ARMKEL, LLC

An affiliate of Church & Dwight Co., Inc. and Kelso & Company

April 17, 2003

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

Docket No. 80N-0280
Over-the-Counter Vaginal Contraceptive Drug Products Containing Nonoxynol-9; Required Labeling
68 Fed. Reg. 2254 (January 16, 2003)

Attached for your convenience are four copies of the Comment submitted electronically yesterday. We are forwarding these hard copies since we noticed that the footnotes which appear in the ARMKEL, LLC White Paper (an attachment to the Comment) did not appear in the electronically transmitted version.

Thank you for this opportunity to provide our views on this important subject.

Respectfully submitted,

David W. Worrell
Associate General Counsel

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ARMKEL, LLC, ("ARMKEL"), the maker of **TROJAN®** brand condoms, * appreciates this opportunity to provide comments on the agency's proposed rule that would require additional labeling information for over-the-counter contraceptive drug products that contain the spermicidal active ingredient nonoxynol-9 ("Proposed Rule").

While ARMKEL does not manufacture or market OTC drug products that are the subject of these rulemaking proceedings, the company includes in its **TROJAN** product line a number of condom products (medical devices) with lubricants that contain nonoxynol-9 ("N-9"). Thus, ARMKEL has a substantial interest in the subject of appropriate labeling for N-9-containing contraceptive products in general.

Condoms, as medical devices, including those with N-9, are regulated by the agency's Center for Devices and Radiological Health ("CDRH"). ARMKEL's N-9-containing condoms are marketed under various 510(k) clearances issued in accordance with the agency's 1982 classification of these products as Class II medical devices. The inclusion of N-9 in these condom products is intended to provide a secondary means of pregnancy prevention if the condom is used incorrectly and as a result some semen spills outside the condom. Thus, N-9-containing condoms provide important consumer and public health benefits.

ARMKEL agrees with the approach taken by FDA in the CDER Proposed Rule to allow continued availability of N-9-containing contraceptives while requiring additional cautionary labeling to address those limited user groups that should avoid using the products. We strongly believe that condom labeling should provide appropriate cautionary information in a way that does not unduly alarm the public or cause confusion or misuse of condoms. In line with this, our company has been engaged in ongoing

ARMKEL, LLC

White Paper

Nonoxynol-9 Lubricated Condoms

EXECUTIVE SUMMARY

For many years, the consistent and correct use of condoms has been recommended by the Centers for Disease Control and Prevention ("CDC"), World Health Organization ("WHO") and other leading public health authorities as an effective means of reducing the risk of sexually transmitted diseases ("STDs") as well as unwanted pregnancies.

Condoms lubricated with the spermicide nonoxynol-9 ("N-9") have been available in the U.S. since 1983. They are very popular among couples concerned about the risk of pregnancy. The addition of N-9 in the condom lubricant is intended to reduce the risk of pregnancy if condoms are used incorrectly and erection is lost before withdrawal and some semen spills outside the condom.

Much of the data discussed in the WHO/CONRAD report concerning the potential for STD transmission from irritation caused by N-9 derive from studies conducted among prostitutes in Asia and Africa. These data have little relevance when it comes to the use of N-9 lubricated condoms by the general U.S. population. Further, the studies were of N-9 alone or in combination with other contraceptive devices -- not N-9 lubricated condoms -- and the data were equivocal even in those circumstances.

Even the theoretical risk identified in the WHO/CONRAD report can be virtually eliminated by warning against the use of N-9 lubricated condoms for rectal intercourse or for high-frequency vaginal use (multiple daily acts of sexual intercourse). Although the risk is theoretical, ARMKEL, LLC [1/] believes it is appropriate to modify the labeling of N-9 lubricated condoms to caution against use in these two special situations. This change will provide assurance that such condoms are safe and effective when used according to the labeling, without unduly alarming the public or causing confusion or misuse of condoms.

I. BACKGROUND

Condoms are a very effective method of contraception and the only known means of reliably preventing sexually transmitted diseases ("STDs"). Nonoxynol-9 ("N-9") has been used as a stand-alone vaginal contraceptive since the 1950s. In 1982, the U.S. Food and Drug Administration ("FDA") granted a classification petition seeking regulation of condoms lubricated with N-9 as Class II medical devices. This classification permits N-9 lubricated condoms to enter commercial distribution only after FDA's clearance of a "510(k) premarket notification." [2/]

To obtain such 510(k) clearance, FDA requires manufacturers to show that their N-9 lubricated condoms meet rigorous performance standards with regard to parameters such as quality, size, thickness, burst pressure, leakage and package integrity. [3/] In addition, the condom package must have prominent expiration dating, supported by extensive testing requirements. [4/] FDA also requires that the condom's labeling bear the following statement:

> "This product combines a latex condom and spermicidal lubricant. The spermicide, nonoxynol-9, reduces the number of active sperm, thereby decreasing the risk of pregnancy if you lose your erection before withdrawal and some semen spill outside the condom. However, the extent of decreased risk has not been established. This condom should not be used as a substitute for the combined use of a vaginal spermicide and a condom." [5/]

Since their advent twenty years ago, N-9 lubricated condoms have enjoyed widespread use in the U.S. It is currently estimated that approximately

$500 million worth of condoms are sold in the U.S. every year. [6]/ Of these, about one-third are lubricated with N-9.

