

Authority: 49 U.S.C. 106(g), 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR, 1959–1963 Comp., p. 389.

§ 71.1 [Amended]

■ 2. The incorporation by reference in 14 CFR 71.1 of Federal Aviation Administration Order 7400.9R, *Airspace Designations and Reporting Points*, signed August 15, 2007, and effective September 15, 2007, is amended as follows:

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Paragraph 6002 Class E Airspace Designated as Surface Areas.

AAL AK E2 McGrath, AK [Revised]

McGrath, McGrath Airport, AK
(Lat. 62°57'10" N., long. 155°36'20" W.)

That airspace within a 7.6-mile radius of the McGrath Airport. This Class E airspace area is effective during the specific dates and times established in advance by a Notice to Airmen. The effective date and time will thereafter be continuously published in the Airport/Facility Directory.

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Paragraph 6005 Class E Airspace Extending Upward from 700 feet or More Above the Surface of the Earth.

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AAL AK E5 McGrath, AK [Revised]

McGrath, McGrath Airport, AK
(Lat. 62°57'10" N., long. 155°36'20" W.)

That airspace extending upward from 700 feet above the surface within a 8.1-mile radius of the McGrath Airport and within 4 miles north and 8 miles south of the 123° bearing from the McGrath Airport, AK extending from the 8.1-mile radius to 16 miles southeast of the McGrath Airport, AK, and within 4 miles east and west of the 008° bearing from the McGrath Airport, AK, extending from the 8.1-mile radius to 11.2 miles north of the McGrath Airport, AK; and that airspace extending upward from 1,200 feet above the surface within a 74-mile radius of the McGrath Airport.

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Issued in Anchorage, AK, on December 11, 2007.

Anthony M. Wylie,

Manager, Alaska Flight Services Information Area Group.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 1980N–0280] (formerly Docket No. 80N–0280)
RIN 0910–AF44

Over-the-Counter Vaginal Contraceptive and Spermicide Drug Products Containing Nonoxynol 9; Required Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing new warning statements and other labeling information for all over-the-counter (OTC) vaginal contraceptive drug products (also known as spermicides, hereinafter referred to as vaginal contraceptives or vaginal contraceptives/spermicides) containing nonoxynol 9 (N9). These warning statements will advise consumers that vaginal contraceptives/spermicides containing N9 do not protect against infection from the human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS), or against getting other sexually transmitted diseases (STDs). The warnings and labeling information will also advise consumers that use of vaginal contraceptives and spermicides containing N9 can irritate the vagina and rectum and may increase the risk of getting the AIDS virus (HIV) from an infected partner. This final rule is part of FDA's ongoing review of OTC drug products. FDA is issuing this final rule after considering public comments on its proposed regulation, and all relevant data and information on N9 that have come to our attention.

DATES: *Effective Date:* This rule is effective June 19, 2008.

Compliance Date: The compliance date for all products subject to this final rule, including products with annual sales less than \$25,000, is June 19, 2008.

FOR FURTHER INFORMATION CONTACT:

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I. Background

In the **Federal Register** of January 16, 2003 (68 FR 2254), FDA (we) published a proposed rule (the proposed rule) to require new labeling warning statements for all OTC vaginal contraceptive drug products containing N9. These proposed warning statements are intended to

advise consumers that vaginal contraceptives containing N9 do not protect against infection from HIV, the virus that causes AIDS, nor against getting other STDs. The warnings also would advise consumers that frequent use of vaginal contraceptives containing N9 can increase vaginal irritation, and that increased vaginal irritation from the use of N9 may increase the possibility of becoming infected with the AIDS virus (HIV) or other STDs from infected partners. The proposed rule contains the data and scientific evidence that we considered to require these warnings.

N9 is a nonionic surfactant that works as a vaginal contraceptive (spermicide) by damaging the cell membrane of sperm. As stated in the proposed rule (68 FR 2254 at 2255), there are in vitro studies showing that N9 causes damage to the cell wall of certain STD pathogens and has activity against certain bacterial and viral STD pathogens, including HIV. Because N9 inhibits the replication of the AIDS virus (HIV) and other STD pathogens in vitro, it has been suggested over the years that N9 might help prevent or reduce the risk of transmission of the AIDS virus and other STDs in humans (68 FR 2254 at 2255). Thus, research was undertaken to see if N9 would prevent HIV and STDs. In the proposed rule, FDA discussed the evidence that demonstrates that N9 does not prevent or reduce the risk of transmission of the AIDS virus and other STDs in humans (68 FR 2254 to 2259). FDA also discussed recent scientific data that suggest that frequent use of N9 may increase the risk of HIV

infection for women at risk for HIV (68 FR 2254 to 2259). Thus, FDA issued the proposed rule to provide a clear, consistent message that N9 is not effective in preventing HIV transmission, and that N9 can facilitate transmission of the disease. We also proposed labeling (warnings and other information) to encourage the use of condoms as a method to help sexually active persons reduce the risk of becoming infected with the AIDS virus (HIV) and other STDs. We requested feedback on whether the proposed warnings adequately convey the safety concerns about N9 and whether there are additional data to support, expand, or refute the proposed warnings.

In response to the proposed rule, we received 153 comments. Two comments were submitted from industry, 8 from consumer advocacy groups, 10 from health associations, 16 from health professionals, and 117 from individual consumers. These comments are on display in the Division of Dockets Management. For access to the docket to read background documents or comments received, go to <http://www.fda.gov/ohrms/dockets/default.htm> and insert the docket number (s), found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5360 Fishers Lane, rm. 1061, Rockville, MD 20852. We are responding to the comments, and discussing some additional data that has come to our attention, in this document.

The majority of comments from consumers, consumer advocacy groups, health organizations, and health professionals supported FDA for proposing warnings for N9 vaginal contraceptive OTC drug products that inform consumers that N9 does not protect against HIV and other STDs and that frequent use (more than once a day) may increase the risk of infection of HIV from infected partners. The comments stated that the proposed warnings will inform consumers of the risks so that they can make responsible health care decisions. Forty-six consumers reported getting vaginal irritation, burning, itching, swelling, or increased yeast and urinary infections after using contraceptive products containing N9. These comments stated that the proposed labeling is necessary to warn consumers of the risks related to irritation associated with N9 and to educate consumers who mistakenly believe that vaginal contraceptives/spermicides containing N9 also prevent STDs.

Some comments did not support the proposed warnings. Other comments asked for clarification of the warning language, recommended changes in the wording of the warning language, or provided data to expand the proposed warnings. After reviewing the comments, FDA has revised the proposed warnings in this final rule. The differences between the warning language in the proposed and final rules are as follows:

TABLE 1.—DIFFERENCES IN THE WARNING LANGUAGE IN THE PROPOSED AND FINAL RULES

Proposed Rule	Final Rule
<p>"For vaginal use only"</p>	<p>"For vaginal use only Not for rectal (anal) use" We explain the reason for this change in section II.H, comment 12, of this document.</p>
<p>"Sexually transmitted diseases (STDs) alert: This product does not protect against the AIDS virus (HIV) or other STDs"</p>	<p>"Sexually transmitted diseases (STDs) alert: This product does not protect against HIV/AIDS or other STDs and may increase the risk of getting HIV from an infected partner" We discuss this change in section II.B.2, comment 3 of this document.</p>
<p>"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."</p>	<p>"Do not use if you or your sex partner has HIV/AIDS. If you do not know if you or your sex partner is infected, choose another form of birth control." "When using this product you may get vaginal irritation (burning, itching, or a rash)" We discuss these changes in sections II.B.2, comment 3 and II.C, comment 5 of this document.</p>

