Kirkpatrick & Lockhart LLP

1800 Massachusetts Avenue, NW
Suite 200
Washington, DC 20036-1221
202.778.9000
202.778.9100 Fax
www.kl.com

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Gary L. Yingling
202.778.9124
Fax: 202.778.9100
gyingling@kl.com

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Via Federal Express and Electronic Mail

Attn: Arlene Solbeck
Center for Drug Evaluation and Research
HFD-560
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: FDA Docket No. 80N-0280: Over-the-Counter Vaginal Contraceptive Drug Products Containing Nonoxynol 9; Required Labeling

Dear Sir/Madam:

On behalf of our client, Apothecus Pharmaceutical Corp. ("Apothecus"), we respectfully submit comments on the Food and Drug Administration's ("FDA") proposed rule to require additional warning language on nonoxynol 9-containing over-the-counter ("OTC") vaginal contraceptive drug products (hereafter "Proposed Rule"). 68 Fed. Reg. 2254 (January 16, 2003). The Proposed Rule would require these products to bear additional labeling information describing a possible link between the use of nonoxynol 9-containing vaginal contraceptive drug products and the transmission of the Human Immunodeficiency Virus ("HIV") or other sexually transmitted diseases ("STDs") from infected partners, and remind consumers that nonoxynol 9 does not prevent the transmission of HIV and other sexually transmitted diseases ("STDs").

I. INTRODUCTION

Apothecus is the manufacturer of a 70 milligram (mg) nonoxynol 9-containing vaginal contraceptive film marketed under the proprietary name VCF. Apothecus supports FDA in its mission to assure the availability of safe and effective pharmaceuticals, and that is why it must disagree with portions of the Proposed Rule. As a preliminary matter, Apothecus fully agrees

80N-0280 C53

with FDA's proposal to require nonoxynol 9 vaginal contraceptive drug products to bear the labeling statement: "This product does not protect against the AIDS virus (HIV) or other STDs." While these products are not marketed to prevent such conditions, Apothecus recognizes that consumers may mistakenly believe that there is a preventative effect.[1]

However, Apothecus believes that the proposed labeling implying a link between the use of nonoxynol 9 and an increased risk of HIV infection is not sufficiently supported by the scientific literature, and that it will unnecessarily frighten consumers in a manner that could affect the continued availability of a safe and effective contraceptive that represents an important birth control option for women. While slightly less effective than oral contraceptives such as the pill, or the intrauterine device ("IUD"), this spermicide provides women with control to personally assure a method of birth control at the time of, or shortly before, sexual activity. In addition, it is frequently used as a back-up option or to augment the effectiveness of IUD's, condoms, or fertility awareness methods. As the only currently available spermicide in the United States, it would be a clear disservice to consumers if the proposed labeling caused this product to effectively disappear from the market place.

Apothecus understands that FDA is basing the proposed warning on two forms of scientific literature. First, FDA cites two studies that it believes demonstrate a link between nonoxynol 9 use and increased risk of HIV and STD infection from infected partners. Second, FDA cites a number of clinical study reports that discuss the association between nonoxynol 9 use and vaginal irritation. As will be discussed further below, not only are the conclusions FDA has drawn from these studies flawed, Apothecus is confused by FDA's failure to fully consider the results and conclusions of a very large double-blind, placebo controlled study, in which the authors concluded that there was no difference in the rate of HIV transmission between a group using a nonoxynol 9 vaginal contraceptive film and a group using a placebo film. See Ronald E. Roddy et al, *A Controlled Trial of Nonoxynol 9 Film to Reduce Male-To-Female Transmission of Sexually Transmitted Diseases*, 338 THE NEW ENGLAND JOURNAL OF MEDICINE 504 (1998) [hereafter the "Roddy Study"). Moreover, FDA did not consider a fourth published study in which the authors concluded that there was no significant difference between nonoxynol 9 users and placebo users with regard to HIV transmission. Barbara A. Richardson et al., *Evaluation of a Low-Dose Nonoxynol 9 Gel for the Prevention of Sexually Transmitted Diseases, a Randomized Trial*, 28 SEX TRANS. DIS. 394-400 (2001) ("Richardson Study").