II. RECENT CONCERN

As mentioned above, not only is N-9 used to lubricate condoms, but it is also used as a stand-alone vaginal contraceptive in film (70 mg), foams (70-85 mg), suppositories (100 mg), gels (52-200 mg), and sponges (1000 mg). By way of contrast, the amount of N-9 on lubricated condoms ranges from 25 to 60 mg.

The stand-alone use of N-9 has engendered safety concerns about whether it produces irritation that could be a pathway to infection, despite its acknowledged microbicidal properties. Within the last decade or so, a number of clinical studies have been performed to evaluate the safety of N-9 alone. Some of these studies indicated that N-9 use may be associated with epithelial disruption in the vagina and in rectal tissue. Theoretically, this disruption could predispose users to increased risk of STDs, although such causation has not been demonstrated.

In October, 2001, the World Health Organization ("WHO"), in partnership with the CONRAD Program (Arlington, VA), convened a Technical Consultation on the safety and effectiveness N-9 alone, based largely on a review of published literature. [7]/ ARMKEL has also commissioned The Weinberg Group to perform an extensive literature review relating to N-9 safety. [8] Each of these reports is discussed below, along with the implications for condoms lubricated with N-9.

A. WHO/CONRAD Report

1. Purported Increased Risk of STDs

The published literature discussed in the WHO/CONRAD report focuses on N-9 used by itself, in the form of a suppository, gel, film or impregnated in a sponge. None of the studies addressed N-9 lubricated condoms and only one study explicitly looked at condom use with N-9.

The WHO/CONRAD report summarizes 16 studies in which the effect of N-9 on epithelial disruption in the vagina was examined. The report concluded that the data "showed a trend towards a greater frequency of disruption with greater frequency of use and higher doses of N-9." [9] However, the report also concludes that "infrequent use of products containing low doses of N-9 is probably safe" (emphasis added). [10] The report also indicates that there are "major obstacles" to interpreting the data. In particular, there is no known way to "distinguish between epithelial changes resulting from sexual intercourse and the impact of the study product." Furthermore, "the clinical significance of signs and symptoms of [epithelial] disruption is not known." [11]

Thus, while there is evidence that N-9 use alone can result in vaginal irritation, there is no evidence that this irritation translates into an increased risk of STD transmission. The WHO/CONRAD report indicates that when data from all of the relevant studies are combined and analyzed together there is no increased

risk of gonorrhea, chlamydia, cervical infection, trichomoniasis, bacterial vaginosis, candidiasis, or HIV associated with N-9 use. [12/]

The WHO/CONRAD report focused on N-9 in stand-alone products. No studies were discussed in the report regarding the safety of N-9 lubricated condoms. While there may be a theoretical link between N-9 and increased risk of STDs based upon irritation, the WHO/CONRAD report shows that this link has not been established, even for N-9 when used alone. When N-9 is combined with a condom, the theoretical risk would not generally apply, because the condom itself provides very significant protection against STDs. Stated differently, the condom provides a very high level of protection against infection even if the theoretical risk of N-9-induced irritation is given credence.

2. Prevention of STDs

The WHO/CONRAD report discusses the effectiveness of N-9 in prevention of STD transmission. Several studies showed a statistically significant reduction in gonorrhea and chlamydia infection with use of N-9 products. Most studies, however, did not demonstrate statistically significant reductions in STDs. A meta-analysis was performed combining data from almost 5000 women in nine different studies. This analysis showed that there was a numerical reduction in infection with gonorrhea, chlamydia, trichomoniasis, bacterial vaginosis, and candidiasis, but that none of these reductions were statistically significant. The reductions for chlamydia, trichomoniasis, and bacterial vaginosis were very close to

being statistically significant. These studies also showed a numerical increase in HIV infection that was not statistically significant.

As before, none of the studies in this analysis involved the use of N-9 lubricated condoms. Thus, it cannot be determined what effect N-9 has in reducing the risk of STDs, over and above the use of a condom without N-9.