TABLE 1.—DIFFERENCES IN THE WARNING LANGUAGE IN THE PROPOSED AND FINAL RULES—Continued

Proposed Rule	Final Rule
<ul style="list-style-type: none"> • “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.” 	<ul style="list-style-type: none"> • “studies have raised safety concerns that products containing the spermicide nonoxynol 9 can irritate the vagina and rectum. Sometimes this irritation has no symptoms. This irritation may increase the risk of getting HIV/AIDS from an infected partner” We discuss this change in section II.B.2, comment 3 of this document. • “you can use nonoxynol 9 for birth control with or without a diaphragm or condom if you have sex with only one partner who is not infected with HIV and who has no other sexual partners or HIV risk factors”. We discuss this change in sections II.F.3, comment 10 and II.G, comment 11 of this document. • “use a latex condom without nonoxynol 9 if you or your sex partner has HIV/AIDS, multiple sex partners, or other HIV risk factors”. We discuss this change in section II.F.2, comment 9 of this document. • “ask a health professional if you have questions about your best birth control and STD prevention methods”. We discuss this change in section II.J.2, comment 15 of this document.
<ul style="list-style-type: none"> • “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”. 	<ul style="list-style-type: none"> • “when used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate, the risk of catching or spreading HIV, the virus that causes AIDS. We discuss this change in section II.F.1, comment 8 of this document.
<p>Use of N9 products may increase the risk of HIV and other STDs.</p>	<p>Use of N9 products is associated with an increased risk of HIV. We discuss this change in section II.I, comment 13 of this document.</p>

We describe and respond to the comments received in section II of this document.

II. Comments on the Proposed Rule and FDA’s Responses

A. Should N9 Remain Available as an Active Ingredient in OTC Vaginal Contraceptive Drug Products?

(Comment 1) Some comments stated that N9 vaginal contraceptive drug products should be removed from the OTC market or changed from OTC to prescription status for the following reasons:

- N9 does not protect against HIV or STDs.
- N9 causes damage to the vaginal lining and increases the risk of contracting HIV due to this vaginal irritation.
- Many new cases of HIV and STDs will develop if contraceptives with N9 are available without consultation with a health professional.
- Consumers who may not see, read, understand, or follow the advice contained on the warning labels need to be protected from the risks of using N9. They should have to see a health professional before using products containing N9.

Some of these comments also suggested that, alternatively, manufacturers should be required to reformulate their

products with other safe and effective spermicides or microbicides.

Many other comments stated that N9 products should remain an OTC contraceptive option for women at low risk for HIV infection for the following reasons:

- N9 products are effective in preventing pregnancy, particularly when used with a barrier method such as a condom or diaphragm.
- N9 products are a contraceptive option for women who cannot tolerate hormone-based birth control methods.
- N9 products are a contraceptive option for women at low risk for HIV and STDs.
- N9 products represent one of the few methods available for women that are controlled by women.
- N9 products offer a “substantial” benefit to a “small but important” group of users.

(Response) FDA does not agree that vaginal contraceptive drug products containing N9 should be removed from the OTC marketplace. As part of FDA’s review of the safety and effectiveness of this class of OTC drugs, the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products classified N9 as Category I (safe and effective) as a spermicide for the prevention of pregnancy on December 12, 1980 (45 FR 82014 at 82028). Comments were received following

publication of the panel’s report and additional scientific data became available. FDA published the proposed rule on OTC vaginal contraceptive drug products on February 2, 1995 (60 FR 6892). In that proposed rule, FDA considered N9 safe as a vaginal contraceptive; however, data indicated that its effectiveness in final product formulations was highly variable. Therefore, FDA proposed clinical trials for N9 spermicidal products to validate their effectiveness in final formulations.

In November 1996, four FDA advisory committees (Nonprescription Drugs, Reproductive Health Drugs, Antiviral Drugs, and Anti-infective Drugs) met to discuss the type and quality of data needed to support and ensure the spermicidal effectiveness of N9 in final formulations. The advisory committees concluded that the existing data provided evidence of some effectiveness, but they had concerns about variability in dose, different formulations, and duration of effect. The advisory committees recommended that FDA allow interim marketing of N9 vaginal contraceptive drug products pending further clinical trials (68 FR 2254 at 2255).

Current data suggest that the number of women out of 100 who become pregnant in the first year of typical use of N9 spermicide drug products is as follows (Ref. 1):

- 16 for the diaphragm with spermicide.
- 16 to 32 (depending on whether the women have had prior births) for the cervical cap with spermicide.
- 29 for spermicides alone (gel, cream, foam, film, suppository).

The number of women who become pregnant using no contraception is 85 out of 100 (Ref. 1). The Centers for Disease Control and Prevention (CDC) (Ref. 2) report that the combined use of diaphragms with N9 spermicide prevents approximately 460,000 pregnancies in the United States each year. It is important to the public health that consumers have access to multiple methods of contraception to choose from that help prevent unplanned pregnancy.

FDA is currently reviewing newly published data regarding the efficacy of N9 containing spermicides (Ref. 3), and we will publish our conclusions in a future issue of the **Federal Register**. These data are from a clinical trial which compares the effectiveness and safety of five spermicides, which include three gels containing 52.5 milligrams (mg), 100 mg, and 150 mg of N9 per dose and a film and a suppository, each containing 100 mg of N9 per dose. In the meantime, based on its history of safety and effectiveness, we have determined that N9 should remain on the market while we complete our review. Based on the information currently available, we have also determined that women at low risk for HIV can safely use N9 products for their contraceptive needs and that the intervention of a doctor or health care provider is not necessary.

B. What Issues Were Raised by Comments That Did Not Support the Proposed Warning Statements?

1. Will Warning Labels Be Seen, Understood, or Followed?

(Comment 2) Two comments stated that FDA's proposed warnings may not adequately protect consumers against the health risks posed by N9 products because consumers may not see, read, understand, or follow the advice contained on the warning labels. One of the comments referred to a study sponsored by the National Council on Patient Information and Education (NCPIE), conducted in 2001, which surveyed adult consumers and health care professionals on the self-medicating behaviors of the American public. The comment stated that the survey clearly established that consumers do not consistently read caution labels. The comment also mentioned a 1997 study by "Sansgiry et

al." of industry labeling practices which stated, according to the comment, that as the OTC package size increased, the font size used for the product increased, except that the font size for warnings remained constant. The comment stated that the study also showed that 22 percent of the product packages examined used smaller than 6-point font type for warnings. The comment concluded from this study that consumers may have difficulty seeing and reading the N9 warning language. The second comment stated that many consumers consider OTC drug products to be safe and present no risks because they are available without a prescription. Thus, consumers may ignore the product labeling because of this false impression. The comment recommended that FDA use consumer surveys and focus groups to test for comprehension of the proposed labeling before publishing a final rule mandating specific language.

(Response) FDA thinks that the warning statements for N9 vaginal contraceptive drug products will be seen, read, understood, and followed by consumers. We are aware of the studies cited by the comment, i.e., the Sansgiry, Cady, and Patil study (Ref. 4), which described OTC industry labeling practices at that time, and the NCPIE study (Ref. 5) that examined the self-medicating behaviors of the American public, including what information consumers seek when reading an OTC drug product label. These studies reinforced the need for FDA to improve the OTC drug product label and also to enhance educational programs to teach consumers about the risks and benefits of OTC drugs. FDA issued new labeling requirements for OTC drug products on March 17, 1999 (64 FR 13254). This labeling regulation, codified in 21 CFR 201.66, requires OTC drug products to be labeled with a standardized "Drug Facts" label. The "Drug Facts" label offers a more structured, organized, and compact presentation of the product information, which allows consumers to process the information with improved understanding, and provides clear signals regarding important information. The new requirements include a 6-point minimum type size, and bolded type headings and subheadings. When the warning requirements in this final rule for OTC vaginal contraceptive drug products containing N9 become effective, all manufacturers will be required to revise their label using the "Drug Facts" format. Use of the revised labeling in the "Drug Facts" format will enable consumers to better read and understand the information presented

and apply the information to the safe and effective use of OTC vaginal contraceptive drug products.

