FDA Center for Drug Evaluation and Research (CDER)
Antiviral Drug Advisory Committee Meeting, August 20, 2003, Bethesda, MD
Topic: Clinical trial design issues in the development of topical microbicides

Statement of the Global Campaign for Microbicides

The Global Campaign for Microbicides is a broad-based, international effort designed to build support among policymakers, opinion leaders, and the general public for increased private- and public-sector investment in alternatives to the male condom. Through advocacy, policy analysis, and social science research, the Campaign works to accelerate product development, facilitate widespread access and use, and protect the needs and interests of end users, especially women. The Campaign presently has almost 200 partner organizations worldwide that mobilize political will through education, constituency building and legislative advocacy.

It is on behalf of this constituency that we offer the following comments and recommendations with regard to the important questions before this Committee. In short, we encourage you to address these questions with a strong sense of urgency, creativity, and sensitivity to the epidemic's global context.

Urgency

As an advocacy organization, the Global Campaign's foremost consideration is balancing the urgency of the HIV pandemic with protecting the interests of eventual users. We fully recognize that scientific rigor requires time and patience and that rushed results may compromise quality. But the quest for a safe, effective microbicide is occurring in a cataclysmic context --- 15,000 people are infected with HIV daily, half of the people living with HIV globally are women and more than a third of all women of childbearing age are already infected in some countries.

We must keep the human face of the epidemic before us at all times in our deliberations. As we construct a critical path through this uncharted territory, we must understand that our mission is an urgent one and that the price of delay is paid in human lives.

Creativity

This Committee faces a challenge of unprecedented difficulty. Designing guidelines for microbicide trials is more difficult than for treatment trials because the field has no clear correlates of protection and prevention trials must enroll healthy--but highly vulnerable--volunteers.

Fortunately, the FDA has already shown that it can balance the need for scientific rigor on one hand with the need for creative flexibility on the other. Concepts such as "expanded access" and "accelerated approval" did not exist two decades ago. They were created in response to the urgency with which new AIDS treatments were needed and now stand as proof of how flexible the FDA can be when necessary.

We ask that the FDA demonstrate the same level of flexibility and creativity when considering how traditional approaches to drug evaluation can be adapted to meet the challenges of microbicide testing.

Context

Microbicides are not just another new drug or prevention tool in a field of many. Until an effective vaccine is developed, microbicides (even partially effective ones) will stand as the only means of prevention for millions of women who presently have nothing at all with which to protect themselves from HIV.

Data worldwide indicate that even with proper counseling and support, many women are unable to convince their partners to use condoms. This is especially true in the context of on-going relationships, where issues of trust, fidelity and power loom large.[1]

Regrettably, steady partners are increasingly the source of women's HIV risk globally. This is particularly relevant in settings where cultural norms grant men sexual license to have multiple partners but expect women to remain faithful. In a recent Thai study, for example, 76% of women living with HIV/AIDS had no risk factors other than being in a monogamous union.[2]

We recognize that the FDA's legal mandate is to review products in light of the risk/benefit profile of the United States, but we ask that you keep this global reality in mind.

We also urge you to recognize the impact that FDA pronouncements can have on regulatory thinking and strategy in other countries. Although the FDA's legal mandate extends only to the United States, its influence extends far beyond that. The FDA and the European Agency for the Evaluation of Medicinal Products (EMEA) often serve as the "default" standard-bearers for regulatory authorities in the developing world. Statements made by the FDA regarding minimal expectations for regulatory approval, will be read and applied in public health contexts very different from our own.

We urge you to frame your recommendations in such a way as to acknowledge that different regulatory authorities may face different realities than those informing FDA decision making. The FDA, for example, may decide that a single phase 3 trial powered to $p<.05$ would not be adequate to support licensure in the United States. But other countries, responding to the pressure of a far more advanced epidemic, may be motivated to act on such data. Their ability and willingness to do so will be enhanced if the FDA explicitly frames its expectations regarding trial minimums as specific to the US regulatory and epidemiologic context.

Specific Recommendations

Below are our recommendations regarding the key questions before the Committee. We developed them with two imperatives in mind – the need to get valid data into the hands of regulators and policy makers as quickly as possible and the need to know as much as we can, with the highest degree of certainty, about the candidate products.

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[1] A recent review conducted by the London School of Hygiene and Tropical Medicine found that across the board, levels of condom use decrease with the intimacy and regularity of the relationship. It further documents that consistent condom use is rarely achieved in more than a small proportion of couples in regular partnerships, even after concerted intervention. In the 15 Sub-Saharan African countries for which there are data, less than 5 percent of women in the general population reported using condoms during the last sex act with their regular partner (except for South Africa, where the figure was 7 percent). The review documents much greater rates of success increasing condom use with paying and casual partners.