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[1] Apothecus would not generally support the addition of warning language identifying conditions that an OTC drug product is not intended to treat or prevent (e.g., acetaminophen does not prevent indigestion). However, in light of the significant media attention on this ingredient, and the fact that *in vitro* studies indicated that nonoxynol 9 might be effective in the prevention of HIV and some STDs, we believe that FDA's proposed warning is essential to correct misinformation.

II. REQUEST FOR PARTIAL WITHDRAWAL OR CLARIFICATION

Based on Apothecus' review of the scientific literature, the link between nonoxynol 9 use and an increased risk of HIV transmission is mere speculation that is not even suggested by a comprehensive review of the body of scientific literature. In fact, based on the Roddy Study, Apothecus is confident that use of its nonoxynol 9 product does not increase the risk of HIV infection from infected partners. As a result, because nonoxynol 9-containing vaginal contraceptive drug products are an important form of contraception, and misinformation could result in the unnecessary withdrawal of such products from the market, Apothecus respectfully requests that FDA partially withdraw the Proposed Rule by removing the proposed warning language that inaccurately links nonoxynol 9 use with an increased risk of HIV infection. In the alternative, the language could clarify that the research on the link between nonoxynol 9 use and HIV transmission is inconclusive at this time.

III. NONOXYNOL 9 CLINICAL RESEARCH

A. Prevention Studies

As discussed above, FDA identified three studies that were designed to measure the effect of nonoxynol 9 in the prevention of HIV/STD infections. None of the studies established a preventative effect. FDA is relying on the data from two of these studies to support its position that there is a link between nonoxynol 9-containing vaginal contraceptive products and an increased risk of HIV/STD infection. Van Damme, L. et al., *Effectiveness of COL-1492, a Nonoxynol-9 Vaginal Gel, on HIV-1 Transmission in Female Sex Workers: A Randomized Controlled Trial*, THE LANCET, 360:974-977 (2002) ("Van Damme Study"); Kreiss, L. et al., *Efficacy of nonoxynol 9 contraceptive sponge use in preventing heterosexual acquisition of HIV in Nairobi prostitutes*, 268 THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 477 (July 22, 1992) ("Kreiss Study"). However, FDA failed to fully consider the results of the Roddy Study, which supports a conclusion opposite to the Van Damme Study and Kreiss Study. Further, there is a question as to the general applicability, strength, and credibility of the Van Damme and Kreiss Study. Finally, Apothecus provides information on the Richardson Study, which was not cited or discussed in the Proposed Rule and further weakens the basis for a conclusion that frequent use of nonoxynol 9-containing vaginal contraceptives increases the risk of HIV infection from an infected partner.

1. The Roddy Study

While FDA mentions the Roddy Study in the Proposed Rule, it is only cited for the purpose of stating that nonoxynol 9 does not prevent HIV or STD infections. 68 Fed. Reg. at 2257. However, the Roddy Study is also important in that it helps to dispel the unfounded concern that all nonoxynol 9 vaginal contraceptive products increase the risk of HIV transmission from

infected partners. This study was funded by the United States Agency for International Development ("USAID"), the Mellon Foundation, and the National Institutes of Health, and is the largest study to date that was designed to determine if nonoxynol 9 could provide some level of protection for those exposed to HIV-infected partners. The test product used in this study was Apothecus' VCF film, and the authors concluded that, while VCF did not provide additional protection against transmission of HIV and STDs, use of VCF *did not increase the risk of HIV transmission* over placebo.

The population considered for primary analysis in the Roddy Study was comprised of 1170 sex workers (prostitutes) from Cameroon who were HIV-negative upon initial screening and who had at least one HIV test after study enrollment. They were randomly assigned to use a film for vaginal insertion prior to sexual intercourse—595 participants were given the 70 mg nonoxynol 9-containing VCF film and 575 were given a placebo film. The women were also given condoms (without spermicide) for the use of their male partners. At monthly follow-up visits, the women were examined for genital lesions, and for infection with HIV and other STDs (as well as treated for curable STDs). The study spanned a 33-month period, with 73% of the participants continuing in the study at 1 year, and with a mean follow-up period of approximately 14 months. Participants reported approximately the same number of coital acts (including vaginal, oral, and anal) and the same level of condom use (approximately 90%).