3. Contraception

The WHO/CONRAD report discusses the results of 31 clinical studies that measured pregnancy rates among women using spermicide (including N-9) alone. These studies had certain limitations, but the report concluded that "use of spermicide alone reduces risk of pregnancy compared with use of no product." [13/] The report also notes that spermicide is often used in conjunction with other barrier methods, such as diaphragms, cervical caps, sponges and condoms. There is some evidence that diaphragms used with spermicide are more effective contraceptives than diaphragms without spermicide. However, the WHO/CONRAD report does not cite any well-controlled studies comparing the contraceptive effectiveness of N-9 lubricated condoms with that of other lubricated condoms. As FDA has pointed out, such clinical studies "would be difficult to conduct and may not produce evidence justifying the effort of collecting it." [14/]

B. The Weinberg Group Report

The Weinberg Group, Inc, (Washington, DC), at the request of ARMKEL, performed an extensive literature search relating to the safety of N-9

("the Weinberg Report"). Their literature review included estimation of background rates of tissue injury, safety profile by delivery vehicle, and safety profile by ingredient. Injury to vaginal, penile and rectal tissue were all included. In addition, the report discusses the correlation between objective and subjective measures of tissue injury.

The Weinberg report specifically identified studies that compared condom use with and without N-9. Of eleven studies identified in which condoms were used, only two involved N-9 lubricated condoms. The authors concluded that "[t]hese two studies indicate that N-9 condoms are not associated with more safety events than are lubricated condoms [that do not employ N-9]."[15]/ The other nine studies involved condom use in conjunction with N-9 gels or films. Several of these studies showed a numerical increase in adverse events in the N-9 groups, but none of the differences were determined to be statistically significant.

As with the WHO/CONRAD report, the Weinberg report also evaluated studies in which stand-alone N-9 products (gels, films, suppositories) were used by themselves (without condoms) and compared to placebo. There were no studies of N-9 film that reported statistically significant differences between N-9 and placebo groups. One study examining gel use found a statistically significant elevation of genital symptoms among N-9 users but the study authors acknowledged that they could not discern what percentage of the lesions in the N-9 arm were due to N-9 versus intercourse itself.

The Weinberg report's overall female urogenital safety conclusions on the total of eighteen studies stated that "[n]one of the studies was of adequate quality to draw solid conclusions. Most had important methodological limitations including small sample size, poor retention (high drop out), and statistical methodology was poorly described. . . . Overall, these studies do not demonstrate a causal relationship between N-9 and tissue damage."[16]/

The Weinberg report also examined dose response relationships, as well as penile and rectal adverse events. Most of the studies examined in these respects were inconclusive, and in many cases the studies were not of sufficient quality to adequately address safety issues

III. PUBLIC HEALTH ANALYSIS

The WHO/CONRAD report and other recently published high profile study reports have prompted various public health organizations to modify messages relating to N-9. FDA's Center for Drug Evaluation and Research has issued a proposed rule that would require revised product labeling addressing the possible risks associated with OTC drug products that contain N-9. ARMKEL has been working with FDA's Center for Devices and Radiological Health (condoms are regulated as medical devices), along with other U.S. public health agencies, industry members and others to develop appropriately revised labeling for condoms.

ARMKEL, a manufacturer of N-9 lubricated condoms, believes there is

considerable value in maintaining the availability of N-9 lubricated condoms with revised labeling. Our rationale is as follows:

When used properly, condoms are themselves an extremely effective method of contraception. But condoms are not always used exactly as directed and they sometimes may slip or break, allowing seminal fluid to leak into the vagina. In these cases, there is considerable evidence to suggest an additional contraceptive benefit of the addition of N-9 to condoms. *In vitro* studies have clearly demonstrated the spermicidal effects of N-9 and clinical studies have shown that N-9 even when used alone is an effective contraceptive. It is logical that its presence in the event of misuse or breakage would decrease the risk of pregnancy. ARMKEL believes it would be unwise to deny condom users this added protection.

At the same time, whatever the value of the studies discussed in the WHO/CONRAD report, they have little or no relevance to N-9 lubricated condoms or to the general U.S. user population. None of the studies examine the safety of N-9 lubricated condoms. At most, the studies showed that vaginal irritation occurs in N-9 users, but it cannot be determined whether, and to what extent, the irritation may have been caused by the act of act of intercourse. Furthermore, the studies did not provide evidence that this irritation translates into an increased risk of STD transmission.

