

**M E M O R A N D U M**

**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
Division of Antiviral Drug Products**

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**DATE:** July 24, 2003

**TO:** Antiviral Drug Products Advisory Committee Chair, Members, Consultants, and Speakers

**FROM:** Teresa C. Wu, M.D., Ph.D., Medical Officer  
Rafia Bhore, Ph.D. Mathematical Statistician

**THROUGH:** Debra Birnkrant, M.D., Division Director

**SUBJECT:** Advisory Committee Meeting to discuss clinical trial design issues in the development of topical microbicides for the reduction of HIV transmission

The Food and Drug Administration (FDA) will be convening the above meeting on August 20, 2003, from 8 a.m. to 5 p.m. at the Holiday Inn, Versailles Ballroom, 8120 Wisconsin Avenue, Bethesda, MD 20814. This memo will serve as a background document for this meeting.

The objective of the meeting is to discuss the design of phase 2 and 3 trials of topical microbicides for the reduction of HIV transmission in order to facilitate and expedite development of topical microbicides. Of note is that many of the clinical trials to evaluate topical microbicides are conducted primarily in foreign countries. Marketing approval in the U.S. of a safe and effective topical microbicide will benefit both U.S. and foreign populations.

Globally, women are the fastest growing demographic group of people living with HIV or AIDS. In developing countries, gender issues and culturally specific sexual role definitions further add to the vulnerability of risk for HIV and other sexually transmitted infections (STIs). Consequently, there is an urgent public need for developing safe, efficacious and female-controlled topical microbicides. A global perspective will be provided in the presentation by Dr. Salim Karim. His presentation is entitled: HIV and STIs in Women, the Urgent Need for an Efficacious Microbicide.

Topical microbicides are chemical preparations in the form of gels, creams, foams, impregnated sponges, suppositories or films. These products are designed for vaginal self-administration prior to sexual intercourse to protect against the transmission of HIV and other STIs. They are not intended to replace other prevention measures such as condoms, or vaccines when they become available. It is likely that some microbicides are also spermicides and some products may be suitable for rectal use. Prior to phase 2 and 3 clinical studies, rigorous nonclinical evaluation and phase 1 human studies of candidate

microbicides are essential to the selection of the lead products for continued development.

The first microbicides actively studied were various formulations of the surfactant nonoxynol-9, an active ingredient of over-the-counter spermicide products. Clinical trials of nonoxynol-9 have shown that frequent use in a high-risk population not only fails to protect against HIV transmission, but also increases a woman's risk of HIV infection by causing genital epithelial disruptions. Results of one of these trials, COL-1492, will be presented by Dr. Lut Van Damme in her talk, entitled: Lessons Learned from COL-1492, a Nonoxynol-9 Vaginal Gel Trial.

The failure of nonoxynol-9 in preventing HIV transmission in conjunction with the failure of existing interventions to slow the epidemic in developing countries have spurred pursuit of clinical development of many promising candidate topical microbicides. Currently, approximately 20 vaginal microbicides are in early phases of human testing. Less than half of these have been submitted under the Investigational New Drug Application (IND) process to the FDA. Among them, at least 4 products are entering phase 2/3 testing.

Despite the rapid expansion of microbicide research and a development pipeline, there are many challenges to the clinical development of topical microbicides. The two major challenges to trial designs evaluating microbicides are: low incidence of seroconversion and condom counseling. Using HIV incidence as an outcome measure has been adopted by the research community as the most meaningful and appropriate endpoint for evaluating the efficacy of a microbicide in the prevention of HIV transmission. Given the low incidence of seroconversion rates even among populations with the highest prevalence of HIV infection (e.g. 7 per 100 person-years among sex workers in Cameroon and 9 per 100 person-years among individuals in serodiscordant couples in Zambia), a very large sample size (several thousand) is necessary to provide adequate power to detect a statistically significant effect of a microbicide on HIV seroconversion. Whereas the ethical conduct requires the provision of condoms and safer sex counseling, both interventions are likely to further reduce low rates of seroconversion and increase the need for an already large sample size. For these and other challenges, the following speakers have been asked to consider, and offer their views on, the issues concerning topical microbicide phase 2 and 3 trials designs. Dr. Teresa Wu and Dr. Andrew Nunn will each present considerations for topical microbicide phase 2 and phase 3 trial designs from a regulatory and an investigator's perspective, respectively; Dr. Tom Fleming and Dr. Rafia Bhore will each present statistical considerations for topical microbicide phase 2 and 3 trial designs from an investigator's and a regulatory perspective, respectively.

For this meeting, we have selected several key issues and drafted a list of specific questions for discussion (please see attachment). Due to the time and resource constraints, this meeting will not address many other issues such as behavioral evaluations, combination microbicides, over-the-counter approval, rectal use, etc.

In order to provide the context for those questions, we have summarized the Agency's current recommendations and will be asking for the Committee's input on these issues.