The Roddy Study authors noted that, in this population at high risk for HIV transmission (i.e., sex workers with multiple partners), there was no difference in the rate of HIV transmission between the group using VCF and the group using the placebo film. Further, virtually identical event rates were noted for gonorrhea and chlamydia in the two groups. In addition, although the Roddy Study found a slight increase in genital ulcers in the nonoxynol 9 group, the increase was not statistically significant, and the participants who developed genital ulcers did not experience a higher rate of HIV infection. Nor was there a difference in the HIV infection rate between the nonoxynol 9 group who experienced genital ulcers and the placebo group who experienced them.

Thus, the Roddy Study clearly does not support FDA's belief that frequent use of nonoxynol 9 - containing vaginal contraceptive drug products increases the risk of HIV transmission.

2. The Van Damme Study

In reporting on the Van Damme Study, FDA relies on the preliminary results reported at the International AIDS Conference occurring between July 9-14, 2000, instead of on the final report, which was issued approximately two years later, and which significantly modified the results reported during the conference. See 68 Fed. Reg. at 2255. According to the FDA notice, this was a 4 year study conducted on 991 HIV negative high risk female sex workers in Africa and Thailand to determine the effectiveness of a nonoxynol 9 gel (COL-1492) versus placebo

(Replens) in preventing the transmission of HIV and STDs. Participants reported on average 3.6 partners per day and 70 coital acts per month. Condom use was encouraged, but not necessarily required. According to FDA's report on the preliminary finding, nonoxynol 9-using women had a higher incidence of new HIV infections (59) than those who used the placebo (41), and the more frequently the nonoxynol 9 was used alone, the higher the transmission rate.

However, the Van Damme Study final report was significantly different. For example, while 892 women were randomly allocated, 765 women were included in the primary analysis and only 563 women completed the study. Thus, the study sample in the Van Damme Study was significantly less than reported at the International AIDS Conference. Clearly, this has some level of significance in connection with the strength of this study, especially in light of the size of the Roddy Study. Further, in the Van Damme Study final report, HIV infection resulted in 59 users of the nonoxynol 9 gel and 45 users of the placebo gel. Thus, the level of statistical significance had obviously changed from the preliminary report.

In fact, as a review of the intent-to-treat analysis indicates, statistical analysis of the study data collected shows that a statistically significant difference between the two study groups (i.e., nonoxynol 9 users and placebo users) was just barely achieved in this study ($p<0.047$, with statistical significance defined as $p<0.05$). See Van Damme Study, Table 2 at p. 974. Thus, any weaknesses in the study could call into question the credibility of the study results and its statistical significance to the general population.

Indeed, *a major problem with the Van Damme Study is the percentage of subjects that were "lost-to-follow-up"*. A review of the Van Damme Trial Profile shows that, while 795 participants were included in the primary analysis, 165 or slightly more than 20% of these participants were completely lost to follow-up, which means that the investigators never determined the HIV status of these participants. A lost-to-follow-up percentage that equals or exceeds 20% clearly effects the study strength. The Roddy Study, on the other hand, only suffered a 10% lost-to-follow-up, indicating a more credible study.

The possibly protective effect of the Van Damme Study placebo also affects the credibility of the study. In a recent issue of THE LANCET, scientists state that the comparison placebo product, Replens, *may have contributed* to the significantly higher HIV seroconversion rate among COL-1492 users and placebo users in the Van Damme Study. Kilmarx PH, Paxton L., *Need for a true placebo for vaginal microbicide efficacy trials*, 361 THE LANCET 785 (March 1, 2003). Stating that both the test product (COL-1492) and Replens contained carbopol and polycarbophil, negatively charged polymers that could have microbicidal properties, the scientists noted that "gram for gram, Replens has more than twice the acid-buffering capacity of COL-1492, and therefore contains substantially more carbopol or polycarbophil." Id. In fact, the scientists refer to Replens manufacturer statements indicating that Replens "helps protect against infection." Id.

Looking at the significantly high "lost-to-follow-up" rate, in conjunction with the possibly protective effect of the Replens placebo, FDA must carefully consider whether the Van Damme study can be used to support the position that frequent use of nonoxynol 9 vaginal contraceptive products may increase the risk of HIV transmission.