The weight of evidence presented in the WHO/CONRAD report actually suggests a slight <u>decrease</u> in risk of STD transmission associated with N-9 use. [17/] Nonetheless, three individual studies discussed in the WHO/CONRAD

report have been selectively cited as demonstrating an increase in risk. [18]/ There was an increased risk of gonorrhea associated with N-9 use in all three of these studies, but this increase was not statistically significant in any of them. In fact, Richardson, *et al.*, concluded that the increased risk of gonorrhea very possibly resulted from chance alone. [19]/ In the study performed by Van Damme, *et al.*, there was an increased risk of HIV infection associated with N-9 use, but this increase was only marginally statistically significant in the overall analysis ($p=0.047$) and not statistically significant among women who used the study product less than an average of 3.5 times daily ($p=0.87$ for use less than 1.5 times daily; $p=0.56$ for use 1.5-3.5 times daily). [20]/ All three studies were of high-risk women (prostitutes or STD clinic attendees) in Africa or Asia. Most notably, in the Van Damme study both test and control groups reported a median of three sexual encounters per day at baseline, the N-9 study group reported using the study product a median of 2.2 times daily, and the placebo group reported using the study product a median of 2.4 times daily. [21]/ There is no basis for extrapolating these data to the general U.S. population.

Finally, even if N-9 in stand-alone products were linked to an increased risk of STDs, there is no reason to believe that this mechanism would generally apply to N-9 lubricated condoms in any case, due to the considerable protection against STDs afforded by the condom itself. Therefore, based on currently available data, there is insufficient evidence to call into question the safety of N-9 lubricated condoms.

Accordingly, we believe that the WHO/CONRAD report does not appreciably alter the benefit-risk equation for N-9 lubricated condoms. Still, the theoretical risk of STD transmission identified in the WHO/CONRAD report can be virtually eliminated by warning against N-9 lubricated condom use in two special situations. First, in the case of rectal use, there is obviously no need for the contraceptive benefit of N-9. At the same time, the data identified in the WHO/CONRAD report seem to show that rectal tissue is more susceptible to irritation than vaginal tissue. Given the absence of a benefit, we believe it would be an appropriate precaution to label N-9 lubricated condoms against rectal use in light of the theoretical risk.

Second, the data identified in the WHO/CONRAD report suggest that N-9 related risk of STD transmission, if any, would be primarily associated with multiple sex acts in the same day, such as was reported by the sex workers in the Van Damme study. As a precautionary measure, it might be prudent to caution against using N-9 lubricated condoms for multiple daily use, since the available data suggest that the theoretical risk, if it exists, is associated with multiple daily use.

Accordingly, ARMKEL believes that appropriate labeling changes for N-9 lubricated condoms would be as follows:

- Addition of a caution box: "Caution: Spermicidal Lubricants Are Not For Rectal Use Or More-Than-Once-A-Day Vaginal Use."

- Addition of additional explanatory text: "Nonoxynol-9 does not provide extra protection against HIV or other STDs. Multiple (more than once a day) use of nonoxynol-9 spermicide may cause vaginal irritation that may increase the risk of transmission of STDs or HIV."

We believe the use of this modified labeling is the most appropriate way to address the theoretical risk raised by the WHO/CONRAD report. As a practical matter, the labeling would exclude use of N-9 lubricated condoms in the two situations where the theoretical risk of N-9 is greatest (multiple daily use) or the benefit of N-9 is not applicable (rectal use). With this labeling, we believe that condoms lubricated with N-9 would continue to have a reasonable assurance of safe and effective use. At the same time, this labeling change is sufficiently specific that it would not be expected to cause public confusion about the value of condom use or otherwise lead to misuse of condoms. It is vitally important to avoid making any changes that risk causing public confusion or misuse, because condoms are an important contraceptive option and are crucial to preventing the spread of STDs.

This approach would be consistent with FDA's proposed rule regarding stand-alone N-9 products. [22/] If anything, the WHO/CONRAD report data are more applicable to such products than to N-9 lubricated condoms. The FDA's proposal would require N-9 contraceptive drug products to state in the labeling that N-9 does not protect against STDs and that more-than-once-a-day use can cause irritation which could increase the risk of STD transmission. [23/]

While this proposal does not directly affect N-9 lubricated condoms, it clearly shows FDA's conclusion that appropriate labeling changes can be used to provide reasonable assurance of safe and effective use. In this case, because N-9 lubricated condoms are one step further removed from any possible implications of the WHO/CONRAD report data, we believe that the labeling changes suggested above are clearly adequate to maintain reasonable assurance of safety and effectiveness in N-9 lubricated condoms.

Although the FDA, WHO and CDC are not proposing to ban N-9, a few outside groups have issued calls for a ban. We believe that there is no evidence to support this kind of drastic action, which could unintentionally cause consumer confusion and upset public perception about the proven value of condoms, to the detriment of the public health. Also, we believe that a ban would be inconsistent with FDA's general statutory mandate to permit products to be marketed if there is reasonable assurance of their safety and effectiveness under the labeled conditions of use. Here, the statutory requirement is clearly met.

1/ ARMKEL, LLC, the maker of TROJAN brand condoms, is a joint venture comprised of Church & Dwight Co., Inc. and Kelso & Company

2/ 47 Fed. Reg. 49,021 (Oct. 29, 1982) (final rule *codified at* 21 C.F.R. § 884.5310).

