FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
ANTIVIRAL DRUGS ADVISORY COMMITTEE (AVAC) MEETING

Questions to the Committee

August 20, 2003
Holiday Inn, Versailles Ballroom, 8120 Wisconsin Avenue, Bethesda, MD 20814

Clinical Trial Design Issues in the Development of Topical Microbicides for the Reduction of HIV Transmission

1. For topical microbicides, a conventional clinical development approach of conducting Phase 2 'proof-of-concept' trials before embarking on Phase 3 trials may require large numbers of participants. For antiretroviral drugs, HIV RNA levels have been shown to be a valid surrogate marker for predicting clinical outcome and short-term drug-induced changes in HIV RNA have been employed in phase 2 proof-of-concept trials. However, biological correlates of the effectiveness of topical microbicides for the reduction of HIV transmission have not been determined. Please comment on the following alternative approaches for clinical development of topical microbicides:

   A. A phase 2-run in phase 3 trial design, with safety monitoring emphasized in the phase 2 portion.

   B. A stand-alone phase 2 trial design targeted at high-risk populations (e.g. commercial sex workers) in regions with high HIV seroincidence rates. If the results of the phase 2 trial are promising, please comment on the feasibility of conducting a subsequent phase 3 trial in general population. A phase 3 trial(s) of a microbicide conducted in a more representative population of expected users is considered essential by FDA for submission of a marketing application.

   C. Does the Committee have alternative design recommendations?

2. Given the advantages and disadvantages of including a no-treatment arm (i.e. condom-only) in the design of phase 3 trials, please discuss and rank the following design options:

   A. 3-arm design (candidate microbicide, placebo, and no-treatment)

   B. 2-arm design (candidate microbicide, placebo)

   C. 2-arm design (candidate microbicide, no-treatment)

3. If the committee is in favor of the 3-arm design, does the committee agree with FDA's definition of a 'win', i.e., the microbicide arm has to show a significantly better reduction in HIV seroconversion rate than **both** the placebo and 'no-treatment' arms?

4. High drop-out rates are a major concern when determining the length of follow-up for phase 3 microbicide trials. Factors such as mobility, adherence to product use, desire to be pregnant, etc. can play a role. Please discuss the following questions regarding on-treatment and off-treatment follow-up duration.

   A. How long should the on-treatment evaluation be for a topical microbicide product?

      1). 12 months for every participant
      2). 24 months for every participant
      3). Follow-up continues until last patient enrolled completes 12 or 24 months
      4). Less than 12 months

   B. Should there be an off-treatment follow-up period after participants are off the study treatment (premature discontinuation or completed) in order to collect efficacy endpoints (with emphasis on HIV seroconversion)? If yes, then how long?

5. Given the urgent public need for effective topical microbicides and the potential difficulty in conducting a second confirmatory trial in the setting of positive results from an initial phase 3 trial, the Agency considers that a single large well-controlled trial is an acceptable alternative to two adequate and well-controlled phase 3 trials. Under this approach, does the Committee agree with the range of p-values specified by the Division (< 0.01, 2-sided)? In interpreting results from a single large well-controlled trial, what other supportive evidence does the Committee like to have?