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SUPPLEMENTARY INFORMATION:

I. Background

In the advance notice of proposed rulemaking (ANPRM) for OTC vaginal contraceptive drug products (45 FR 82014, December 12, 1980), the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products (the Panel) placed nonoxynol 9 in category I (safe and effective). However, the Panel concluded that the contraceptive effectiveness of active ingredients cannot be considered separately from the vehicle and recommended that FDA require in vitro testing to determine the spermicidal effectiveness of each final formulation before marketing. In the preamble to the Panel's report (45 FR 82014), the agency stated that in vitro testing alone is an inadequate measure of a vaginal contraceptive product's effectiveness in humans. The agency explained that clinical trials of each product or final formulation may be the only certain predictor of its effectiveness in humans. The agency added that if clinical trials are necessary, manufacturers may be required to submit a new drug application (NDA) or supplement an existing NDA.

In the notice of proposed rulemaking (NPRM) for OTC vaginal contraceptive drug products (60 FR 6892, February 3, 1995), the agency proposed that manufacturers of OTC vaginal contraceptive drug products obtain approved NDAs for marketing of their products. The agency proposed this action because effectiveness of these products is dependent upon the final formulation. Therefore, the agency proposed that each product be tested in appropriate clinical trials under actual conditions of use.

In response to the NPRM, the agency is aware of ongoing clinical trials of vaginal contraceptives containing nonoxynol 9 (Refs. 1, 2, and 3). Pending the completion and analysis of these clinical trials, the agency is allowing the continued marketing of these products under the ongoing OTC drug review. These issues were discussed at the November 22, 1996, Nonprescription Drugs Advisory Committee (NDAC) meeting. NDAC concurred with the agency to allow interim marketing of nonoxynol 9 containing vaginal spermicides pending results from the proposed trials (Ref. 1). However, based on the studies discussed in section I of this document, the agency believes that vaginal contraceptive drug products

containing nonoxynol 9 need to be labeled to inform users of these products that nonoxynol 9 does not prevent the transmission of the AIDS virus (HIV) and other STDs. Furthermore, users should be informed that frequent use of nonoxynol 9 can cause vaginal irritation and possibly increase the risk of becoming infected with the AIDS virus (HIV) and other STDs from infected partners. This rulemaking addresses certain safety concerns with the use of nonoxynol 9.

Nonoxynol 9 is a nonionic surfactant that works as a vaginal contraceptive by damaging the cell membrane of sperm. It has been shown in certain in vitro studies to damage the cell wall of certain STD pathogens and to have activity against certain bacterial and viral STD pathogens, including HIV. However, based on the in vivo data described in section I of this document, the agency believes that this same cell membrane damaging effect can damage the vaginal and cervical epithelium (cell lining). Thus, nonoxynol 9 can have a negative impact on the vaginal lining and may increase the user's risk of getting STD/HIV and other genital infections. Irritation includes the range of physical findings from mild inflammation to epithelial disruption (damage to cells lining the vagina or cervix). Vaginal irritation may be symptomatic (with symptoms such as itching and burning) to asymptomatic (no symptoms).

Because nonoxynol 9 kills the AIDS virus (HIV) and other STD pathogens in vitro, it has been suggested, over the years, that the drug might help prevent or reduce the risk of transmission of the AIDS virus and other STDs in humans. Information currently available to the general public creates the misperception that nonoxynol 9 might help decrease the risk of becoming infected with the AIDS virus and other STDs (Refs. 4 through 7). Thus, the agency believes that this proposed rule is necessary to provide a clear, consistent message that nonoxynol 9 is not only ineffective in preventing HIV transmission, but that it could facilitate transmission of the disease.

At the International AIDS Conference (July 9-14, 2000), researchers from the Joint United Nations Programme on AIDS (UNAIDS) presented the preliminary findings of a 4-year study conducted in a very high-risk population of 991 HIV negative female sex workers in Africa and Thailand to determine the effectiveness of a nonoxynol 9 gel (versus placebo) in preventing the transmission of HIV and STDs (Ref. 8). The test product contained 52.5 milligrams (mg) of

nonoxynol 9 and a polymer with bioadhesive properties. The placebo contained only the polymer. Participants could be enrolled in the study if they did not use intravenous drugs or intravaginal spermicides other than the study drug. The participants reported an average of 3.6 partners per day and about 70 coital acts per month during the study. Condom use was encouraged. The preliminary study findings showed that women who used nonoxynol 9 gel had a higher incidence of new HIV infections (59) than those who used the placebo gel (41). Further, the more frequently women used only the nonoxynol 9 gel (without a condom to protect themselves), the higher their risk of becoming infected. Researchers also found that women who used nonoxynol 9 had more vaginal lesions, which might have facilitated the HIV transmission. Based on these preliminary study findings, on August 4, 2000, the Centers for Disease Control and Prevention (CDC) issued a letter (Ref. 9) stating "given that N-9 [nonoxynol 9] has now been proven ineffective against HIV transmission, the possibility of risk, with no benefit, indicates that N-9 should not be recommended as an effective means of HIV prevention." The final results of this study were recently published (Ref. 10) and substantiate the preliminary findings. The investigators stated that their data support the following conclusions: (1) Nonoxynol 9 increased the risk of HIV infection compared to placebo; (2) nonoxynol 9 had an adverse effect on vaginal epithelium when used frequently, thus increasing women's susceptibility to HIV; and (3) at low frequency use, nonoxynol 9 had no effect, either positive or negative, on HIV infection.

Earlier studies (Refs. 11 through 14) suggested that nonoxynol 9 vaginal spermicides may reduce gonococcal and chlamydial cervical infection and may even reduce the incidence of HIV infection. However, most of these studies did not assess the risk of acquiring HIV and the investigators stressed the need for more definitive randomized clinical trials. More recently, the International AIDS Conference report and the CDC letter (Refs. 8 and 9) have raised concerns that frequent use of nonoxynol 9 can increase vaginal and genital irritation and increase the risk of HIV transmission. Based on these safety concerns, the agency has reviewed studies on nonoxynol 9 conducted in Africa, Thailand, South America, Belgium, the Netherlands, and the United States that address the toxicity of