[2] Xu F, Kilmark PH, Supawitkul s, Yanpaisan S, et al. HIV-1 seroprevalence, risk factors, and preventive behaviors among women in Northern Thailand. Journal of Acquired Immune Deficiency Syndromes 2000; 25(4):353-359.

Recommendation 1: The FDA should maintain a high degree of flexibility in its requirements regarding acceptable trial design elements

Normally clear and specific guidance from the FDA about expected trial design features is in the best interests of sponsors and of speeding the approval of new products. This may not be the case, however, with microbicide testing. First, microbicide testing is an evolving field of study and there is little to guide strict decision making around key issues (such as the ability to recruit and retain participants in condom only arms or the likely impact of gel provision on risk-taking behavior). Given this uncertainty, it would be premature to restrict flexibility on the part of sponsors. At this historical moment, it may even benefit the field to have different sponsors pursuing different design strategies so as to generate data from a range of scenarios that can better inform future design decisions.

Second, microbicide candidates vary greatly in their proposed mechanisms of action and their likely safety profile. What may be an appropriate safety protocol and follow up time for a polysaccharide compound that is not absorbed may be very difference from a NNRTI that poses an entirely different set of potential safety risks. Thus the type of product being considered must inform decisions regarding trial design.

Recommendation 2: The FDA should *NOT* require as a matter of policy that sponsors include a "condom-only" control arm in addition to a placebo control.

The desire to include a condom-only control arm (in addition to a placebo control arm) derives from two separate impulses. One, most frequently displayed by microbicide enthusiasts, seeks to avoid a situation where a product might be prematurely abandoned because it is impossible to detect a difference between active product and placebo because the placebo itself has some protective effect. This is the concern voiced by Padian (2003) and Jones, van de Wijgert and Kelvin (2003) in the attached commentaries from the journal Epidemiology.

The second, contrasting impulse is usually displayed by regulators intent on establishing that a candidate microbicide works *better* than condom promotion alone (the existing standard) and/or that it is the *active ingredient* rather than excipients that account for any protective effect measured. This view is reflected in the memo from Dr. Wu to the Antiviral Drug Products Advisory Committee Chair, Members, Consultants and Speakers, issued in preparation for this meeting. Dr. Wu defines a "win" as follows: "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."

We respectfully disagree with this latter interpretation and believe that adding a condom-only arm increases the size and cost of trials while adding little information useful for decision-making. Moreover, by generating data that could easily be misinterpreted, the addition of a condom only arm may slow progress toward licensing an effective product.

As Stein and colleagues point out in their article in Epidemiology (2003), a microbicide trial containing two control arms could result in any of nine possible combinations of findings (see Table 1 attached). The outcomes described in Table 1 assume a) that true levels of condom use do not vary across trial arms, and (b) that self-reports of condom use reflect reality. (As we argue below, however, because the "condom-only" arm is unblinded, both true levels and self-reports of condom might well vary systematically across trial arms).

In the case of A, B, and C, the results among arms are similar and thus the likely response of regulators is clear (and would be the same whether data from a second control arm is present or not).

In scenario D and E, however, the response of regulators might well differ if they had access only to the data from the placebo-control arm versus data from both control arms. In both D and E, the microbicide is clearly better than the placebo -- a case that would support licensure if no other data were available. But if the risk of women in the condom-only arm was either equivalent to or higher than the risk of women in the experimental arm, how would regulators be likely to respond?

We believe that most regulators in this situation would feel *less comfortable* considering licensure of such a product, even though the underlying risk and adherence behavior between the two control arms cannot be assumed to be equivalent. As noted above, the FDA has already suggested that "to claim effectiveness, a candidate has to show a significantly better reduction in HIV seroconversion rate than BOTH the placebo and no treatment arm."

We believe that the standard for approval of a new microbicide should be that (1) it is proven safe and (2) it demonstrates reduction in risk in comparison to a single placebo arm. The need to establish the effectiveness of the active as separate from the vehicle or inert ingredients is overly stringent given the urgent need to find some user-controlled product that reduces risk. What is important is establishing that the combined package is protective, not dissecting which elements of the product contribute to its efficacy.

Likewise, we cannot reliably assume that comparison to a condom-only arm gives a better indication of the product's likely effectiveness in "real world." This would only be true if we could guarantee that the behavior of women in the condom-only arm does not differ significantly from that of women in the product and placebo arms. In an un-blinded study, however, it is highly likely that this would *NOT* be the case. The advantage of the placebo control arm is that we can more reliably assume that behavior related to gel and condom use, sexual behavior, and willingness to stay in the study will not vary by arm. Once you introduce a non-blinded arm – especially one that only offers condoms, you can no longer make this assumption.

In fact, it is highly likely that the women in a condom-only arm will have different risk-taking and adherence behaviors than women who receive both gel and condoms, although it is impossible to reliably predict exactly how.