Additionally, FDA is involved in various initiatives to encourage awareness of the safe and effective use of drugs and the importance of reading drug labels. FDA provides consumer articles, public service announcements, websites, etc., and also partners with many organizations to promote better understanding of the risks and benefits of drug products. For example, in cooperation with FDA, the Consumer Healthcare Products Association (CHPA) and NCPIE's "Be MedWise" campaign provide information to consumers on the new OTC drug labels.

2. "Are the Warnings Supported by the Scientific Literature?"

(Comment 3) Three comments stated that FDA's proposed warning language for N9 vaginal contraceptive drug products implies a link between the use of N9 and an increased risk of HIV that is not sufficiently supported by the scientific literature. These comments stated that the proposed warnings will frighten consumers in a manner that could affect the continued availability of a safe and effective contraceptive. The first comment contended that FDA relies primarily on two studies to support its position that there is a link between the use of N9 vaginal contraceptive drug products and an increased risk of HIV infection as follows: (1) The Van Damme et al. study (2002) (Ref. 6) and (2) the Kreiss et al. study (1992) (Ref. 7). The comment provided the following reasons why the Van Damme et al. study should not be used to support FDA's proposed warnings for N9 products:

- Twenty percent of the study subjects were lost to followup (so the investigators never determined the HIV status of these participants).
- The results between the two test groups (N9 and placebo) were "barely" significant ($p=0.047$).
- The placebo may have had a protective effect.
- A much higher number of unprotected anal sex acts were reported from one of the study centers (Durban) where the most HIV seroconversions (conversions from HIV negative status to HIV positive status) occurred. The comment also contended that the Kreiss et al. study should not be used to support FDA's proposed warnings for N9 products because:
 - The study was terminated early when it was determined that the HIV seroconversion results became inconsistent with the hypothesis that N9 has a clinically beneficial effect in

preventing HIV. The statistical analysis of the data at the time the study was terminated did not support a statistically significant conclusion that N9 increased the risk of HIV transmission.

- The comparator product was changed midstream, indicating design problems.
- More women had preexisting genital ulcers in the N9 test group, indicating randomization problems.
- The sponge dosage form could raise safety issues not associated with other dosage forms.

This comment added that FDA did not consider the results and conclusions of two other studies, Roddy et al. (1998) (Ref. 8) and Richardson et al. (2001) (Ref. 9). The comment stated that these studies either support a conclusion opposite to the Van Damme et al. and Kreiss et al. studies or weaken the conclusion that frequent use of N9 vaginal contraceptives increases the risk of HIV infection from an infected partner. The comment concluded that the link between N9 use and an increased risk of HIV infection is speculation. The comment requested that FDA remove the following proposed warning language that links N9 use with an increased risk of HIV infection:

- “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.”

- “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.”

The comment recommended the following language, which it contended more accurately reflects the known science and places the warnings in a more relevant context:

- “Ask a doctor before use if you have frequent sex (more than three times a day). Frequent use (more than three times a day) of nonoxynol 9 may

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.”

- “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 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, see a doctor or other health professional for your best birth control and methods to prevent STDs.”

The second comment stated that the Van Damme et al. study results are “exploratory” and that the study’s “generalizability” is a problem because the subjects were sex workers and had highly “atypical” sexual activity. This comment contended that previous trials of N9, conducted in sex workers, have shown conflicting results and, taken together, do not show a harmful or a protective effect. The third comment expressed similar concerns about the Van Damme study’s generalizability.

(Response) FDA believes that the proposed warning language, which implies a link between frequent use of N9 vaginal contraceptive drug products and an increased risk of HIV, is supported by the scientific literature. As discussed elsewhere in this document, we are deleting the term “frequent” from the labeling requirements of this final rule because we believe that if a woman is at risk of HIV/AIDS, she should not be using N9 products, regardless of the frequency of use (see section J.1 of this document). In the proposed rule, FDA cited many studies that demonstrated that daily use of N9 products causes vaginal irritation (i.e., inflammatory changes in the epithelial cells lining the vagina and disruption of these epithelial cells), and causes disruption of the vaginal flora (68 FR 2254 at 2254 to 2258). Some studies suggested that the risk of these adverse events can be increased by frequent or

chronic use of N9 products. In general, the various studies cited in the proposed rule defined infrequent or low frequency use as “use once a day or less.” It appears from these studies that infrequent use does not result in an increased rate of epithelial disruption. Therefore, FDA defined frequent use in the proposed rule as “more than once a day” and believes that the scientific literature supports the statement that frequent use (more than once a day) can increase vaginal irritation.

In the proposed rule, FDA discussed studies that demonstrated that frequent use of N9 products causes increased disruption of the vaginal epithelium which may increase the risk of transmission of the AIDS virus (HIV). The most pivotal of these studies is the Van Damme et al. study (cited at 68 FR 2254 at 2255) (Ref. 6). This was a randomized, placebo-controlled clinical trial to assess the effectiveness of a vaginal gel containing N9 on HIV-1 transmission in female sex workers in Africa and Thailand, all at high risk for HIV. The study gel (COL-1492) contained 52.5 mg N9 (other constituents included a bioadhesive carbomer). The placebo gel differed from COL-1492 in that it did not contain N9 and had more carbomer. At enrollment, women received a supply of study gel (N9 or placebo) and male condoms to use until the next visit. Women were asked to return to the clinic every month for a follow-up visit. There was no limit on the number of gel doses that could be used per day. The primary endpoint of the study was incident HIV-1 infection. Secondary objectives included the effectiveness of this drug in prevention of chlamydial infection, gonorrhea, trichomoniasis, and genital ulcer disease, and safety and acceptability of the gel under situations of long-term use. The treatment period was 48 weeks.

A total of 765 women were included in the primary analysis (376 in the N9 group and 389 in the placebo group) and 563 women completed the 48-week study. The overall retention rate of the participants in the study was 71 percent after 24 weeks and 68 percent after 48 weeks, which is similar to rates projected by the study investigators for their sample size (60 percent retention per year).

Of the 765 women, 59 in the N9 group and 45 in the placebo group seroconverted from HIV-1 negative to HIV-1 positive. Women who used an N9 vaginal gel had a significantly higher risk of becoming infected with HIV-1, compared with women using the placebo gel (p=0.047). The HIV-1 incidence per 100 women-years was

14.7 for the N9 group and 10.3 for the placebo group. This conclusion did not change when statistical adjustments were made for differences in the frequency of vaginal and anal sex not protected by condoms.

To test the hypothesis of dose-dependent toxic effects of N9, the investigators divided the mean gel use per working day into three categories based on tertiles. The investigators compared HIV-1 incidence per treatment group and per category of gel use. HIV-1 incidence increased with increasing gel use in the N9 group versus the placebo group. In the N9 group, HIV-1 incidence rose from 8.8 per 100 woman-years in women reporting mean use of 3.5 or fewer applicators per day to 30.6 in women reporting a higher mean daily use (hazard ratio 3.5; 95% Confidence Interval (CI) 2.1–5.8; $p < 0.0001$). In the placebo group, HIV-1 incidence in those categories was 8.1 and 14.5 per 100 woman-years, respectively (1.8; CI 1.0–3.3, $p = 0.05$). It is important to note that this analysis simply suggests a dose response between the amount of gel used per day and the risk of HIV-1 infection. The data does not support a conclusion that using less than 3.5 applications of N9 per day is associated with an incidence risk for HIV-1 infection similar to placebo. Dividing the data by other methods (e.g., into quartiles), would identify other amounts of N9 per day supporting an association between the amount used and increasing risk.