Moreover, Apothecus is concerned about the weight that FDA has apparently given to conclusions drawn from the Van Damme Study exploratory analyses. The Van Damme Study authors conducted exploratory analyses to review: (1) the relationship between the frequency of product use and the increased risk of HIV transmission; and (2) the relationship between genital lesions, frequency of product use, and the increased risk of HIV transmission. While the authors state that the results of the exploratory analyses should be interpreted with caution, especially in light of the fact that the data is based on the validity of self-reported sexual behavior, FDA's Proposed Rule does not qualify the study conclusions in this manner, and thus, leads the reader to believe that the study supports the conclusion that nonoxynol 9 had an adverse effect on the vaginal epithelium when used frequently, which then increased women's susceptibility to HIV infection with infected partners.

Even if it could be accepted that the self-reported sexual behavior data is valid, other factors affect the relevance of the conclusions. Based on the exploratory analyses, the Van Damme Study authors state that women who used the nonoxynol 9 gel more than 3.5 times a day were at a significantly higher risk of contracting HIV-1 infection than their placebo-using counterparts. However, the sample size of frequent users represents only 239 women (32% of the study participants), and thus, the statistical significance of this sample, as applied to the general public must be considered. Further, if FDA is to accept this conclusion, it must further accept the conclusion that use of the nonoxynol 9 gel less than 3.5 times a day does not pose a risk to users. Of the 765 women included in the primary analysis, 516 (68% of the study participants) women reported use of the test product less frequently than 3.5 times a day. In these women, the Van Damme authors stated *that there was no difference in risk of HIV transmission between the nonoxynol 9 users and the placebo users*. Based on this study, there is no basis for FDA's description of frequent use as "more than once a day", and the Proposed Rule definition of "frequent use" would need to be changed to "more than 3 times a day."

Finally, we note that at the Durban study center, where the most HIV seroconversions occurred (42 nonoxynol 9 users and 30 placebo users), a much higher number of unprotected anal sex acts were reported in the nonoxynol 9 group (33%) as compared to the placebo group (19%). While the study authors state that this did not "seem" to be a confounding factor based on a review of the hazard ratio, we question this outcome. Clearly, this percentage difference between the groups has the ability to affect results of the study. In fact, while the authors point to the hazard ratio in the groups with and without unprotected anal sex (1.7 and 1.3 respectively) as the basis for determining the lack of a confounding affect, these numbers, in

themselves, show that the practice of unprotected anal sex increased the risk the HIV transmission.

3. The Kreiss Study

FDA also reports on The Kriess Study, which involved the comparison of a vaginal contraceptive sponge containing 1000 mg of nonoxynol 9 with a comparator suppository or cream that did not contain spermicide. This study included 138 Nairobi prostitutes that were highly exposed to the HIV infection, with 74 using the nonoxynol 9 product and 64 using the suppository or cream. As with the Roddy and Van Damme Studies, the purpose of the Kreiss Study was to measure any nonoxynol 9 preventative effect on the transmission of HIV. However, before reaching a conclusion, the study was terminated because the data safety and monitoring committee determined that the HIV seroconversion results had become inconsistent with the hypotheses that nonoxynol-9 has a clinically beneficial effect in preventing HIV transmission, and because of concerns that there was a link between the use of the nonoxynol 9 sponge and HIV seroconversion.

While the investigators cannot be faulted for prematurely halting a study in which it became clear that the data did not support the protocol hypotheses, for a number of reasons, this study cannot be used to support a link between nonoxynol 9 use and an increased risk of HIV transmission. First and foremost, at the time the study was terminated, the statistical analysis of the data did not support a statistically significant conclusion that nonoxynol 9 use increased the risk of HIV transmission. Second, the need to change the comparator midstream during this study indicates study design problems. Initially, a mineral-based suppository was used. However, because of concerns about the adverse impact of the mineral oil on condoms, the comparator was subsequently changed to a water-based vaginal cream specifically tested to have no effect on condom strength. Third, the fact that 16% of the nonoxynol 9 sponge users had genital ulcers versus 3% of the comparator users at the time of study entry raises questions about randomization problems with this study. Certainly, preexisting genital ulcers could have increased the risk of HIV seroconversion in the nonoxynol 9 sponge group. While the authors state that exclusion of women with genital ulcers did not change the results, obviously, the exclusion of these women further decreases the sample size from which conclusions can be drawn, thereby reducing the significance of this study and the ability to apply the results to the general public.