3/ Condoms must generally meet standards based on ASTM Standard Specification for Rubber Contraceptives (Male Condoms), D3492 pertaining to rubber quality, toxicity, size, thickness, burst pressure, leakage and package integrity. *See* FDA's Guidance, "Latex Condoms for Men: Information for 510(k) Premarket Notifications: Use of Consensus Standards for Abbreviated Submissions" (July 23, 1998).

4/ 21 C.F.R. § 801.435.

5/ 47 Fed. Reg. at 49,022.

6/ McGreevy, M.,Condom merchandising: The key to untapped sales and profits. Exposé 6(11):24-26, 2003. (see http://www.ecrm-online.com/Expose/V6_11/24.pdf)

7/ WHO/CONRAD Technical Consultation of Nonoxynol-9, World Health Organization, Geneva, 9-10 October 2001. Summary Report. Hereinafter, "WHO/CONRAD report."

8/ The Weinberg Group is a worldwide scientific and regulatory consulting organization with recognized expertise in epidemiology and biostatistics, among a number of other disciplines.

9/ WHO/CONRAD report at 4.

10/ *Id.*

11/ *Id.*

12/ *Id.* at 8, 16.

13/ *Id.* at 6.

14/ 47 Fed. Reg. 18,670, 18,672 (Apr. 30, 1982) (preamble to proposed rule).

15/ Weinberg Report at 21.

16/ *Id.* at 24, 25.

17/ WHO/CONRAD report at 16.

18/ Richardson BA, Lavreys L, Martin HLJ, et al. Evaluation of a low-dose nonoxynol-9 gel for the prevention of sexually transmitted diseases: a randomized clinical trial. Sexually Transmitted Diseases 2001; 28:394-400. Roddy RE, Zekeng L, Ryan KA, Tamoufe U, Tweedy KG. Effect of nonoxynol-9 gel on urogenital gonorrhea and chlamydia infection: A randomized control trial. JAMA 2002; 287:1117-22. Van Damme L, Ramjee G, Alary M, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-transmission among female sex workers. *Lancet* 2002 360:971-7.

19/ Richardson, *et al.* at 398.

20/ Van Damme, *et al.* at 974, 975.

21/ Van Damme, *et al.* at 973, 974.

22/ *Over-the-Counter Vaginal Contraceptive Drug Products Containing Nonoxynol-9; Required Labeling*, 68 Fed. Reg. 2254 (Jan. 16, 2003).

23/ *Id.* at 2259.

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ARMKEL agrees with the approach taken by FDA in the CDER Proposed Rule to allow continued availability of N-9-containing contraceptives while requiring additional cautionary labeling to address those limited user groups that should avoid using the products. We strongly believe that condom labeling should provide appropriate cautionary information in a way that does not unduly alarm the public or cause confusion or misuse of condoms. In line with this, our company has been engaged in ongoing

discussions with CDRH to develop appropriately revised labeling to inform N-9 lubricated condom users that the products are not for rectal use or more-than-once-a-day vaginal use, while clearly communicating, consistent with the Proposed Rule, that:

> **Correct use of a latex condom with every sexual act will help reduce the risk of getting the AIDS virus [HIV] and other STDs from infected partners.**

Attached to this letter is our ***White Paper*** on the subject of ***Nonoxynol-9 Lubricated Condoms***, which sets out in more detail ARMKEL's position in support of appropriately labeled N-9 lubricated condoms.

Thank you for this opportunity to provide our views on this important subject.

Respectfully submitted,

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Attachment: ***White Paper, Nonoxynol-9 Lubricated Condoms***

ARMKEL, LLC

White Paper

Nonoxynol-9 Lubricated Condoms

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Even the theoretical risk identified in the WHO/CONRAD report can be virtually eliminated by warning against the use of N-9 lubricated condoms for rectal intercourse or for high-frequency vaginal use (multiple daily acts of sexual intercourse). Although the risk is theoretical, ARMKEL, LLC [1/] believes it is appropriate to modify the labeling of N-9 lubricated condoms to caution against use in these two special situations. This change will provide assurance that such condoms are safe and effective when used according to the labeling, without unduly alarming the public or causing confusion or misuse of condoms.