The study also investigated the frequency of N9 use and the incidence of lesions with epithelial breach, and whether the risk of HIV transmission increases with increasing number of lesions with epithelial breach. They found that the incidence of lesions with an epithelial breach rose with increasing gel use. The increase in incidence of lesions with an epithelial breach was seen in both the placebo and N9 groups, but it happened most rapidly in the N9 group.

FDA finds that one comment's concern about certain aspects of the Van Damme et al. study are valid as follows:

- There was a high loss to followup rate overall (retention rate was 68 percent at 48 weeks). However, the study was designed with an assumption of an annual retention rate of 60 percent.
- There was a higher loss to followup rate in the N9 group compared to the placebo group.
- The highest rates of both seroconversion and retention were observed at the largest center in the

study (Durban). This center also reported the highest rate of anal sex.

Although the study was not flawless, it was a large, well designed, randomized, placebo-controlled, multi-center clinical trial. Both the treatment and placebo groups were balanced with respect to baseline characteristics. Even with the noted limitations, we believe that the study is evidence that N9 may increase the risk of HIV-1 infection in a population already at increased risk for HIV-1 infection.

The comment also expressed concerns about the Kreiss et al. study (Ref. 7) that we cited in the proposed rule (68 FR 2254 at 2257). In this study, HIV negative sex workers in Nairobi, Kenya used either a vaginal sponge containing 1,000 mg N9 or a placebo. Women using the N9 sponge had a higher conversion from HIV negative to HIV positive. A total of 21 women (43 percent) of the N9 group and 19 women (35 percent) of the placebo group converted from HIV negative to HIV positive. We acknowledge the study's shortcomings, as noted in the comment. However, we believe that early termination of the study for safety reasons (i.e., that the seroconversion results had become inconsistent with the hypothesis of clinically beneficial effects of N9 in preventing HIV seroconversion) was ethically appropriate, and suggests an outcome consistent with the results of the Van Damme et al. study.

The comment contends that two other studies, Roddy et al. (Ref. 8) and Richardson et al. (Ref. 9), support a conclusion opposite to the Van Damme et al. and Kreiss et al. studies or weaken the conclusion that use of N9 spermicide products may increase the risk of HIV infection from an infected partner. We do not agree. The Roddy et al. study was conducted to determine whether a 70-mg N9 vaginal film provided protection against HIV, gonorrhea, or chlamydia. The study population consisted of 1,170 HIV-negative female sex workers (575 in the placebo group, 595 in the N9 group) residing in Cameroon, Africa, who averaged at least 4 sexual partners per month. The study results showed no difference in the rate of HIV transmission in the N9 group versus the placebo group (48 vs. 46, respectively), although the incidence of genital lesions was slightly higher in the N9 group. The results from this study, while not consistent with the data from the Van Damme et al. study, do not invalidate the Van Damme et al. study results. Roddy et al. reported the total number of sexual acts for placebo and N9 users but did not report the average number of sexual acts per day or per week.

There were 595 study participants in the N9 group who recorded a total of 147,996 coital acts. The average length of study followup was 14 months. This averages out to 1 coital act every 1.7 days. The study participants may not have used the N9 film often enough to demonstrate a difference in HIV risk compared to those using the placebo product. The results of the Roddy et al. study do not diminish the importance of the safety signal observed in the Van Damme et al. study. We believe that concerns about an increased risk of HIV transmission with frequent N9 use would apply to all products containing N9, regardless of the formulation. We do not agree with the comment's suggestion that the proposed warnings be revised to read "Other studies have shown no such risk for certain formulations (i.e., N9 film and gel) in these high risk populations".

The Richardson et al. study was conducted to determine the effect of a 52.5 mg N9 gel on the acquisition of STDs in HIV negative sex workers in Kenya. The study enrolled a relatively small number of subjects (total of 278 women, 139 in the N9 group and 139 in the placebo group) at only one clinic site. The sample size and the low extent of exposure may not have been sufficient to detect rare events. The authors stated that women enrolled in the Richardson et al. study came from another ongoing prospective cohort study at the same clinic site. Selection of subjects from that study population might have introduced confounding factors into their study. There was relatively low frequency of sexual intercourse and exposure to the test products (median of twice a week). The median compliance with product use was 75 percent in the N9 group and 80 percent in the placebo group (median compliance was 78 percent; the range was 0 to 100 percent). However, only 32 percent of the women in the N9 group and 36 percent of the women in the placebo group were 100 percent compliant. It is not clear how reliable the data collection methods were. The study did not mention if women kept a diary of product use and frequency of sexual intercourse, or if this information was collected by the study staff during the follow-up visits. For all of these reasons, we conclude that this study cannot be reliably used to support the comment's contentions.

In conclusion, FDA does not accept the first comment's request to remove the proposed warning language that links N9 use with an increased risk of HIV infection. FDA is providing information about whether it is safe for consumers to use these products based

on their risk for HIV and STDs. Based on the available scientific evidence, we have determined that women should be advised that use of N9 can cause vaginal irritation and that use of N9 has been associated with an increased risk for HIV transmission in women at high risk for HIV/AIDS. Use of N9 can result in irritated and inflamed genital tissue and may increase a person's risk of getting HIV/AIDS if they have sex with an HIV infected partner. We are, however, revising the proposed warnings to more clearly convey the message that N9 spermicides cause vaginal irritation, may increase the risk of getting HIV from an infected partner, and should not be used by women at high risk for HIV/AIDS. The warnings in § 201.325(b)(2) and (b)(3) of the proposed rule stated:

• **Sexually transmitted diseases (STDs) alert:**

This product does not protect against HIV/AIDS or other STDs

• **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 becoming infected with the AIDS virus (HIV) or other STDs from infected partners. Ask a doctor or other health professional for your best birth control method.

The revised warnings in this final rule appear under the subheadings "Sexually transmitted diseases (STDs) alert," "Do not use," and "When using this product" and state:

Sexually transmitted diseases (STDs) alert: This product does not protect against HIV/AIDS or other STDs and may increase the risk of getting HIV from an infected partner.

Do not use if you or your sex partner has HIV/AIDS. If you do not know if you or your sex partner is infected, choose another form of birth control.

When using this product you may get vaginal irritation (burning, itching, or a rash).

We are also revising the additional labeling information in proposed § 201.325(c)(1) (redesignated as § 201.325(d)(1) in this final rule) to more accurately reflect the scientific literature and to convey the message that N9 spermicides should not be used by women at risk for HIV. (Rectal use of N9 is discussed later in section II.H, comment 12 of this document.) The revised additional labeling information states:

• "Studies have raised safety concerns that products containing the spermicide nonoxynol 9 can irritate the vagina and rectum. Sometimes this irritation has no symptoms. This

irritation may increase the risk of getting HIV/AIDS from an infected partner."

3. Is FDA Required To Prove Actual Causation to Justify the Warnings?

(Comment 4) One comment stated that the proposed labeling implies a link between the use of N9 and an increased risk of HIV infection that is not sufficiently supported by the scientific literature. The comment contended that the link between N9 use and an increased risk of HIV transmission is "mere speculation" that is not suggested by a comprehensive review of the scientific literature. In response to FDA's statement that we need not show actual causation to mandate the proposed warning, the comment stated that it disputes a lesser standard unless FDA can show it will prevent a public harm. The comment suggested that there is not a public harm to prevent, so actual causation must be shown. The comment further asserted that 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, and suggested that FDA has not provided such proof.