Finally, FDA must recognize the difference between the sponge dosage form and other formulations of nonoxynol 9. Unlike other dosage forms of nonoxynol 9, which are fully dispersed at the time of dosing, the nonoxynol 9-containing sponge disperses nonoxynol 9 over the entire period of 6 hours following intercourse before the sponge is removed. Clearly, this type of dosing could raise safety issues not associated with the other nonoxynol 9-containing

vaginal contraceptive drug products. Taking all of these factors together, FDA must carefully consider the credibility of the Kreiss study results.

4. *The Richardson Study*

As stated above, Apothecus is surprised that FDA did not reference the Richardson Study . While smaller in size, this study was essentially the same in design as to the Van Damme study in that the same nonoxynol 9 gel and placebo gel were used in this randomized double-blind placebo controlled study in a population of female sex workers in Mombasa, Kenya. In this study, 139 women were randomized to the nonoxynol 9 gel and 139 women were randomized to the placebo gel. There was no significant difference between the groups for acquisition of HIV infection. While the authors concede that no conclusions can be drawn regarding the effects of nonoxynol 9 on HIV transmission due to the insufficient statistical power of the study, clearly, this study raises further questions about the credibility of the Van Damme study, and whether the marginal significance in that study resulted from chance alone.

B. Safety Studies

In its Proposed Rule, FDA also provides a review of a number of safety studies that compare different nonoxynol 9 vaginal contraceptive drug products to use of placebo. The studies reviewed the extent of vulva, vaginal, and cervical irritation caused by the nonoxynol 9 products compared to placebo. Many of the cited studies were small (i.e., less than 50), and this fact, along with the variety of study designs used in these studies (double blind, single blind, cross-over, multiple dose, single dose, etc.), raise questions about their applicability to the general population. While most reported studies found some level of irritation from use of nonoxynol 9, the sample size of these studies raises questions about their significance.[2] In other studies, only rare signs of irritation were observed, and there were no reports of genital lesions or breaks in the epithelial lining.[3]

In a much larger study involving 534 women, while irritation from use of nonoxynol 9 was clearly evident, there was no sign of epithelial disruption.[4] The authors of this study questioned the significance of genital lesions in the absence of epithelial disruption in increasing the risk of HIV

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[2] See Rustomjee, R. et al., *Phase 1 Trial of Nonoxynol 9 Film Among Sex Workers in South Africa*, AIDS, 13:1511-1515, 1999.

[3] See Coggins, C. et al., *Safety of Three Formulations of Nonoxynol-9 Containing Vaginal Spermicides*, INTERNATIONAL JOURNAL OF GYNECOLOGY AN OBSTETRICS, 68:267-268, 1999. See Watts, H. et al., *The Effects of Three Nonoxynol-9 Preparations on Vaginal Flora and Epithelium,* JOURNAL OF INFECTIOUS DISEASES, 180:426-437, 1999.

[4] See Van Damme, L. V. et al., *Safety Evaluation of Nonoxynol-9 Gel in Women at Low Risk of HIV Infection*, AIDS, 12:433-437, 1998.

transmission, stating that large scale intervention trials in populations at high risk for HIV were necessary to make such a connection.

In one study involving 20 women, 15 women received a 150 mg nonoxynol 9-containing suppository every hour for a 4-hour period for 14 days while 5 women received a placebo suppository.[5] Despite the concentration of nonoxynol 9 administered over a very short period of time, only 6 of the 15 women receiving the nonoxynol 9 suppositories had physical findings. Nonetheless, this study adds very little to the discussion of safe use as the proposed usage is not consistent with the general use of this product in the U.S. Most U.S. women are very unlikely to use a nonoxynol 9 product with the tested level of frequency.

