation for including a third arm would require a 50% increase in the size of phase III trials (*16*), vastly increasing time, cost, and strain on the limited capacity of clinical sites (see the figure, page 1911) and would impose delays in launching trials. Although the no-gel arm was stated as a recommendation rather than a requirement, sponsors who disregard this advice run the risk of conducting large, expensive trials with no guarantee that results which prove efficacy and safety will be accepted as sufficient for licensure.

Another regulatory hurdle is the guidelines that cover licensure of combination products. Products containing more than one active ingredient must show clinical superiority, in the case of microbicides in field trials, of each added active agent over the individual components. It is likely that microbicides containing two or more active ingredients will be more efficacious than single active compounds, because HIV is adept in developing resistance to active products with a single viral inhibition target and has more than one mechanism of effecting intravaginal infection (*17*). Anything that expedites licensure of microbicides that combine two or more active pharmaceutical ingredients while ensuring safety and efficacy can save years of delay in availability. With antiretroviral oral therapy, it took 10 years from the licensure of the first antiretroviral drug (zidovudine in 1987) to the licensure of the first combination antiretroviral product [combivir or zidovudine+3TC in 1997].

Moreover, there are ramifications in terms of numbers of volunteers. For example, about 5600 volunteers would be needed to demonstrate superior efficacy for a microbicide with 50% efficacy relative to a placebo group. For a two-agent microbicide with 70% efficacy compared with a single-component product with 50% efficacy, about 19,000 women would be needed. At rates of about 5 million new infections per year (*18*), roughly 20 million new infections would occur globally in the time needed to enroll 19,000 instead of 5600 volunteers (see the figure).

Positive Directions

Important steps have been taken to strengthen the capacity of developing country NRAs to make licensing decisions (*7*), although there are still inadequate resources. To help fill the gaps, the European Parliament has approved a proposal (article 58) for the EMEA to provide scientific assessments, but not marketing authorization, of products intended principally for distribution in developing countries (*19*). In-country NRAs would then make the final licensing decision. This assessment by the EMEA would be initiated upon request by WHO for products manufactured in Europe only.

We believe the following steps would do much to remove potentially rate-limiting regulatory hurdles:

1) The mission of regulatory agencies such as the FDA and the EMEA should be expanded to include evaluation of the safety and efficacy of products on behalf of NRAs in developing countries, while risk-benefit analyses are left to the NRAs.

2) Links between NRAs should be strengthened and fostered to enhance regional, south-south, and developing country–industrialized country collaboration to allow for joint reviews of product dossiers.

3) The transparency of decision-making by developed country NRAs should be increased so that rejection of licensure applications based on risk versus benefit, not safety or efficacy, does not unduly prejudice independent assessment by developing country NRAs.

4) Donor organizations should provide additional resources, including funding and training, to enhance the capacity of developing countries' NRAs for autonomous decision-making.

5) An international advisory group of scientific, clinical, and regulatory experts (analogous to the FDA's advisory committees or the EMEA's scientific advice working groups) should be established to assist developing country NRAs in making regulatory decisions.

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