

April 16, 2003

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



Dear Sir/Madam,

I am pleased to submit these comments on behalf of the Global Campaign for Microbicides regarding the proposed new labeling warning for all over-the-counter vaginal contraceptive drug products containing nonoxynol-9 [21 CFR Part 201].

The Global Campaign for Microbicides is an international coalition of over 150 non-governmental organizations that work to mobilize support among policymakers, opinion leaders, and the general public for increased investment in microbicides and other user-controlled methods of HIV protection. 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 users, especially women. The Campaign pursues its work through a small core staff, headquartered at the Program for Appropriate Technology in Health (PATH), and by funding partner groups to pursue activities that directly advance the Campaign goals and objectives.

The Campaign wishes to congratulate FDA on its effort to provide users with accurate and reliable information regarding the benefits, limitations and potential risks posed by OTC contraceptive products containing N-9. We believe that the decision to add warning labels to these products represents the appropriate balance between preserving women's access to an important non-hormonal contraceptive option, while countering the widespread perception that N-9 provides protection against STDs and HIV. Vaginal spermicides containing N-9, either alone or in combination with cervical barriers, presently represent the only non-hormonal, form of contraception that is fully within the control of women. Thus, despite the risks posed by N-9 to some users, we believe that it is important to maintain vaginal spermicides on the market until a safe and effective alternative becomes available.

At the same time, we share the FDA's concern that women may be inadvertently putting themselves at risk, either because they falsely believe that N-9 products provide protection from HIV and/or STDs or because they are using N-9 birth control products with a frequency that could exacerbate any underlying risk of HIV infection. Thus we endorse the FDA's decision to provide additional information to users via the product label and package insert.

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We welcome the opportunity to give input on the FDA's proposed strategy for re-labeling N-9 containing contraceptives. We have a number of observations, suggestions and concerns that we outline below.

1. **STD Alert:** We strongly suggest that the proposed "STD Alert," as worded, appear on the package carton in addition to the product label. It is our belief that consumers are more likely to see and acknowledge a warning that appears on the box rather than the tube or package insert.

2. **Proposed Warning on Frequent Use:** We support a warning regarding the possible danger of frequent use of N-9 containing contraceptives for women at risk of HIV. The data available to operationalize "frequent use" for the purposes of guiding behavior are admittedly sparse; nonetheless, we concur that the label should provide some concrete guidance to help women interpret what might constitute frequent use. We believe the proposed qualifying statement (more than once a day) is a reasonable way forward in the absence of more specific data to guide action.

The challenge in constructing this warning is that the risk evolves from a combination of the woman's underlying risk of HIV/AIDS *and* the prospect of frequent use. Presumably if a woman is not at risk of HIV (because she is in a mutually monogamous relationship with an HIV negative partner), then frequent use of N-9 poses no additional hazard. Thus women at low risk of HIV could safely use N-9 on multiple intercourse occasions in single day (e.g. a woman in a stable, mutually monogamous relationship with an HIV-negative partner who is using N-9 and a diaphragm for contraception). In order to reassure such women, FDA may wish to add a qualifying statement to this effect (see below).

3. **Vaginal Irritation.** The current warning language refers to "vaginal irritation" --a term that in common usage connotes physical symptoms and discomfort. Since epithelial disruption and inflammation often occur in the absence of perceived symptoms of "irritation," we recommend that the label avoid reference to this term. Women who do not experience what they subjectively perceive as "irritation" may be left with the mistaken impression that they are safe. An alternative wording might be:

a. "Frequent use of this product (more than once a day) can damage the cells lining the vagina, a condition that may increase one's risk of becoming infected with HIV or other STDs if exposed to an infected partner.

NOTE: Women at low risk of HIV (i.e. those in a mutually monogamous relationship with an HIV negative partner) *can* safely use N-9 (with or without a diaphragm) on multiple intercourse occasions in single day. Frequent use of N-9 is only problematic for women exposed to HIV and other STDs.

4. **Reference to physician consultation.** The current language begins by exhorting women to seek guidance on N-9 use from a physician. We believe a more productive course would be to help women draw appropriate conclusions from the safety data provided and empower them to act upon it directly. For example, rather than saying "Ask a doctor before use," we suggest the label explicitly state: "Women who may be at risk of HIV and who plan

to use the product more than once a day should consider another form of birth control. Vaginal contraceptive products containing N-9 (either along or in combination with a diaphragm) remain a safe contraceptive option for women who are at low risk of HIV and do not use the product more than once a day.”