Finally, in a study that was part of a larger randomized placebo-controlled, triple blind trial, the investigators looked at the effect of more frequent use of a nonoxynol 9 vaginal contraceptive among 320 female sex workers.[6] In that study, the authors noted that multiple daily use of the nonoxynol 9 gel *did not show* an increase in local toxicity over the placebo gel.

Thus, while FDA relies on a number of safety studies to support the proposed warning language that frequent nonoxynol 9 use may increase the risk of HIV infection, these studies are insufficient to even suggest that use of nonoxynol 9 more than once a day causes a level of vaginal irritation or disruption that can be linked to an increased risk of HIV infection.

IV. ANALYSIS

FDA has stated that it need not show actual causation to mandate a warning such as the present one. See 68 Fed. Reg. at 2258. Apothecus disputes a lesser standard unless FDA can show it will prevent a public harm. Here, the scientific studies offered in support of the proposed warning language, do not really "suggest" a causal link between the frequency of use of nonoxynol 9 and an increased risk of HIV infection and other STDs. As discussed above, both the Van Damme Study and the Kreiss Study have limitations that were not adequately addressed in FDA's proposed rule, and which raise questions about the credibility of the results. Further, FDA has not explained why it did not fully consider either the Roddy Study or the Richardson Study in its analysis of a potential risk. In fact, as the largest study, the Roddy Study would appear to have been the highest powered study, and thus, the most reliable study from which to draw conclusions.

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[5] See Niruthisard, S., R. E. Roddy, and S. Chutivongse, *The Effects of Frequent Nonoxynol-9 Use on the Vaginal and Cervical Mucosa*, JOURNAL OF THE AMERICAN VENEREAL DISEASE ASSOCIATION, 18:176-179 (1991).

[6] See Van Damme, L.V., et al., *Safety of Multiple Daily Applications of COL-1492, A Nonoxynol-9 Vaginal Gel, Among Female Sex Workers*, AIDS 2000, 14(1):85-88 (2000).

Clearly, FDA must have a level of support for the addition of warning language that will undoubtedly frighten many women away from the use of these products, thus taking away a viable contraceptive option. Nonoxynol 9 vaginal contraceptives currently appeal to many women seeking contraception because the products do not require a prescription, they are easy to use, and sometimes they can be used without a sexual partner's knowledge. They are particularly attractive to low income women who may not be able to afford more expensive prescription alternatives. Further, while they kill sperm, nonoxynol 9 products do not have effects on various systems throughout a women's body (e.g., circulatory). Thus, these products are very popular among women who are breastfeeding, or women who otherwise cannot or do not want to use hormonal contraceptive methods. Nonoxynol 9 is also popular among women who have intercourse infrequently, or who need a back-up method of contraception, either along with other forms of contraception such as the condom or the diaphragm, or while waiting for recently started hormonal contraceptives to become effective. While less effective than oral contraceptives, the scientific literature supports the conclusion that nonoxynol 9 alone reduces the risk of pregnancy when compared with use of no product.

FDA must carefully consider the fact that the proposed labeling may result in the effective disappearance of all nonoxynol 9 containing vaginal contraceptives. Already, many companies have removed their nonoxynol 9 contraceptive products from the U.S. market due to negative international organization, government, and media statements alleging a link between nonoxynol 9 use and an increased risk of HIV. FDA has a responsibility to make warning statement policy based on valid scientific evaluation, and it should not merely rubber stamp positions taken up by entities such as the World Health Organization for political expedience. To do so would be irresponsible and a disservice to U.S. women.

Thus, the proof to require this warning must be sufficient to avoid a determination that the warning language requirement is arbitrary and capricious under 5 U.S.C. § 706. Although one may argue FDA may not be required under a safety standard to make specific and detailed findings and conclusions of the kind customarily associated with formal proceedings, the agency is obligated to examine the available evidence and to articulate a rational connection between that evidence and its exercise of discretion. See *Shoreham Cooperative Apple Products Ass'n. Van Donoran*, 764 F2d 135, 140-141 (2d Cir. 1985). Apothecus believes that when FDA reanalyzes the scientific literature as a whole, it will conclude that there is an absolute lack of clear evidence to support a connection between frequent use of nonoxynol 9 and an increased risk of HIV, particularly as that warning pertains to Apothecus' nonoxynol 9 vaginal contraceptive film.