(Response) FDA disagrees with the comment. Based on a review of the available data, FDA believes the known scientific evidence supports its proposed warnings (see section II.B.2, comment 3 of this document). Furthermore, FDA does not need a causal relationship to be definitely established to mandate new warnings. To protect the public health, FDA has determined that the warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the Federal Food, Drug and Cosmetic Act (the act). The warnings reflect FDA's conclusion that there is reasonable evidence of a causal relation between a clinically significant hazard and the drug.

Courts have upheld FDA's authority to issue regulations requiring label warnings and other affirmative disclosures (see, e.g. *Cosmetic, Toiletry and Fragrance Ass'n v. Schmidt*, 409 F. Supp. 57 (D.D.C. 1976), aff'd without opn., Vic. No. 75-1715 (D.C. Cir., August 19, 1977), even in the absence of a proven cause-and-effect relationship between product usage and harm (see *Council for Responsible Nutrition v. Goyan*, Civ. No. 80-1124 (D.D.C. August 1, 1980) (see also section III.B of this document). Mandating the warnings included in this final rule does not violate the Administrative Procedure Act's prohibition against arbitrary and

capricious conduct, because FDA's action is reasonable based on the sufficiency of the available data and the need to protect the public health.

C. *Should Women Ask a Doctor Before Using N9 Products?*

(Comment 5) Some comments did not agree with FDA's proposed warning language which advises women to ask a doctor before using N9 vaginal contraceptive drug products if they have a new sex partner, multiple sex partners, or unprotected sex. The comments questioned the need for women to consult physicians about the role of N9 in their pregnancy or STD prevention strategies. One comment doubted that the average physician could provide enough special expertise or insight about the role for N9 in a planned sexual encounter with a new partner to offset the inconvenience, discomfort, or cost of involving a health professional. Several comments stated that it was unclear what a woman should do before she is able to consult a physician (e.g., avoid sex, use alternative methods). Some comments contended that women should be given enough information in the labeling to empower them to act directly, without a health professional intermediary. These comments recommended replacing "Ask a doctor before use" with explicit statements such as "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" or "If you use these products more often than once a day and/or have a new sex partner, multiple sex partners, or unprotected sex you should consider another form of birth control". The comments suggested that adding a clarifying statement for women at low risk and a statement that reinforces the use of latex condoms is preferable to having consumers consult a physician for this information.

(Response) FDA agrees with the comments that questioned the need for women to have to consult with a physician before using N9 vaginal contraceptive drug products if they have a new sex partner, multiple sex partners, or unprotected sex. We try to provide consumers with the appropriate information on the OTC drug product label to make informed decisions on the use of these products. We believe that, by revising the warning language under "Ask a doctor before use if you have" and placing it under the subheadings "Do not use" and "When using this product," consumers will be able to make appropriate decisions without consulting a physician. We consider this information particularly important for

women who do not see a physician regularly, who will not consult a physician due to the expense, or who cannot get an appointment or consultation with a physician in a timely manner. Therefore, as discussed in section II.B.2, comment 3 of this document, we are revising the warnings under "Ask a doctor before use if you have" and placing them under the subheadings "Do not use" and "When using this product."

We are also revising the additional labeling information proposed in § 201.325(c) to include more information about the use and safety of N9, so women will not have to consult a physician before use. We do not want to discourage consumers from speaking with physicians or other health care providers at any time about important health issues such as birth control and STD prevention. Therefore, we are including a statement in the additional labeling information that women should ask a doctor or other health professional for advice if they choose. The revised additional labeling statements are discussed in sections II.B.2, comment 3; II.F.1, comment 8; II.F.2, comment 9; II.F.3, comment 10; II.G, comment 11; and II.J.2, comment 15 of this document.

D. Where Will the Warnings Appear in the Labeling?

(Comment 6) Several comments addressed the placement of the proposed warning statements on the OTC package. The comments requested that FDA require prominent placement of the proposed warning statements on both the outer carton and package insert to warn consumers most effectively. One comment recommended using large and bold font to help attract the consumer's attention and encourage reading of the package insert.

(Response) FDA is requiring that the warning statements discussed in section II.B.2, comment 3 of this document (under the subheadings "Do not use" and "When using this product"), the warning statements discussed in section II.H., comment 12 of this document ("For vaginal use only" and "Not for rectal (anal) use"), and the warning statement under the subheading "Stop use and ask a doctor if" (under § 201.325(b)(4) in the proposed rule (68 FR 2254 at 2262)), appear on the outside container or wrapper of the retail package, or on the immediate container label if there is no outside container or wrapper, in the Drug Facts labeling format, in accordance with § 201.66(c)(7). We also proposed additional labeling information in § 201.325(c) that could be placed either on the outside container or wrapper of

the retail package, under the "Other information" section of the Drug Facts labeling, in accordance with § 201.66(c)(7), or in a package insert. In this final rule, the revised condom usage statement, "when used correctly every time you have sex, latex condoms greatly reduce but do not eliminate the risk of catching or spreading HIV, the virus that causes AIDS." must be located in the Drug Facts labeling under the heading "Other information" on the outside container or wrapper of the retail package. The rest of the additional labeling information now located in § 201.325(d) of this final rule can be located on the outside container or wrapper of the retail package, under the "Other information" section of the Drug Facts labeling in accordance with § 201.66(c)(7), or in a package insert. In instances where the manufacturer chooses to provide a package insert for the additional information required in § 201.325(d) of this final rule, FDA recommends that a bolded statement such as "before using this product read the enclosed package insert for complete directions and information" be included on the outside container or wrapper labeling to alert consumers and encourage reading of the package insert.

E. Where Will the Condom Usage Statement Appear in the Labeling?

(Comment 7) Several comments requested that the proposed condom message, "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," should directly follow the STD alert on the outside container or wrapper as well as appear in a package insert so that consumers are immediately advised that STD/HIV protection is available OTC.

(Response) FDA agrees with the comments that information about HIV/STD protection (i.e., condom use) is important information and is now requiring that it be located on the outside container or wrapper in close proximity to the STD alert and other pertinent warnings. Because the information is not a warning, the statement appears in the Drug Facts labeling, under the heading "Other information." In addition, we are revising the condom usage statement (see section II.F, comment 8 in this document).

F. What Were the Comments on Condoms, Sexual Lubricants, and Barrier Methods?

1. Do Warnings Apply to Condoms and Sexual Lubricants?

(Comment 8) Some comments questioned whether FDA's proposed warnings apply to the labeling of condoms lubricated with N9. Several comments noted that women using condoms and sexual lubricants containing N9 may have a risk similar to those women using vaginal contraceptives and so both groups need to receive the same warnings. Some of these comments stated that FDA should propose warning language similar to the proposed warnings for vaginal contraceptive products for condoms and sexual lubricants containing N9, because of the substantial public health risk posed by N9 containing products when used rectally.

(Response) This final rule requiring warnings for all OTC vaginal contraceptives/spermicides containing N9 applies to drug products. It does not apply to condoms lubricated with N9, which are primarily regulated as medical devices (not drugs). Through rulemaking, spermicidal condoms were classified as Class II medical devices (21 CFR 884.5310) and, as such, FDA's Center for Devices and Radiological Health (CDRH) has primary jurisdiction over their regulation.

Although this final rule does not apply to condoms lubricated with N9, it does contain information for consumers about using condoms as a method to help reduce the risk of becoming infected with the AIDS virus (HIV) and other STDs. In the January 16, 2003, proposed rule, FDA discussed the public health benefit of such information and proposed the following condom usage statement for spermicides containing N9: "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" (see 68 FR 2254 at 2258 to 2259 and 2262). Subsequently, FDA reviewed the labeling of condoms (with and without N9) and issued a revised draft guidance (Ref. 10) on condom labeling. Therefore, FDA revised the proposed condom usage statement to be consistent with the statement it recommended in this new guidance. The new revised condom usage statement (in § 201.325(c) in this final rule) reads: "[bullet] when used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate the risk of catching or spreading HIV, the virus that causes AIDS."