I. BACKGROUND

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The WHO/CONRAD report summarizes 16 studies in which the effect of N-9 on epithelial disruption in the vagina was examined. The report concluded that the data "showed a trend towards a greater frequency of disruption with greater frequency of use and higher doses of N-9." [9] However, the report also concludes that "infrequent use of products containing low doses of N-9 is probably safe" (emphasis added). [10] The report also indicates that there are "major obstacles" to interpreting the data. In particular, there is no known way to "distinguish between epithelial changes resulting from sexual intercourse and the impact of the study product." Furthermore, "the clinical significance of signs and symptoms of [epithelial] disruption is not known." [11]

Thus, while there is evidence that N-9 use alone can result in vaginal irritation, there is no evidence that this irritation translates into an increased risk of STD transmission. The WHO/CONRAD report indicates that when data from all of the relevant studies are combined and analyzed together there is no increased

risk of gonorrhea, chlamydia, cervical infection, trichomoniasis, bacterial vaginosis, candidiasis, or HIV associated with N-9 use. [12/]

The WHO/CONRAD report focused on N-9 in stand-alone products. No studies were discussed in the report regarding the safety of N-9 lubricated condoms. While there may be a theoretical link between N-9 and increased risk of STDs based upon irritation, the WHO/CONRAD report shows that this link has not been established, even for N-9 when used alone. When N-9 is combined with a condom, the theoretical risk would not generally apply, because the condom itself provides very significant protection against STDs. Stated differently, the condom provides a very high level of protection against infection even if the theoretical risk of N-9-induced irritation is given credence.

2. Prevention of STDs

The WHO/CONRAD report discusses the effectiveness of N-9 in prevention of STD transmission. Several studies showed a statistically significant reduction in gonorrhea and chlamydia infection with use of N-9 products. Most studies, however, did not demonstrate statistically significant reductions in STDs. A meta-analysis was performed combining data from almost 5000 women in nine different studies. This analysis showed that there was a numerical reduction in infection with gonorrhea, chlamydia, trichomoniasis, bacterial vaginosis, and candidiasis, but that none of these reductions were statistically significant. The reductions for chlamydia, trichomoniasis, and bacterial vaginosis were very close to

being statistically significant. These studies also showed a numerical increase in HIV infection that was not statistically significant.

As before, none of the studies in this analysis involved the use of N-9 lubricated condoms. Thus, it cannot be determined what effect N-9 has in reducing the risk of STDs, over and above the use of a condom without N-9.

3. Contraception

The WHO/CONRAD report discusses the results of 31 clinical studies that measured pregnancy rates among women using spermicide (including N-9) alone. These studies had certain limitations, but the report concluded that "use of spermicide alone reduces risk of pregnancy compared with use of no product." [13/] The report also notes that spermicide is often used in conjunction with other barrier methods, such as diaphragms, cervical caps, sponges and condoms. There is some evidence that diaphragms used with spermicide are more effective contraceptives than diaphragms without spermicide. However, the WHO/CONRAD report does not cite any well-controlled studies comparing the contraceptive effectiveness of N-9 lubricated condoms with that of other lubricated condoms. As FDA has pointed out, such clinical studies "would be difficult to conduct and may not produce evidence justifying the effort of collecting it." [14/]

B. The Weinberg Group Report

The Weinberg Group, Inc, (Washington, DC), at the request of ARMKEL, performed an extensive literature search relating to the safety of N-9

("the Weinberg Report"). Their literature review included estimation of background rates of tissue injury, safety profile by delivery vehicle, and safety profile by ingredient. Injury to vaginal, penile and rectal tissue were all included. In addition, the report discusses the correlation between objective and subjective measures of tissue injury.

The Weinberg report specifically identified studies that compared condom use with and without N-9. Of eleven studies identified in which condoms were used, only two involved N-9 lubricated condoms. The authors concluded that "[t]hese two studies indicate that N-9 condoms are not associated with more safety events than are lubricated condoms [that do not employ N-9]."[15]/ The other nine studies involved condom use in conjunction with N-9 gels or films. Several of these studies showed a numerical increase in adverse events in the N-9 groups, but none of the differences were determined to be statistically significant.

As with the WHO/CONRAD report, the Weinberg report also evaluated studies in which stand-alone N-9 products (gels, films, suppositories) were used by themselves (without condoms) and compared to placebo. There were no studies of N-9 film that reported statistically significant differences between N-9 and placebo groups. One study examining gel use found a statistically significant elevation of genital symptoms among N-9 users but the study authors acknowledged that they could not discern what percentage of the lesions in the N-9 arm were due to N-9 versus intercourse itself.

The Weinberg report's overall female urogenital safety conclusions on the total of eighteen studies stated that "[n]one of the studies was of adequate quality to draw solid conclusions. Most had important methodological limitations including small sample size, poor retention (high drop out), and statistical methodology was poorly described. . . . Overall, these studies do not demonstrate a causal relationship between N-9 and tissue damage."[16]/

The Weinberg report also examined dose response relationships, as well as penile and rectal adverse events. Most of the studies examined in these respects were inconclusive, and in many cases the studies were not of sufficient quality to adequately address safety issues

III. PUBLIC HEALTH ANALYSIS

The WHO/CONRAD report and other recently published high profile study reports have prompted various public health organizations to modify messages relating to N-9. FDA's Center for Drug Evaluation and Research has issued a proposed rule that would require revised product labeling addressing the possible risks associated with OTC drug products that contain N-9. ARMKEL has been working with FDA's Center for Devices and Radiological Health (condoms are regulated as medical devices), along with other U.S. public health agencies, industry members and others to develop appropriately revised labeling for condoms.