V. RECOMMENDATIONS

Based upon our review of this matter, we respectfully urge FDA to partially withdraw the Proposed Rule as it pertains to inclusion of the following warning language in the Drug Facts Panel:

> "Ask a doctor before use if you have a new sex partner, multiple sex partners, or unprotected sex. Frequent use (more than once a day) of this product can increase vaginal irritation, which may increase the risk of getting the AIDS virus (HIV) or other STDs from infected partners. Ask a doctor or other health professional for your best birth control method."

Similarly, we request the withdrawal of the proposal to require the following language to appear in either the "Other information" section of the Drug Facts Panel, or in an inner package insert:

> "Studies have raised safety concerns that frequent use (more than once a day) of products containing nonoxynol 9 can increase vaginal irritation, which may increase the risk of getting the AIDS virus (HIV) or other STDs from infected partners. Vaginal irritation may include symptoms such as burning, itching, or a rash, or you may not notice any symptoms at all. If you use these products frequently and/or have a new sex partner, multiple sex partners, or unprotected sex, see a doctor or other health professional for your best birth control and methods to prevent STDs."

As explained above, there is no basis for such statements in light of the current science, and the requirement of such language could clearly result in a significant decrease in the use of nonoxynol 9-containing vaginal contraceptive products and could potentially result in removal of these products from the market.

However, if FDA chooses to ignore the science and wishes to require warning language that discusses an alleged increased risk of HIV/STD infection, this warning should be clarified to reflect what is known today. First, the "Ask a doctor before use" warning is not properly limited to the alleged suggested risk discussed in the Proposed Rule preamble, which is "frequent use" of nonoxynol 9 containing vaginal contraceptive products. The warning goes much further, informing women to refrain from use without first speaking with a doctor if they have a new sex partner, multiple sex partners, or unprotected sex. These activities, by themselves, do not imply "frequent use." Moreover, many persons in safe monogamous relationships engage in unprotected sex. The proposed warning calls into question the safety of even this safe activity.

Further, it is questionable how FDA arrived at the definition of "frequent use" as "more than once a day." The only discussion of a definition of "frequent use" is found in the flawed Van Damme study and, in that study, "frequent use" is defined as use of the nonoxynol 9 product more than 3.5 times a day. It is under these conditions that the Van Damme authors concluded that there was a statistically significant increase in the risk of HIV infection from infected partners.

Thus, at a minimum, the following modifications to the proposed "Ask a doctor" warning are necessary:

> "Ask a doctor before use if you have frequent sex (more than three times a day).~~a new sex partner, multiple sex partners, or unprotected sex.~~ Frequent use (more than ~~once a day~~three times a day) of ~~this product~~ nonoxynol 9 may~~can~~ increase vaginal irritation, which may increase the risk of getting the AIDS virus (HIV) or other STDs from infected partners. Ask a doctor or other health professional for your best birth control method."

The second warning would require the following modifications:

> "Studies concerning some nonoxynol 9 formulations (i.e., gel and sponge) in high risk populations (i.e., prostitutes) have raised very preliminary safety concerns that frequent use (more than ~~once a day~~three times a day) of products containing nonoxynol 9 can increase vaginal irritation, which may increase the risk of getting the AIDS virus (HIV) or other STDs from infected partners. Other studies have shown no such risk for certain formulations (i.e., nonoxynol 9-containing film and gel) in these high risk populations. Vaginal irritation may include symptoms such as burning, itching, or a rash, or you may not notice any symptoms at all. While there is no clear link between the frequent use of nonoxynol 9 and the increased risk of HIV infection or other STDs from infected partners, if you use these products frequently ~~and/or have a new sex partner, multiple sex partners, or unprotected sex,~~ see a doctor or other health professional for your best birth control and methods to prevent STDs."

The proposed warning more accurately reflects the known science and places the warning in a more relevant context. Apothecus has great concerns that even these modified warnings will unnecessarily frighten consumers and, thus, impact the continued availability of these products. However, it is hopeful that consumers will recognize the proper level of risk based on their personal sexual behavior and frequency of product use.

Respectfully Submitted,

Gary L. Yingling

Ann M. Begley