We further support the additional language proposed to reinforce condom use: “Correct use of a latex condom with every sexual act will help reduce the risk of getting the AIDS virus and other STDs.”

5. **For vaginal use only.** We strongly suggest that this language be reframed to offer an explicit warning against using these products rectally. Even though the products are designed for vaginal *contraceptive* use, they can and *are* used occasionally for lubrication and/or “extra protection” during anal intercourse. Studies confirm that Nonoxynol-9 is even more toxic to the delicate rectal epithelium than to the squamous epithelium of the vagina. Research by Phillips and colleagues confirms that products that contain even small amounts of N-9 when used rectally cause massive, short-term sloughing of the rectal epithelium in humans, mice and monkeys (Phillips et al, 2000; Phillips et al, 2002; Patton et al, 2002). Given the high likelihood of harm posed by the *misuse* of OTC contraceptive products rectally, we recommend that the label include an explicit warning against rectal use of these products. Possible language includes: “Products containing Nonoxynol-9 should never be used rectally; to do so may substantially increase one’s risk of contracting HIV from an infected partner.”

6. **N-9 as an additive to condoms and lubricants.** Although not within the purview of this particular rulemaking, we respectfully request FDA to take action to address the potential health risks posed by N-9 as an additive on condoms and in sexual lubricants.

The N-9 added to lubricants and condoms is not necessary to the functioning of these products either as lubricants or, in the case of condoms, as physical barriers against pregnancy and disease. Correct and consistent use of condoms provides excellent protection against both pregnancy and HIV even without the addition of N-9. Moreover, all lubricant and condom manufacturers who market N-9-containing versions of their products also market parallel versions of their products that do not contain Nonoxynol-9.

Given that N-9 can cause serious epithelial damage when used rectally, there is no justification for the continued marketing of the N-9 versions of these popular products.

In 2002, the Global Campaign spearheaded an effort to get manufacturers of sexual lubricants and condoms to voluntarily discontinue adding N-9 to future lots of their products. Over 90 eminent scientists and health organizations—including Planned Parenthood, National Women’s Health Network and American Foundation for AIDS Research (amFAR)—endorsed the “Call to Discontinue N-9 for Rectal Use.” A number of prominent manufacturers of condoms and sexual lubricants have responded positively to the Call, although others—including the top three condom manufacturers—have not agreed to take voluntary action (See enclosed).

According to the recent WHO consensus statement on Nonoxynol-9: “There is no published scientific evidence that N-9-lubricated condoms provide any additional protection against pregnancy or STIs compared with condoms lubricated with other products. Since adverse

effects due to the addition of N-9 to condoms cannot be excluded, such condoms should no longer be promoted.” (WHO 2002)

The US Centers for Disease Control and Prevention has issued similar statements.

Because these products offer no proven benefit to any user group and pose substantial risks to some users, we feel that the risk/benefit ratio argues for eliminating the risk rather than relying on a “labeling” solution.

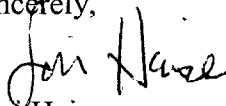
By contrast, we endorse the proposed labeling option for vaginal spermicides containing N-9 because these products can be used safely by and provide a demonstrable benefit to a known group of users.

For a complete description of our reasoning in this regard, please see the enclosed “Explanatory Background Memo for the Call to Discontinue N-9 for Rectal Use.”

7. **Urgent need for new vaginal contraceptives and microbicides.** In closing, we would like to emphasize the urgent need for products that, unlike Nonoxynol-9, *do* hold promise for providing safe and effective protection against sexually transmitted infections, including HIV. Additionally, given the complex safety profile of Nonoxynol-9, we need new vaginal contraceptive products that can be used alone, or in combination with the diaphragm or other cervical barrier, to prevent unwanted pregnancy.

Thank you for the opportunity to comment.

Sincerely,



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References:

Patton DL et al (2002). Safety evaluation for rectal use of buffergel and carraguard in the macaque model. [Abstract A-187]. Microbicides 2002, Antwerp, Belgium May 12-15, 2002.