Vaginal moisturizers and vaginal sexual lubricants are currently being evaluated under the OTC drug review regulatory process. FDA issued a call for data notice on December 31, 2003 (68 FR 75585), requesting safety and effectiveness data on various products, including vaginal moisturizers and vaginal lubricants. FDA will publish its findings in a future issue of the **Federal Register**.

2. Are Condoms Lubricated With N9 Safe to Use?

(Comment 9) Some comments stated that labeling products containing N9 with a warning that usage promotes the transmission of HIV or other STDs may cause sexually active individuals to question whether or not to use a condom at all. One comment expressed concern that after reading FDA's proposed warnings, consumers would perceive that condoms lubricated with N9 were not safe and would use nothing rather than use a condom containing N9. Therefore, several comments stated that the labeling should remind consumers that N9 is still effective in reducing unwanted pregnancies and that we should continue to endorse the use of spermicidal condoms. One of the comments stated that condoms containing N9 provide important consumer and public health care benefits, because N9 in condoms is intended to provide a secondary means of pregnancy prevention if the condom is used incorrectly or breaks.

Other comments were not supportive of N9 condoms. One comment requested that FDA take action to address the health risks posed by N9 as an additive to condoms and sexual lubricants by withdrawing them from the marketplace. This comment stated that N9 is not necessary to the function of lubricants and, in the case of condoms, N9 is not necessary as an additive or lubricant to their function as a physical barrier against pregnancy and disease. Several comments stated that the correct and consistent use of condoms provides excellent protection against pregnancy and HIV even without the addition of N9. One comment concluded that since N9 lubricated condoms and sexual lubricants containing N9 offer no proven benefit to any user group, and pose substantial risks to some users, the risk should be eliminated rather than relying on a "labeling" solution. One comment suggested revising the proposed condom statement to read "Correct use of a (dry) latex condom, (or a silicone lubricated latex condom, but NOT a condom lubricated with N9) with every vaginal sexual act will help

reduce the risk of transmitting the AIDS virus (HIV) and other STDs."

(Response) As discussed in section II.F.1, comment 8 of this document, this rulemaking does not apply to condoms that contain N9. It does, however, provide for information to be added to labeling to inform consumers about using condoms as a method to help reduce the risk of becoming infected with the AIDS virus (HIV) and other STDs. In section II.F.1, comment 8 of this document, FDA discussed a condom usage statement to encourage the use of condoms as a method to help reduce the risk of becoming infected with the AIDS virus (HIV) and other STDs as proposed in the proposed rule. In the revised draft guidance on condom labeling (Ref. 10) discussed previously, FDA recommended the additional warning "if you or your partner has HIV/AIDS, or you do not know if you or your partner is infected, you should choose a latex condom without N-9". Because FDA wishes to provide consistent information to consumers regarding products that contain N9, we are including a new labeling statement in § 201.325(d)(3) for vaginal contraceptive drug products containing N9 to read as follows: "[bullet] use a latex condom without nonoxynol 9 if you or your sex partner has HIV/AIDS, multiple sex partners, or other HIV risk factors."

3. How Do Warnings Apply to N9 Products Used With Barrier Methods?

(Comment 10) Some comments were concerned with how FDA's proposed warnings apply to consumers using an N9 spermicide product with barrier methods. The comments pointed out that FDA's proposed warning language for vaginal contraceptive drug products containing N9 applies to spermicide use alone, and not to concurrent use of N9 with female barrier methods. The comments stated concerns about how consumers who use N9 products with female barrier methods (such as diaphragms and cervical caps) would apply FDA's proposed warning language to their use. Several comments stated that consumers are currently advised (e.g., in product labeling or by physicians) to use spermicide with diaphragms and cervical caps to improve contraceptive effectiveness and to insert more spermicide (without removal of the diaphragm or cervical cap) if repeat intercourse occurs. The comments stated that FDA's proposed labeling does not provide clear advice for women (particularly those at low risk for HIV) who use these barrier methods. These comments contend that there is not enough data about the

effectiveness of diaphragms or caps without additional spermicide to recommend discontinuation of the spermicide. Some comments also stated that FDA's proposed warning language may deter promotion and use of female barrier methods that require additional spermicide. One of these comments stated that a recent report from the CDC (Ref. 2) estimates that N9 used together with diaphragms prevents 460,000 pregnancies each year. The comment stated that the proposed warning language would have a harmful effect on women's health by increasing unintended pregnancies and even STDs among women who would otherwise safely use cervical barriers plus N9, but might switch to a less effective method or no method at all. Another comment stated that clinicians may advise low-risk clients not to use N9 as an adjunct to diaphragm use, which may result in more unintended pregnancies. One comment suggested that FDA advise consumers in the labeling that the studies that have found risks associated with the use of N9 did not study the products with a diaphragm or cervical cap.

(Response) Currently, FDA approved directions for use for cervical caps (Ref. 11) and diaphragms (21 CFR 884.5350) specify use of a spermicide with these devices. FDA believes that women using cervical caps or diaphragms with N9 products are exposed to the same risks as women who use N9 vaginal contraceptive drug products alone because of the nature of the risk. The warning and other labeling information statements that are required by this final rule will inform women how best to use N9 spermicidal jellies and creams with barrier contraceptive methods.

FDA agrees with the comments that women at low risk for HIV should be able to safely use barrier methods along with N9 products and should not be advised to change from a barrier contraceptive method. There have been several studies over the years of cervical caps and diaphragms using N9 that have shown minimal irritation to the vagina and cervical mucosa (Refs. 12, 13, and 14). It is important to note that these were contraceptive studies among women in stable, monogamous relationships and that typical subjects did not use the devices multiple times a day. In section II.G, comment 11 of this document, we discuss labeling revisions that advise women at low risk for HIV that N9 products continue to be safe for contraception for them. Accordingly, FDA is also including barrier method and condom users at low risk for HIV in these statements.

G. Is N9 Safe for Women at Low Risk for HIV/AIDS and STDs?

(Comment 11) A number of comments stated that women at low risk for HIV and STDs should continue to use N9 spermicides as a contraceptive option. One comment stated that some women who use N9 containing vaginal contraceptive drug products for birth control may face a different (lower) STD risk profile than the women studied in the clinical trials, who were at a higher risk for HIV infection. The comment stated that the proposed warnings might exert a harmful net effect on women's health by increasing unintended pregnancy and STDs among women who would otherwise use N9 products safely, but might switch to less effective methods or no method at all because of the warnings. The comment urged that the data need to be properly extrapolated to women at lower risk for HIV who now use N9 products to successfully prevent pregnancy. Another comment stated that until FDA has additional data on the safety of N9 in low risk settings, women currently using N9 containing spermicides for birth control should continue to do so. Similarly, some comments stated that women at high risk for HIV infection should not use N9 products for contraception, but that these products should remain a contraceptive option for women at low risk. These comments stated that if a woman is not at high risk for HIV (because she is in a mutually monogamous relationship with a HIV negative partner), then use of N9 products poses less of a safety hazard. Thus, the comments contended that women at low risk for HIV could safely use N9 products multiple times in a single day.

One comment stated that FDA should qualify the warning language regarding "frequent use" for women who are at no or low risk for HIV. The comment suggested that FDA add the following qualifying statements to the labeling: "Women at low risk of HIV (i.e., those in a mutually monogamous relationship with an HIV negative partner) can safely use nonoxynol 9 (with or without a diaphragm) on multiple intercourse occasions in a single day. Frequent use of nonoxynol 9 is only problematic for women exposed to HIV and other STDs." A similar comment stated that FDA must carefully word the warnings to provide consumers with the ability to accurately assess the risks associated with the product's use.

