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**Comments for Consideration at FDA Over-the-Counter Drug Products Public Hearing,
28-29 June 2000 - Docket No. 00N-1256**

**Submitted by:
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1 June 2000**

THE ALLIANCE The Alliance for Microbicide Development is a coalition of most of the major researchers and organizations involved in the development of "microbicides," topical genital applications being designed to help prevent sexually transmitted infections (STIs), very importantly including HIV. It comprises developers from 34 biopharmaceutical companies, scientists from 26 nonprofit research institutions, and representatives of 20 health research and advocacy groups (see Appendix A). The Alliance is maintained with support from private philanthropies and accepts no federal funding.

RATIONALE The mission of the Alliance is to accelerate the development and availability of microbicides for the millions of individuals globally who could benefit from them. The women of the world lead that list of potential beneficiaries, for two primary reasons. The first is the "feminization" of the AIDS epidemic. In the United States, women constitute the fastest-growing group of those newly infected with HIV and, worldwide, almost half of the almost 14,000 adults infected daily with HIV are women, with over 90% of those new infections being spread through unprotected heterosexual intercourse.

The second reason is that the currently most effective protection against HIV and most other STIs is the male condom. Yet, since many men resist condom use, it is infrequent or irregular in many partnerships and especially problematic where proving fertility is important or where couples want children despite their infectious status, as is often the case in developing countries. Negotiating condom use or refusing unsafe sex may be particularly difficult in primary partnerships where trust becomes an issue and in relationships where women are at risk of violence or abandonment.

DEVELOPMENT COMMUNITY PERSPECTIVES We are talking about a population of many millions and a need that is relentless and immediate, so that speed is of the essence, in the development processes and in terms of practical availability once a product is proved safe and efficacious in appropriately designed clinical trials. The assumption in much of the microbicide development and advocacy community has been that microbicides based on ingredients used mucosally for many years and generally recognized as safe (GRAS) (roughly one-quarter of the microbicides currently in development)

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might reasonably be expected to go to market as over-the-counter products. This view in no way excluded recognition that products dependent on totally new chemical entities (NCEs) would probably—and appropriately—require at least initial launch as Rx products. Nor did this view imply any willingness to sacrifice safety for speed. However, the possibility that ALL microbicides might require initial Rx introduction has raised concerns about what that might mean for market readiness and the various dimensions of availability, importantly including cost, provider barriers, and physical access.

Because these hearings offer a proper venue for commentary and in order to present the perspectives of the microbicide community in a responsible way, this issue was discussed at the May 13-14 meeting of the Alliance and was further addressed in a subsequent poll of those Alliance participants who are developing products. The following paragraphs present the results of those activities.

CONSUMER UTILIZATION OF MICROBICIDES There was consensus without exception that across-the-board and unrelenting Rx classification would hinder access and therefore microbicide utilization in a number of ways, and that the public health and individual human costs could be substantial. In very practical terms, women in general could well find it more difficult to purchase microbicides on an as-needed basis for routine prevention if they were not able to do so in an open marketplace, unconstrained by provider dependence. The shared view was that product costs to consumers would inevitably be higher under prescription labeling, added to which would be provider fees. The observation was made that sexual relations are not, in themselves, a disease requiring provider intervention but, rather, decisions made by individuals on their own time. The related comment was made that condoms are available over the counter for individual decisions by men without requiring the intervention of a Learned Intermediary, by which token microbicides should be available over the counter for individual decisions by women. Particular concern was expressed on behalf of women at risk. Such women are often disadvantaged by poverty, their position in social structures, and age, and might well be intimidated by those conditions and constrained by possible stigma from seeking microbicides dispensed only by physicians and, perhaps, even some public health system providers. Several respondents did note that there would also be market interest were Rx microbicides also to be available, partly deriving from the character of the product itself, partly deriving from the associated endorsement by the medical community, partly deriving from a potentially higher price.

MARKET INTENTIONS Of 12 companies actively developing products, most of whom have advanced beyond the preclinical phases, 4 are planning on over-the-counter introduction, 4 foresee an Rx introduction followed by transition to OTC status, 1 anticipates Rx classification, and 2 are unsure or undecided. The issue of transition from Rx to OTC status emerged as pivotal and is addressed below.

IMPACT OF RX CLASSIFICATION Respondents were asked about the effect a determination to make all microbicides prescription products would have on their current plans and what effect such a

determination might have on a prospective partner. Because the overwhelming majority of those individuals and companies that are developing microbicides will inevitably be dependent on some kind of partnership to take their products forward, this consideration is not small. Of 12 developers, 8 had either anticipated at least initial Rx status or felt that they could adjust to such a determination even if not anticipated, noting that while the objective of reducing the spread of HIV compels them to continue, the requirement for an Rx classification would impose serious cost constraints and timeline extensions. However, of that group, 5 noted that the issue of status could make a difference to a prospective partner. One company felt that it would have to withdraw from the field altogether if initial OTC classification could not be anticipated, while 4 who might have to consider withdrawal would be able to stay in the field if there were a standard procedure for switching their product from Rx to OTC in a relatively brief period. One creative proposal that emerged in the course of Alliance discussions is the notion of developing a formal post-introduction/post-market consumer reporting system that could gather the kind of information the FDA would require for transition from Rx to OTC status. This remains a germ of an idea but has already attracted interest as a subject worthy of pursuit and a topic for discussion with the agency itself.

CRITERIA FOR REGULATORY DECISIONS ABOUT OTC AND PRESCRIPTION STATUS

The final question in the poll asked if proposing criteria for regulatory decisions about status would be helpful. The sense of the responses was that attempting to establish such criteria in any fine-grained way is premature. Although there was some agreement that microbicides based on currently marketed OTC or GRAS active ingredients, or products based on components with long-term safety records could reasonably be considered for initial OTC classification, the point was made that some NCE's might prove to have a better toxicity profile than some older molecules and should not be disqualified from the outset simply because they were "new." From a richly-textured discussion, however, two "bottom lines" emerged. The first was that determinations about initial status should be made on a case-by-case basis. The second was that any rigid, *a priori* decision about launch status for microbicides as a drug category should be assiduously avoided.

CONCLUSION The foregoing opinions are based on a small sample, but the constituency represented and the weight of opinion within that constituency are not trivial. The core message from the microbicide community is an appeal to the Food and Drug Administration for careful but flexible and expeditious consideration of the merit and potential value of each microbicide, against a background of urgent need among the very many who have no other protection from prospective death and disability.

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