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Phillips, D et al. (2002) Effect of N-9 on the human rectal mucosa. [Abstract A-066]. Microbicides 2002 Conference, Antwerp Belgium, May12-15, 2002.

Call to Discontinue Nonoxynol-9 for Rectal Use

We, the undersigned, in light of recent statements by the World Health Organization and the Centers for Disease Control, urge all people to cease the rectal use of products containing Nonoxynol-9 (N-9). We are concerned that many people mistakenly believe that N-9 provides extra protection against HIV and STDs when used rectally when in fact there is reason to think that rectal use of N-9 may increase risk of infection.

The Centers for Disease Control states: "...N-9 can damage the cells lining the rectum, thus providing a portal of entry for HIV and other sexually transmissible agents. Therefore, N-9 should not be used as a microbicide or lubricant during anal sex."

The World Health Organization states: "N-9 should not be used rectally." (Further) "There is no published scientific evidence that N-9-lubricated condoms provide any additional protection against pregnancy or STIs compared with condoms lubricated with other products. Since adverse effects due to the addition of N-9 to condoms cannot be excluded, such condoms should no longer be promoted."

N-9 is an ingredient that is contained in three types of over-the-counter products: in contraceptive products designed exclusively for vaginal use (diaphragm jelly, contraceptive foams and creams); in some sexual lubricants; and on the outer lubrication in some lubricated condoms.

Given the evidence cited above, we call on manufacturers of condoms and sexual lubricants to discontinue adding N-9 to future lots of their product. Consumers should examine labels of lubricants they use for anal sex to ensure that the product does not contain N-9. Providers should advise clients not to use rectally products that are designed for other purposes; specifically, vaginal foams, gels or creams that contain N-9 for contraceptive purposes should not be used rectally.

We are not calling for the removal of N-9 contraceptive products designed exclusively for vaginal use because they remain an important contraceptive option for women who are at low risk of HIV infection or other STDs. Moreover, evidence suggests that N-9 is considerably more toxic at low doses when used in the rectum than the vagina.

In light of the deleterious side effects of rectal use associated with products containing N-9, it is essential that we identify a lubricant safe for rectal use. Therefore, we further call on the public health community and lubricant manufacturers to undertake safety studies in humans to establish minimally that products marketed explicitly or implicitly for rectal use do not cause disruption of the rectal epithelium, as does N-9.

Finally we emphasize the importance of on-going research to develop vaginal and rectal microbicides that are both safe and effective. It is imperative that truly effective microbicides be developed as soon as possible and we commit ourselves to this ongoing effort. A safe and effective microbicide can be developed, but N-9 is not this product.

Signed:

Lori Heise, Director
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AIDS Alliance for Children, Youth and Families
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AIDS Coalition to Unleash Power
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AIDS Survival Project
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International Foundation for Alternative
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National AIDS Trust
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Program for Appropriate Technology in Health
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Explanatory Background Memo for the “Call to Discontinue Nonoxynol-9 for Rectal Use”¹

Types of N-9 products on the market

1. Nonoxynol-9 (N-9) is the active ingredient in most over-the-counter spermicidal products available in the United States, including diaphragm creams and jellies and stand-alone contraceptive products such as Encare Oval, Gynol II, Delfen foam, etc. N-9 disrupts cell membranes, including the membranes of sperm. It has been used vaginally to prevent pregnancy since the 1950s.
2. Manufacturers also add nonoxynol-9 to some sexual lubricants and to some lubricated condoms. Thus there are *three* types of products on the market that contain the ingredient Nonoxynol-9: contraceptive spermicides (intended for vaginal use only), sexual lubricants, and male condoms. The amount of N-9 in vaginal contraceptive products (52-1000 mg) is considerably higher than that incorporated into lubricants and/or condoms (<12 to 62 mg).
3. The practice of adding N-9 to lubricants and condoms accelerated in the early 1990s when it was widely believed that nonoxynol-9 provided some protection against bacterial STDs and possibly HIV. It has since been shown that N-9 does not provide any protection against STDs or HIV when used in the vagina and may increase risk of HIV infection under certain circumstances (see below).
4. The N-9 in over-the-counter spermicides and diaphragm adjuncts is critical to the contraceptive function of these products. The N-9 added to lubricants and condoms is not necessary to the functioning of these products either as lubricants or in the case of condoms, in their role as physical barriers against pregnancy and disease. Correct and consistent use of condoms provides excellent protection against both pregnancy and HIV even without the addition of N-9.
5. All lubricant and condom manufacturers who market versions of their product that contain N-9, also market parallel versions of their products that do not contain Nonoxynol-9.