Data from a variety of existing trials and interventions indicate that adherence to product and condom use goes up when women are offered a choice of methods rather than just one (for a review of this literature, see: Foss et. al. 2003 AIDS 17:1227-37). Given this, we must anticipate that women's adherence behavior (and hence risk) will vary between arms if one control arm offers one item (condoms) and a second control arm offers two (condoms plus placebo).

Similarly, we know that despite investigator's best efforts, women generally assume (or want to believe) that the gel they are taking is the one that will work. Women in the condom-only arm may demonstrate different behaviors precisely because they are not receiving gel. If the general hope for gel effectiveness is high, women in the condom only arm may perceive themselves to be at greater risk than their counterparts receiving gel and may adjust their condom and/or other risk-taking behavior accordingly. Alternatively, women who feel "excluded" from gel use, may be less motivated to stay in the study or to adhere to study requirements.

Thus it quickly becomes impossible to interpret differences observed between a placebo control and a condom-only control.

Some commentators have argued that it is irrelevant whether the observed differences are due to the product or to behavioral changes induced by the product. For the purposes of licensure, however, the question of whether a product actually works should be separated from the question of its likely impact once it is "introduced" in different epidemiological and behavioral environments.

The addition of a condom-only arm is not an effective way to answer this latter question. The interaction of a microbicide's biological effect with its effect on behavior will vary widely from setting to setting and cannot be extrapolated from a single clinical trial. Investigating the protection achieved in real world settings is more appropriately established via pre-introductory studies or post marketing studies where the conditions more closely approximate those under which the product will be promoted. The trial conditions are both "artificial" and an inappropriate test of how people will react once they know a candidate microbicide has been shown to reduce risk of transmission.

Recommendation 3: The FDA should be open to establishing effectiveness based on a one-year follow-up period.

Recommendations regarding minimum length of follow up must balance the need to get valid data on product effectiveness with a desire to assess longer term safety. We are concerned that in many circumstances, it may be difficult to retain women for follow up periods of longer than a year, both because of loss to follow up and women having to discontinue gel use due to pregnancy. In many of the settings that the trials are being conducted the pregnancy rate is high even among women who express a desire and willingness to postpone pregnancy during the period of the trial. Thus, a requirement that trials follow women for more than a year may undermine the validity of the final assessment of effectiveness. Moreover, consistent adherence to gel use may erode over time, further confounding interpretation.

Several observers have proposed doing large, short trials (e.g. 6 months) to evaluate effectiveness and following a sub-set of users for a longer period of time to gain additional safety data. We think this design deserves further consideration for products with an appropriate safety profile. This design would be especially efficient and cost-effective if follow-up were continued at the trial sites with the best retention records. Approval based on shorter trials, however, should be accompanied by carefully controlled Phase 4 studies.

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Recommendation 4: Given urgency and scarce resources, a stand-alone phase 2 or 2b trial is only worthwhile if it enables us to determine which is the most promising among several similar products

We endorse the concept of a combined Phase 2/3 trial as an efficient use of resources because it allows interested Phase 2 participants to roll over into the Phase 3 trial, assuming no safety concerns are identified. This evaluation strategy saves time, prevents the loss of woman-years of follow up, and facilitates the efficient generation of data.

We believe, however, that the stand-alone Phase 2 or Phase 2B trial does not constitute an effective use of resources unless constructed as a multi-product screening trial designed to tell us which of various competing products offer the greatest promise and should be moved forward into Phase 3 trials. A head-to-head screening trial comparing the various "large sticky

molecule" candidates currently under development, for example, might ultimately be a cost-efficient strategy at this point because it would allow us to focus the considerable resources required for a Phase 3 trial on candidates from that category most likely to succeed.

Absent this prioritization function, we feel that "a stand-alone Phase 2 trial" introduces unnecessary delay.

Recommendation 5: The Agency should seek ethics guidance before assuming that it would not be possible to conduct a second confirmatory trial "due to ethical concerns."

The Global Campaign is sponsoring an international consultation on ethical issues in microbicide trials, to be held in Washington D.C. on October 23-24. One of the issues that will be explored in depth is what implications there might be for future trial design of finding evidence of effectiveness in a single clinical trial. Based on our discussions with ethicists to date, we feel that there may be more latitude for confirmatory trials than implied in the FDA's background memo. Given that microbicide trials by their very nature measure effectiveness not "efficacy," the risk reduction observed between arms captures a complex mix of the product efficacy, adherence and condom use. Since the behavioral variables may vary dramatically by setting and may interact differently based on the underlying patterns of STD and HIV, confirmatory studies in other settings (and among other populations) may make scientific sense and therefore be ethically justifiable.

In any event, the ethical implications of different design choices deserve the same kind of thoughtful debate that the Agency has encouraged for the scientific implications of such choices.

Conclusion

In sum, we applaud the Agency's commitment to seeking outside input on these very important issues. We encourage both the Committee and the Agency to make its judgments in light of the urgent need to develop a viable prevention option for women.