ARMKEL, a manufacturer of N-9 lubricated condoms, believes there is

considerable value in maintaining the availability of N-9 lubricated condoms with revised labeling. Our rationale is as follows:

When used properly, condoms are themselves an extremely effective method of contraception. But condoms are not always used exactly as directed and they sometimes may slip or break, allowing seminal fluid to leak into the vagina. In these cases, there is considerable evidence to suggest an additional contraceptive benefit of the addition of N-9 to condoms. *In vitro* studies have clearly demonstrated the spermicidal effects of N-9 and clinical studies have shown that N-9 even when used alone is an effective contraceptive. It is logical that its presence in the event of misuse or breakage would decrease the risk of pregnancy. ARMKEL believes it would be unwise to deny condom users this added protection.

At the same time, whatever the value of the studies discussed in the WHO/CONRAD report, they have little or no relevance to N-9 lubricated condoms or to the general U.S. user population. None of the studies examine the safety of N-9 lubricated condoms. At most, the studies showed that vaginal irritation occurs in N-9 users, but it cannot be determined whether, and to what extent, the irritation may have been caused by the act of act of intercourse. Furthermore, the studies did not provide evidence that this irritation translates into an increased risk of STD transmission.

The weight of evidence presented in the WHO/CONRAD report actually suggests a slight <u>decrease</u> in risk of STD transmission associated with N-9 use. [17/] Nonetheless, three individual studies discussed in the WHO/CONRAD

report have been selectively cited as demonstrating an increase in risk. [18]/ There was an increased risk of gonorrhea associated with N-9 use in all three of these studies, but this increase was not statistically significant in any of them. In fact, Richardson, *et al.*, concluded that the increased risk of gonorrhea very possibly resulted from chance alone. [19]/ In the study performed by Van Damme, *et al.*, there was an increased risk of HIV infection associated with N-9 use, but this increase was only marginally statistically significant in the overall analysis (p=0.047) and not statistically significant among women who used the study product less than an average of 3.5 times daily (p=0.87 for use less than 1.5 times daily; p=0.56 for use 1.5-3.5 times daily). [20]/ All three studies were of high-risk women (prostitutes or STD clinic attendees) in Africa or Asia. Most notably, in the Van Damme study both test and control groups reported a median of three sexual encounters per day at baseline, the N-9 study group reported using the study product a median of 2.2 times daily, and the placebo group reported using the study product a median of 2.4 times daily. [21]/ There is no basis for extrapolating these data to the general U.S. population.

Finally, even if N-9 in stand-alone products were linked to an increased risk of STDs, there is no reason to believe that this mechanism would generally apply to N-9 lubricated condoms in any case, due to the considerable protection against STDs afforded by the condom itself. Therefore, based on currently available data, there is insufficient evidence to call into question the safety of N-9 lubricated condoms.

Accordingly, we believe that the WHO/CONRAD report does not appreciably alter the benefit-risk equation for N-9 lubricated condoms. Still, the theoretical risk of STD transmission identified in the WHO/CONRAD report can be virtually eliminated by warning against N-9 lubricated condom use in two special situations. First, in the case of rectal use, there is obviously no need for the contraceptive benefit of N-9. At the same time, the data identified in the WHO/CONRAD report seem to show that rectal tissue is more susceptible to irritation than vaginal tissue. Given the absence of a benefit, we believe it would be an appropriate precaution to label N-9 lubricated condoms against rectal use in light of the theoretical risk.

Second, the data identified in the WHO/CONRAD report suggest that N-9 related risk of STD transmission, if any, would be primarily associated with multiple sex acts in the same day, such as was reported by the sex workers in the Van Damme study. As a precautionary measure, it might be prudent to caution against using N-9 lubricated condoms for multiple daily use, since the available data suggest that the theoretical risk, if it exists, is associated with multiple daily use.

Accordingly, ARMKEL believes that appropriate labeling changes for N-9 lubricated condoms would be as follows:

- Addition of a caution box: "Caution: Spermicidal Lubricants Are Not For Rectal Use Or More-Than-Once-A-Day Vaginal Use."

- Addition of additional explanatory text: "Nonoxynol-9 does not provide extra protection against HIV or other STDs. Multiple (more than once a day) use of nonoxynol-9 spermicide may cause vaginal irritation that may increase the risk of transmission of STDs or HIV."