Safety data on existing N-9-containing products

1. In recent years, a number of safety concerns have been raised regarding the vaginal and rectal use of N-9 containing products.

¹ Lori Heise of the Global Campaign for Microbicides prepared this memo. The Global Campaign is a coalition of over 120 organizations worldwide that works to accelerate widespread access to microbicides and other user-controlled methods of HIV prevention. The Campaign pursues its work through a small core staff and by funding partner organizations to pursue activities that directly advance the Campaign's goals and objectives. For more information, please see: www.global-campaign.org

2. It appears that when used frequently in the vagina, contraceptive products containing nonoxynol-9 can cause disruption of the vaginal epithelium (cell wall) – a condition that may increase a woman’s risk of becoming infected with HIV. The impact of N-9 on the vaginal epithelial appears to be dose-related. Small infrequent doses of N-9 (once a day or less) appear to cause little or no disruption of the epithelium, whereas more frequent, larger doses consistently cause disruption (WHO/CONRAD Technical Consultation on Nonoxynol-9, June 2002).
3. By contrast, products that contain even small amounts of N-9 when used rectally cause massive, short-term sloughing of the rectal epithelium in humans, mice and monkeys (Phillips et al, 2000; Phillips et al, 2002; Patton et al, 2002). It is reasonable to deduce, although not yet proven, that this may increase individual’s risk of contracting HIV or other STDs. There is animal evidence that use of these products in the rectum of mice dramatically increase their susceptibility to HSV, another viral STD (OAR/NIAD Workshop on Rectal Microbicides, Jun 7-8, 2001)
4. Both the Centers for Disease Control (CDC) and the World Health Organization (WHO) have concluded that for safety reasons, N-9 containing products—either lubricants or contraceptive spermicides--should not be used rectally.
4. Likewise, WHO counsels that women who are at risk of HIV, especially those who engage in multiple acts of intercourse in a day, should not use N-9 containing products for birth control purposes. Among women at low risk of HIV infection, the use of N-9 containing contraceptive products is safe and remains a legitimate contraceptive option.
5. N-9 is considerably more toxic at smaller doses when used in the rectum compared to the vagina. Even the smaller doses found in sexual lubricants and N-9 lubricated condoms cause epithelial sloughing in the rectum.

Public health guidance on Nonoxynol-9 containing products

1. According to the recent WHO consensus statement on Nonoxynol-9: “There is no published scientific evidence that N-9-lubricated condoms provide any additional protection against pregnancy or STIs compared with condoms lubricated with other products. Since adverse effects due to the addition of N-9 to condoms cannot be excluded, such condoms should no longer be promoted.” (WHO 2002)
2. The CDC likewise observes: “In the future, purchase of condoms lubricated with N-9 is not recommended because of their increased cost, shorter shelf life, association with urinary tract infections in young women, and lack of apparent benefit compared with other lubricated condoms” (CDC, May 10, 2002)
3. The CDC 2002 STD treatment guidelines similarly note with respect to N-9 containing lubricants: “...N-9 can damage the cells lining the rectum, thus providing a portal of entry for HIV and other sexually transmissible agents. Therefore, N-9 should not be used as a microbicide or lubricant during anal sex.” (CDC, May 3, 2002)