(Response) FDA agrees that many women who use N9 vaginal contraceptive and spermicide drug products containing N9 have lower STD

and HIV risk profiles than the women studied in some of the clinical trials discussed in the proposed rule (68 FR 2254) (e.g., the Van Damme et al. study). We also agree that frequent use of N9 products poses no risk of HIV transmission for an HIV negative woman who is in a mutually monogamous relationship with an HIV negative partner. We believe that a woman in such a relationship would not suffer any harm, other than incurring vaginal irritation or epithelial lesions, from frequent use of N9. Accordingly, we are revising the additional labeling information proposed in § 201.325(c)(1) (redesignated as § 201.325(d)(2) in this final rule) to include a new statement advising women that they can continue to use N9 vaginal contraceptive and spermicide drug products if they are at low risk for HIV. The statement reads: "[bullet] you can use nonoxynol 9 for birth control with or without a diaphragm or condom if you have sex with only one partner who is not infected with HIV and who has no other sexual partners or HIV risk factors."

H. Is N9 Safe for Rectal Use?

(Comment 12) Ten comments urged FDA to require a warning against the rectal use of vaginal contraceptive drug products containing N9. This is because N9 causes serious damage to the rectal epithelium that may increase the risk of getting HIV or other STDs. The comments stated that although the products are designed for vaginal contraceptive use, they are routinely used for lubrication and (mistakenly) for protection against STDs during anal intercourse. The comments stated that these products are used rectally not only by the male homosexual population, but also by heterosexual couples who engage in both vaginal and anal intercourse. Two comments cited survey studies (Refs. 15 and 16) showing that the routine use of these products within the homosexual male population continues, due to the prevailing misperception that N9 protects against infection by sexually transmitted pathogens. Gross et al. (Ref. 15) surveyed 3,093 gay men from 6 U.S. cities who reported having anal intercourse during the previous 6 months. Of the 2,953 men in the study who used lubricants during anal intercourse, 41 percent actively sought N9 containing products. In another survey study conducted in San Francisco and Oakland in 2001 by Mansergh et al. (Ref. 16), 41 percent (79) of 193 men who had anal sex with men during the previous year used an N9 product without a condom. The men stated that they believed that N9

provided some protection against HIV transmission. The comment stressed that these data were collected after the CDC and the San Francisco Department of Health issued warnings about the dangers of using N9 rectally.

In further support of warnings against rectal use of N9, the comments referred to several studies in animals (Refs. 17 and 18) and one study in humans (Ref. 19) that showed that rectal application of N9 products causes damage to the cells lining the rectum. The comments stated that this damage may compromise a barrier that protects against viral and bacterial infection, thereby increasing the risk of HIV transmission. One comment suggested the following warning: "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." Another comment requested that a warning against rectal use be placed on the outer carton as well as in the package insert.

(Response) FDA agrees that products containing N9 should not be used rectally. The studies provided by the comments show that the rectal use of N9 damages the rectal epithelium in both animals and humans (Refs. 17, 18, and 19). One study in mice (Ref. 17) showed that pretreating the rectums of the mice with 2-percent N9 or with spermicide products containing N9 before inoculation with herpes simplex virus 2 (HSV-2) increased the likelihood of infection and shortened the time until infection. In this study, the rectal epithelium appeared to be repaired by 1 hour. The investigators stated that although they chose to use HSV-2, the results could be generalized to HIV transmission in humans because mouse and human epithelia are morphologically similar and because the same type of target cells of HIV, mononuclear blood cells, are present in the connective tissue and become more numerous after tissue damage. A study in monkeys (Ref. 18) investigated the effect of multiple applications of a 4-percent N9 product, placebo gel, or no product in three groups of monkeys. Each group receiving test product or placebo gel got 1 daily intrarectal application for 3 consecutive days, at 24 hour intervals. Before each treatment, animals were given a saline (pretreatment) rectal lavage. Test product was recovered by rectal lavage 15 minutes after administration. Examination of rectal lavage samples indicated an increase in the presence of epithelial cells and sheets of epithelium 15 minutes after N9 application, as compared with placebo gel and no-

product groups. The investigators noted that 1 day after the first exposure, epithelial sloughing was no longer evident, suggesting that repair had occurred rapidly. However, the investigators noted the continued presence of sloughed epidermal sheets 24 hours after repeated product application, indicating a cumulative effect of N9 on rectal tissues.

In a small study in humans, Phillips et al. (Ref. 19) investigated the effects of rectal application of two OTC products containing 2-percent and 1-percent N9, respectively, and two control formulations (not containing N9) in four subjects (three men, one woman). The experimental procedures were self-administered. After a baseline saline rectal lavage, the four formulations were evaluated by placing each test formulation in the rectum for 15 minutes via a syringe, at a minimum of 72 hours between test formulations. After 15 minutes and again 8 to 10 hours later, rectal lavage was performed. The investigators showed that the rectal lavage collected 15 minutes after N9 application revealed sheets of epithelium.

Sheets of rectal epithelium were not present in lavage fluid collected 8 to 12 hours later, or after treatment with control formulations. The authors concluded that N9 caused rapid exfoliation of the rectal epithelium in humans, which is likely to make users more susceptible to HIV infection.

Recently, Phillips et al. (Ref. 20) studied the effects of rectal use of an OTC vaginal contraceptive drug product containing 2-percent N9 in 18 human subjects. Thirteen of the study participants underwent rectal evaluation at baseline and then at 15 minutes or at 2 hours after N9 treatment. The remaining study participants underwent rectal evaluation at 8 hours after treatment. A physician applied the test formulation and did the rectal evaluation, which included biopsies as well as lavage. The investigators observed sheets of epithelium in lavage specimens collected at 15 minutes after N9 treatment. They observed less material in specimens collected at 2 hours, but what they collected appeared to be degraded cells and bacteria. In specimens collected at 8 hours there was no evidence of cellular material. Similarly, biopsies collected at 15 minutes appeared to be different from baseline biopsies; the epithelial tissue appeared missing or separated from the underlying submucosa. At 2 and 8 hours after treatment, the epithelium appeared similar to the baseline specimens, suggesting that the epithelium can repair itself within 2 hours. The

investigators concluded that N9 use should be avoided during anal sex, because the rectal epithelium, which is rapidly exfoliated after a single use of 2-percent N9, protects HIV target cells in the submucosa from HIV infection.

We conclude that these data demonstrate that N9 is an irritant to cells lining the rectum. The rectal epithelial damage that occurs with N9 exposure could increase the risk of getting HIV from an infected partner. Furthermore, a one-time rectal application of N9 is sufficient to cause rapid sloughing of extensive areas of the rectal epithelium. Accordingly, FDA is requiring a warning to inform users that these products should not be used rectally. This warning is required to be prominently displayed on the outside container or wrapper of the retail package or the immediate container label if there is no outside container or wrapper, in accordance with the requirements of § 201.66(c). The warning states: “Not for rectal (anal) use” [in bold type]. This warning follows the warning that reads “For vaginal use only” [in bold type]. In addition, as discussed in section II.B.2, comment 3 of this document, we are revising the additional labeling proposed in § 201.325(c)(1) to convey the message that studies show that N9 can irritate the vagina and rectum and that this may increase the risk of getting HIV/AIDS from an infected partner.

I. Does N9 Use Increase the Risk of STDs Other Than HIV?

(Comment 13) Two comments contended that there is no evidence that N9 increases the risk of getting other STDs, such as *Neisseria gonorrhoea* (gonorrhea) and *Chlamydia trachomatis* (chlamydia). The comments asked FDA to delete all referrals to a possible increased risk of getting STDs other than HIV in its proposed warnings for vaginal contraceptive drug products containing N9.

