

examinations showed that vaginal irritation, such as ulcerations, abrasions (on the cervix and external genitalia), lesions, and erythema, was observed in both the treatment and the placebo groups. However, based on the number and incidences of colposcopic lesions per followup period of up to 12 weeks, the incidence of colposcopic lesions was low and there was no difference between the treatment groups. The authors reported that in both groups the chance of having a lesion increased with an increase in the mean daily use of the product. The authors concluded that multiple daily use of the nonoxynol 9 containing gel did not show an increase of local toxicity over the placebo gel.

Rustomjee et al. (Ref. 28) studied a vaginal contraceptive film containing 72 mg of nonoxynol 9 versus a glycerin placebo film in a randomized, double-blind, crossover trial. The 20 subjects were female sex workers, and HIV infection was not an exclusion criteria. Subjects used either the treatment film or placebo film for 1 month and, after a 1-month film-free washout period, used the other film for the last month. Condoms were provided. The differences in signs and symptoms of genital lesions from use of the nonoxynol 9 film and the placebo film did not reach statistical significance. However, the authors cautioned that the clinical findings of an increase in minor erythematous genital lesions in the nonoxynol 9 group, together with an increased HIV viral load associated with the presence of a minor genital lesion, is worrisome.

In summary, many of the studies (Refs. 8, 15 through 18, 20 through 24, and 28) suggest that nonoxynol 9 vaginal contraceptive formulations can increase the chances of vaginal and genital tract irritation, and cause disruption of the vaginal epithelium or the vaginal flora. Some studies (Refs. 8, 20, 22, and 23) suggest the risk of these adverse events can be increased by frequent and/or chronic use. One study (Ref. 25) concluded that once a day use was safe, but noted that the power to detect a small increase in epithelial toxicity may be limited by the short duration of use. Investigators in one study (Ref. 27) concluded that multiple daily use of nonoxynol 9 (52.5 mg) gel was safe, but in a previous study (Ref. 23) of nonoxynol 9 (52.5 mg) gel in women with low risk of HIV infection, the investigators concluded that women using nonoxynol 9 gel were significantly more likely to develop lesions than those in the placebo or no-treatment groups. The authors stated that large scale intervention trials were needed to

determine if genital lesions increase the risk of acquiring HIV infection.

Several studies suggested a causal link between the frequency of use of nonoxynol 9, increased vaginal irritation, and the possibility that vaginal irritation (such as the disruption of the vaginal epithelium) may increase the risk of transmission of the AIDS virus (HIV) and other STDs. The preliminary findings of a study on nonoxynol 9 (52.5 mg) gel presented at the International AIDS Conference in July 2000 (Ref. 8) suggested that nonoxynol 9 does not prevent the transmission of HIV and other STDs and may facilitate the transmission of these pathogens. Another study (Ref. 26) concluded that the use of a nonoxynol 9 containing film did not reduce the rate of new HIV, gonorrhea, or chlamydia infection even when latex condoms were used. Other studies (Refs. 20, 24, and 28) also suggested that the adverse effects of nonoxynol 9 on the vaginal flora and epithelium may increase the risk of transmission of the AIDS virus (HIV), certain other STDs, and/or genital infections. The studies in high risk populations (sex workers) (Refs. 8, 24, 25, 27, and 28) suggested the possibility that the frequency of use of nonoxynol 9 can increase vaginal irritation and epithelium disruption. Such increased irritation may increase the risk of becoming infected with STDs, including the AIDS virus (HIV) from infected partners.

The CDC, on May 10, 2002, published a report containing a recommendation that women, particularly those at risk for HIV or STDs, be informed that nonoxynol 9 contraceptives do not protect against these infections (Ref. 29). The CDC report described the extent of nonoxynol 9 contraceptive use in women in 1999 and summarized recent publications on nonoxynol 9 and HIV/STDs. According to this report, most women in the United States with HIV become infected through sexual transmission. Thus, the report underscores the importance of alerting women about the safety concerns surrounding nonoxynol 9.

On June 28, 2002, the World Health Organization (WHO) issued revised public health guidelines for the use of nonoxynol 9 for HIV and STD prevention and for pregnancy prevention in populations at high risk for HIV (Ref. 30). The guidelines were based on a review of current clinical safety and effectiveness data on nonoxynol 9 (Ref. 31). The WHO guidelines advised that "Spermicides containing nonoxynol 9 do not protect against HIV infection and may even increase the risk of HIV infection in

women using these products frequently." The guidelines also advised women at high risk of HIV infection against using nonoxynol 9 spermicides for contraception.

Based on safety concerns, the agency considers it important to alert users of OTC vaginal contraceptives containing nonoxynol 9 that these products do not prevent transmission of the AIDS virus (HIV) and other STDs, and that frequent use of these products can increase vaginal irritation, which may increase the risk of getting certain STDs, including the AIDS virus (HIV) from infected partners. The agency also believes that product labeling should include a statement to encourage the use of condoms as a method to help reduce the risk of becoming infected with the AIDS virus (HIV) and other STDs.

FDA's proposal to require these warnings and other information does not require a finding that any or all of the OTC drug products that contain nonoxynol 9 actually caused an adverse event, and FDA does not so find. Nor does FDA's requirement of warnings and other information repudiate the OTC drug monographs under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that these additional warnings and other information are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the Federal Food, Drug, and Cosmetic Act. This judgment balances the benefits of these drug products against their potential risks, and reflects our conclusion that even a potential link between the use of nonoxynol 9 and serious adverse health consequences warrants this action (see CFR 330.10(a)).

FDA's decision to act in an instance such as this one need not meet the standard of proof required to prevail in a private tort action (*Glastetter v. Novartis Pharmaceuticals, Corp.*, 252 F.3d 986, 991 (8th Cir. 2001). To mandate a warning, or take similar regulatory action, FDA need not show, nor do we allege, actual causation.

In the NPRM (60 FR 6892 at 6901), the agency stated that consumers should be warned about possible allergic reactions such as burning and itching of the vagina and penis that may occur when using vaginal contraceptive drug products. The agency recommended that the following warning be included in the labeling: "If you or your partner develops irritation, such as burning or itching in the genital area, stop using this product. If irritation continues,