Anal sex and use of N-9 containing products

1. Studies show that most men who have sex with men (MSM) use lubricants during anal intercourse, and many actively seek out products containing nonoxynol-9. Among 3093 gay men who had had intercourse in the last 6 months, Gross et al (1998) found that more than three-fourths used lubricants more than 80% of the time. Among them, 41% actively sought products containing nonoxynol-9. Some of these men insert lubricating products internally into the rectum in addition to using them externally.
2. At the Barcelona AIDS conference, Dr. Gordon Mansergh of CDC presented data from a 2001 study in San Francisco that showed that even after the CDC issued its guidance against rectal use of N-9 and after the San Francisco Department of Health undertook activities to get the word out, gay men in San Francisco continued to use products containing N-9 rectally (Mansergh et al, 2002). Among a diverse sample of 573 MSM in San Francisco, 61% had heard of N-9. Of these 349 men, 83% had used N-9 in their lifetime and 67% in the previous year (median, 50% of anal sex encounters in the past 12 months). Among men who used N-9 during anal sex in the last year, 41% did so without a condom because they thought it might be protective against HIV infection. 74% used N-9 with a condom because they thought it might be protective (and this is after CDC and San Francisco DOH issued warnings).
3. Studies from the United States indicate that anywhere from 6 to 13% of women also report engaging in anal sex within the last year (Gross et al 2000). In a six-city study of women at high risk of HIV, 32% reported anal sex in the previous 6 months (Gross et al, 2000).
4. N-9 lubricated condoms and sexual lubricants containing N-9 are still widely available in drug stores, sex shops and on the web and are still being distributed by some family planning agencies. Approximately 42% of condoms sold commercially in the United States are lubricated with Nonoxynol-9. In a recent CDC-sponsored survey of Title X family planning facilities, respondents indicated that 87% of condoms distributed were lubricated with N-9 (CDC, May 10, 2002).

The future of N-9 containing products

1. Since adding N-9 to sexual lubricants provides no demonstrable benefit to *any* user group and may cause considerable harm if used rectally we call on all manufacturers to voluntarily remove Nonoxynol-9 from all sexual lubricants.
2. Likewise, since there are no data to demonstrate that adding N-9 lubrication to condoms offers any benefit to individuals using them vaginally in terms of pregnancy or disease prevention and N-9 on condoms may cause harm if used rectally, we call upon manufacturers to remove N-9 from future lots of their condoms. Since lubrication itself helps prevent condom breakage, we recommend replacing N-9 with other forms of lubrication rather than reducing the overall portion of lubricated condoms.

We recognize that some heterosexual couples seek out N-9 lubricated condoms with the hope of achieving back up protection against pregnancy in case of condom breakage or slippage. However, there are no data to substantiate whether or not the amount of N-9 bio-available on condoms is adequate to provide back up protection from unwanted pregnancy. (There is considerable less N-9 on condoms than in most over the counter contraceptive products). The study required to answer this question would be prohibitively large (>50,000), so it is unlikely that data will ever be available to answer this question. By contrast, there is compelling evidence that emergency contraception can reduce the risk of unwanted pregnancy in the event of condom failure.

In the case of N-9 lubricated condoms, therefore, we must balance the known harm to one group (individuals practicing anal sex) against a potential, but unclear, benefit to heterosexuals seeking added pregnancy prevention. Given that condoms are an excellent contraceptive even in the absence of N-9 and that rectal exposure to N-9 could facilitate transmission of a fatal disease, we feel that the public health benefits of phasing out N-9 should take precedence over concerns of reducing options for heterosexual users.

3. Although less effective than other forms of contraception, N-9-containing spermicides (used alone or in combination with a diaphragm or cervical cap) represent one of only two woman-controlled, non-hormonal forms of contraception available to women in the United States and globally.² For example, the diaphragm used together with N-9 spermicide prevents approximately 460,000 pregnancies in the United States each year (Trussel 1998).

It is possible that some consumers may use contraceptive products rectally (even though they are labeled for vaginal use only), potentially put themselves at risk. However, we feel these products should remain on the market because they offer a substantial benefit to a small but important group of users. Eliminating the option of a user-controlled, non-hormonal contraceptive method should not be taken lightly. Every effort should be made to limit potential harm from using these products rectally, including adding labels warning against rectal use, conducting public education campaigns against rectal use, and positioning such products next to feminine hygiene, menstrual and other "woman-focused" products, rather than in the condom and lubricant sections.

References:

CDC (May 3, 2002). Guidelines for treatment of sexually transmitted diseases. MMRW 51(RR06):1-80.

For a copy see: <http://www.cdc.gov/std/treatment/default.htm>

CDC (May 10, 2002). Nonoxynol-9 Spermicide Contraceptive Use – United States 1999. MMRW 51(18):389-392.

For a copy see: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5118a1.htm>

² The female condom is another user-controlled method of contraception and HIV prevention, though it is not as widely available or affordable as male condoms.

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