We believe the use of this modified labeling is the most appropriate way to address the theoretical risk raised by the WHO/CONRAD report. As a practical matter, the labeling would exclude use of N-9 lubricated condoms in the two situations where the theoretical risk of N-9 is greatest (multiple daily use) or the benefit of N-9 is not applicable (rectal use). With this labeling, we believe that condoms lubricated with N-9 would continue to have a reasonable assurance of safe and effective use. At the same time, this labeling change is sufficiently specific that it would not be expected to cause public confusion about the value of condom use or otherwise lead to misuse of condoms. It is vitally important to avoid making any changes that risk causing public confusion or misuse, because condoms are an important contraceptive option and are crucial to preventing the spread of STDs.

This approach would be consistent with FDA's proposed rule regarding stand-alone N-9 products. [22/] If anything, the WHO/CONRAD report data are more applicable to such products than to N-9 lubricated condoms. The FDA's proposal would require N-9 contraceptive drug products to state in the labeling that N-9 does not protect against STDs and that more-than-once-a-day use can cause irritation which could increase the risk of STD transmission. [23/]

While this proposal does not directly affect N-9 lubricated condoms, it clearly shows FDA's conclusion that appropriate labeling changes can be used to provide reasonable assurance of safe and effective use. In this case, because N-9 lubricated condoms are one step further removed from any possible implications of the WHO/CONRAD report data, we believe that the labeling changes suggested above are clearly adequate to maintain reasonable assurance of safety and effectiveness in N-9 lubricated condoms.

Although the FDA, WHO and CDC are not proposing to ban N-9, a few outside groups have issued calls for a ban. We believe that there is no evidence to support this kind of drastic action, which could unintentionally cause consumer confusion and upset public perception about the proven value of condoms, to the detriment of the public health. Also, we believe that a ban would be inconsistent with FDA's general statutory mandate to permit products to be marketed if there is reasonable assurance of their safety and effectiveness under the labeled conditions of use. Here, the statutory requirement is clearly met.

1/ ARMKEL, LLC, the maker of TROJAN brand condoms, is a joint venture comprised of Church & Dwight Co., Inc. and Kelso & Company

2/ 47 Fed. Reg. 49,021 (Oct. 29, 1982) (final rule *codified at* 21 C.F.R. § 884.5310).

3/ Condoms must generally meet standards based on ASTM Standard Specification for Rubber Contraceptives (Male Condoms), D3492 pertaining to rubber quality, toxicity, size, thickness, burst pressure, leakage and package integrity. *See* FDA's Guidance, "Latex Condoms for Men: Information for 510(k) Premarket Notifications: Use of Consensus Standards for Abbreviated Submissions" (July 23, 1998).

4/ 21 C.F.R. § 801.435.

5/ 47 Fed. Reg. at 49,022.

6/ McGreevy, M.,Condom merchandising: The key to untapped sales and profits. Exposé 6(11):24-26, 2003. (see http://www.ecrm-online.com/Expose/V6_11/24.pdf)

7/ WHO/CONRAD Technical Consultation of Nonoxynol-9, World Health Organization, Geneva, 9-10 October 2001. Summary Report. Hereinafter, "WHO/CONRAD report."

8/ The Weinberg Group is a worldwide scientific and regulatory consulting organization with recognized expertise in epidemiology and biostatistics, among a number of other disciplines.

9/ WHO/CONRAD report at 4.

10/ *Id.*

11/ *Id.*

12/ *Id.* at 8, 16.

13/ *Id.* at 6.

14/ 47 Fed. Reg. 18,670, 18,672 (Apr. 30, 1982) (preamble to proposed rule).

15/ Weinberg Report at 21.

16/ *Id.* at 24, 25.

17/ WHO/CONRAD report at 16.

18/ Richardson BA, Lavreys L, Martin HLJ, et al. Evaluation of a low-dose nonoxynol-9 gel for the prevention of sexually transmitted diseases: a randomized clinical trial. Sexually Transmitted Diseases 2001; 28:394-400. Roddy RE, Zekeng L, Ryan KA, Tamoufe U, Tweedy KG. Effect of nonoxynol-9 gel on urogenital gonorrhea and chlamydia infection: A randomized control trial. JAMA 2002; 287:1117-22. Van Damme L, Ramjee G, Alary M, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-transmission among female sex workers. *Lancet* 2002 360:971-7.

19/ Richardson, *et al.* at 398.

20/ Van Damme, *et al.* at 974, 975.

21/ Van Damme, *et al.* at 973, 974.

22/ *Over-the-Counter Vaginal Contraceptive Drug Products Containing Nonoxynol-9; Required Labeling*, 68 Fed. Reg. 2254 (Jan. 16, 2003).

23/ *Id.* at 2259.