Testimony Regarding Microbicide Clinical Trials
August 13, 2003

Submitted by:
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Director, Connecticut AIDS Education and Training Center
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Co-PI, Microbicide Acceptability Among High Risk Urban US Women, NIMH R01 MH63631

Steering Committee Member, Global Campaign for Microbicides

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Dear Colleagues:

I am pleased that the FDA is exploring the best way to proceed with microbicide trials. I think there is no more urgent challenge in combating the HIV epidemic right now than to find a way to harness current science to expedite the discovery and approval of a safe, effective microbicide and to make it accessible to the millions worldwide in need of an HIV prevention method they can control themselves.

Just as in the 1980s it was necessary for the FDA to reconsider business as usual and develop mechanisms for fast-tracking promising AIDS therapeutic agents, it is time to find a way to fast-track microbicide development. I recognize that it is no easy to task to balance urgency, safety, and good science, and that we are in uncharted waters developing a new class of product that will be used both by those who are healthy and by those who are ill.

That being said, we must remember that caution carries a large price tag, paid in literally thousands of new HIV infections around the globe every day a trial is delayed; new infections that are increasingly among women who cannot control their partner's fidelity or their partner's use of condoms; new infections that for most, will result in a slow, unglamorous death. Given that the vast majority of women who become infected do so within the context of their marriages and other primary partnerships, we must move beyond calls for abstinence and use of a barrier contraceptive device as the only mechanisms of HIV protection available to women and develop biologically-based protection against HIV.

Given the very scarce resources devoted to microbicide development, it is critical that trials be designed to answer questions about efficacy. Promising agents must move expeditiously into phase III clinical trials that are powered to detect even modest effectiveness. Mathematical modeling studies carried out by the London School of Hygiene show that even a microbicide with only moderate effectiveness would avert millions of new infections and deaths when used by individuals among whom condom use is low.

We must recognize that these trials will be conducted in settings and in cultures where our paradigms of research and documentation are new and we must be flexible in setting

reachable standards. Ethical and scientific standards must be adhered to, but they must also be doable within the environmental context the studies are being conducted in.

We must be pragmatic in designing trials. While condom only arms may be theoretically desirable as part of a trial, an analysis should first be done of whether there is real condom use among the sample population to begin with, and what the ability to retain subjects in a condom only arm will be. Sample sizes must be recruitable and retainable, while still powered large enough to see an effect. Standard measures of statistical significance should be used. The bar should not be raised higher, e.g., .001 significance, simply because this is a new class of product. Study samples should not focus primarily on sex workers, who are already among the best condom-users in the world, but on average women, many of whom have primary partners, since these are the women most in need of a microbicide. Our acceptability study of high risk women in Hartford, CT found that in the past thirty days, high risk women had used condoms in 75 percent of their encounters with paying partners compared to only 34 percent of their encounters with primary partners (Weeks, et. al., 2003).

We cannot wait for perfect conditions or the perfect trial. One trial may not answer all of our questions. But a single trial should be able to establish safety and be able to show moderate levels of efficacy. We cannot afford to be wasting time with Phase IIb studies that then will need to move Phase III, delaying answers about moderate efficacy for years. The recent decision regarding the HPTN 035 was most disappointing. A Phase IIb is unlikely to detect efficacy unless a product is highly efficacious. The decisions regarding HPTN 035 appeared to weigh caution and skepticism over urgency and the understanding that even a moderately effective microbicide is of value. A phase II/III design is more likely to answer questions where efficacy may be moderate.

While the FDA's primary responsibility is regulation and approval of products for US use, it must also acknowledge that it is considered a world leader on drug and product safety. Many countries lacking in scientific or regulatory infrastructure use FDA decisions to guide their own policies, as we saw with South Africa (a relatively developed country) and Nevirapine for preventing vertical transmission. While the FDA's responsibility is not to set worldwide policy, the FDA must act within the context of knowing that its role in affecting the global outcomes of the epidemic extends beyond our borders.

I respectfully encourage the FDA to think creatively and flexibly, to develop new paradigms that factor in urgency and feasibility along with scientific rigor and ethical concern, to take risk where it is justified when weighed against the cost of delay, and to harness the great scientific minds devoted to revolutionizing HIV prevention.