1. **Trial Design:** Phase 2 run-in / phase 3

A multicenter phase 2 study as a run-in component of a phase 3 trial is a design where infections and woman-years of exposure collected in the phase 2 portion would count towards the numerator and denominator for safety and efficacy in the phase 3 component. In a phase 2 run-in phase 3 trial, a specified number of participants are enrolled into the phase 2 component of the study and followed up intensively with frequent safety evaluations. Concurrent with the follow-up portion of the phase 2 component of the study and the time required to complete the phase 2 data review, accrual of phase 3 participants will begin. Sponsors have proposed this type of trial design for some of the topical microbicides in the pipeline.

We will ask the Committee to consider the appropriateness of the above design. We will also ask if the Committee could recommend additional alternative approaches.

2. **Control arms and criteria of a 'win'**

During the conduct of these trials, condom promotion and safe sex counseling are ethical imperatives. In this context, the Agency has recommended that two control arms be included in the design: placebo and 'no-treatment' (condom-only). In order for a candidate microbicide to claim effectiveness, it has to show a significantly better reduction in HIV seroconversion rate than **both** the placebo and 'no-treatment' arm. The rationale for this approach is:

- The placebo control provides a means to blind the study and thereby maximizes the likelihood of obtaining an unbiased estimate of the efficacy of the candidate microbicide.
- When a placebo used in the trial is the gel vehicle of the candidate microbicide product, there is a possibility that the placebo might exhibit a beneficial or harmful effect on the rate of HIV seroconversion due to the following considerations:
  - A. Gel vehicle in and of itself may be a barrier that could contribute to an unknown level of protection.
  - B. Gel vehicle might be associated with increased risk of infection by causing vaginal epithelial disruptions.
  - C. *In vitro* data have shown that some gelling chemicals exhibit some levels of anti-HIV and anti-microbial activities.

- In response to the concern described under ‘C’, some sponsors have elected to use other unrelated ‘inert’ chemicals as ‘placebo’. Like gel vehicles, when a placebo used in the trial is an unrelated chemical, the contributions of such an ‘inert’ chemical with respect to efficacy and safety are unknown and therefore need to be evaluated in humans.

For the various concerns described above, it is necessary to have a no-treatment arm (condom-only) in order to validate interpretation of the efficacy and safety data of the candidate microbicide.

However, the recommendation for including a ‘no-treatment’ control arm has raised several concerns. They are:

- Since a ‘no-treatment’ arm cannot be blinded, participants’ might be less motivated to stay in the study or adhere to the study requirements. As a result, there might be differential dropout rates between treatment arms.
- It is generally acknowledged that, even with condom counseling, the rate of consistent condom use is very low. Therefore, the utility of a ‘no treatment’ arm is expected to be of little importance.
- Potential gel sharing between randomized treatment arms may occur.
- A three-arm study containing a ‘no-treatment’ arm will further raise the required number of study participants which is already very large.

The issue of control arms is a complicated one. We will ask the Committee to offer views on the need for a ‘no treatment’ arm in the three-arm trial design. We will also ask the Committee for recommendations if a two-arm trial design is deemed more appropriate (i.e. which control should be used.).

### **3. Trial Duration**

Given that the seroconversion rates are low and a topical microbicide for the reduction of HIV transmission is intended for long-term use, the length of the trial should be adequate for assessing long-term exposure and capturing efficacy endpoints. The Agency has recommended that the length of on-treatment evaluation be 12 – 24 months. The Agency has also recommended that all participants be treated until the last participant enrolled has completed a 12-month or 24 month treatment. In order to reduce anticipated high drop-out rates that have been reportedly associated with trials of nonoxynol-9, we highly encourage sponsors to make every effort to retain participants in the study in order to minimize possible bias resulting from high rates of loss-to-follow-up

At present, the Agency has not made recommendations with respect to off-treatment follow-up (i.e. premature discontinuation or completed).

We will ask the Committee’s input on the appropriate duration of on-treatment evaluation and the need for, and duration of, off-treatment follow-up.

#### **4. One single large trial versus two adequate and well-controlled trials**

Regarding the quantity and quality of evidence needed to establish a product's effectiveness, the Agency has traditionally required at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. Nevertheless, the Agency has approved biological and drug products based on single, multicenter studies with strong results. Given the urgent public need for effective topical microbicides and that a definitive microbicide phase 3 trial is unlikely to be validated in a second trial due to ethical concerns, the Agency has agreed that a single large trial would be acceptable for registrational purposes for microbicides. In order to produce statistically 'persuasive' conclusions for any single studies, the Agency usually recommends that a one-sided significance level of 0.000625 ( $0.025 \times 0.025 = 0.000625$ , 1-sided; 0.001 for 2-sided) be used. Recognizing the inherent difficulty with this small p-value in designing a reasonably sized trial for microbicides, the division would consider a p-value between 0.01 and 0.001 (2-sided), conditioned upon good internal consistency of results, low drop-out rates, good data documentation on microbicide and condom use, and other supportive studies.

We will ask the Committee to provide feedback on this statistical issue of one versus two trials.

In sum, there is tremendous public interest in developing safe and effective topical microbicides for the reduction of HIV transmission. However, the development of a licensed topical microbicide has a unique and complex set of regulatory, social, ethical, and economic challenges. We appreciate the Committee's considerations on the trial design issues of topical microbicide development and look forward to a productive discussion.