(Response) FDA agrees. While the Van Damme et al. study (Ref. 6) suggested that frequent use of N9 increased the risk of HIV infection compared with use of placebo in the population studied, it did not show sufficient evidence of an increased risk of gonorrhea or chlamydia infection. FDA is not aware of evidence suggesting a link between N9 use and increased risk of STDs other than HIV at this time. Accordingly, we are revising the warnings for N9 vaginal contraceptive and spermicide drug products to delete any reference to a possible increased risk of getting STDs other than HIV when N9 is used by people at risk for these infections. However, this does not affect the

warning, which we retain, that N9 does not protect against HIV or other STDs.

J. What Issues Did Other Comments Discuss?

1. Why Did FDA Define Frequent Use of N9 as “More Than Once a Day”?

(Comment 14) Many comments addressed the definition of “frequent use” in the proposed warning language for N9 containing vaginal contraceptive drug products. FDA recommended that “frequent use” be defined as “more than once a day.” Several comments stated that this definition is reasonable. One comment pointed out that many normal men and women from “middle America,” not just prostitutes, have sex several times a day with their partners, and these consumers need to be protected from the risks of using N9.

Other comments stated that FDA’s rationale for proposing “frequent use” as “more than once a day” is unclear. One comment contended that in the Van Damme et al. study (Ref. 6), in which investigators concluded that there was a statistically significant increase in the risk of HIV infection from infected partners, N9 gel use was “more than 3.5 times a day.” The comment stated that when the product was used less frequently than 3.5 times a day, there was no difference in risk of HIV transmission between the N9 and placebo users.

Therefore, the comment stated that the definition of frequent use should be changed to “no more than 3 times a day.” One comment contended that in the Van Damme et al. study, subjects averaged 3.6 coital acts a day, with a mean of 70 sexual acts a month, which is atypical of the sexual activity for the majority of women worldwide. Some comments questioned whether the results for commercial sex workers in Africa and Thailand can be reasonably extrapolated to the general U.S. population and questioned how the proposed definition of frequent use, “more than once a day” was extrapolated from the study data.

Other comments claimed that frequent use, defined as “more than once a day,” overstates the risk for many women and seems very restrictive. One comment proposed that women be informed that low frequency use of N9 products has not been shown to increase HIV infection rates, though it may increase vaginal irritation. Another comment stated that if a woman is not at risk for HIV, then frequent use of N9 poses no additional hazard. The comment proposed that women at low risk for HIV could safely use N9 several times in a single day.

(Response) FDA proposed to define frequent use as “more than once a day” because studies cited in the proposed rule (68 FR 2254 at 2257 to 2258) showed that if N9 is used more than once a day, the risk of vaginal irritation and epithelial lesions increases. When this occurs, the risk of HIV infection from infected partners increases according to studies discussed in the proposed rule (68 FR 2254 at 2258). The one comment erroneously concludes from the Van Damme et al. study that the risk was only present if women used N9 more than 3.5 times per day. As noted previously, the investigators analyzed dose response by dividing N9 use into categories based on tertiles. The use category of greater than 3.5 times per day identified the lower limit of the upper tertile. The analysis does not identify a dose below which there is not an increased risk. We are not aware of any available data to assist us in identifying a dose of N9 where there is no increased risk for HIV-1 infection in a susceptible population. Because of the nature of the risk, we believe that if a woman is at risk for HIV/AIDS, she should not be using N9 products, regardless of the frequency of use.

In this final rule, we are eliminating references to “frequent use” and revising the warning statements as described in section II.B.2, comment 3 of this document. We also agree with the comments that if a woman is not at risk for HIV, then frequent use of N9 poses no additional hazard of HIV infection. Thus, women at low risk for HIV can use N9 for birth control, with or without a diaphragm or condom, regardless of frequency. Accordingly, we are revising the labeling information to include a statement for women at low risk for HIV/AIDS (see section II.G, comment 11 of this document). It is also important to note that as explained in the response to section II.B.2, comment 3 of this document, the comment regarding risk only being present if women used N9 more than 3.5 times a day is erroneous.

2. Should “Pharmacist” or “Health Care Provider” Be Included on the Label?

(Comment 15) Some comments requested that the proposed warnings that begin with the words “Ask a doctor” and “Stop use and ask a doctor” be revised to include “health care provider,” because consumers receive health information from providers other than doctors. Other comments suggested that FDA include the term “pharmacists” in the labeling because pharmacists are the most accessible health providers for consumers.

(Response) In this final rule, we revised the warnings proposed after the subheading “Ask a doctor before use if you have” and moved them to after the subheadings “Do not use” and “When using this product.” Therefore, whether the subheading states “Ask a doctor before use” or “Ask a health care provider before use” is moot. Regarding the use of the terms “doctor” and “health care provider” in the subheadings “Ask a doctor before use if you have” and “Stop use and ask a doctor if,” FDA addressed this issue in the final rule for labeling of OTC human drugs (64 FR 13254 at 13261 to 13262). FDA acknowledged that in addition to physicians, other licensed professionals play an important role in delivering clinical services directly to consumers. FDA decided not to endeavor to list each specific practitioner who is licensed and qualified and decided that “doctor” is sufficiently broad and inclusive for this warning. Nonetheless, we are including in the “Other information” statements in § 201.325(d) of this final rule, a statement that contains the term “health professional” and advises women to ask a “health professional” if they have questions about their birth control and STD prevention methods. The statement reads: “[bullet] ask a health professional if you have questions about your best birth control and STD prevention methods”.

3. What Does “Unprotected Sex” Mean?

(Comment 16) Several comments questioned use of the words “unprotected sex” in the proposed warning language. The comments asked FDA to clarify whether “unprotected sex” means sex without a condom or sex without birth control.

The comments contended that the words “unprotected sex” are confusing in the proposed “Other information” statement “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” because sex with N9 is not unprotected sex. One comment recommended using the words “unprotected vaginal intercourse.” Another comment recommended replacing “unprotected sex” with the phrase “sex without condoms.”

(Response) FDA agrees that the wording “unprotected sex” could be clearer. As discussed in sections II.B.2., comment 3, II.C., comment 5, II.F.2., comment 9, II.F.3., comment 10, II.G., comment 11 and II.J.2., comment 15 of this document, FDA revised the

wording of the warnings and “Other information” statements and the words “unprotected sex” are no longer used.

4. What Does the Word “Irritation” Mean When Referring To “Vaginal Irritation” in the Warning Language?

(Comment 17) Two comments recommended that FDA not use the term “irritation” when referring to “vaginal irritation” in the warning language. The comments stated that epithelial disruption and inflammation can occur in the absence of perceived symptoms of irritation. Therefore, women who do not perceive what they believe is “irritation” might mistakenly believe they are safe from N9 hazards. The comments suggested that the proposed warning language (“Frequent use (more than once a day) of this product may increase vaginal irritation, which may increase the risk of getting the AIDS virus (HIV) or other STDs from infected partners”) be revised to read “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.”

(Response) FDA understands the comments’ concerns, but considers the term “irritation” the proper term to use in the warning language. This term is used throughout the scientific literature to describe the effects of N9 on the vaginal epithelia. Because “irritation” is also used widely in educational literature written for consumers, we believe that this term has more meaning for consumers than “damage to the cells lining the vagina.” We recognize that vaginal irritation may be asymptomatic; therefore, to protect women at risk for HIV, we advise them in § 201.325(b) in this final rule not to use N9 contraceptive products at all. We are also including in the “Other information” statements in § 201.325(d) of this final rule a statement that advises women that sometimes this irritation has no symptoms.

5. Should Warnings Be Printed in Both English and Spanish?

(Comment 18) One comment stated that it would be helpful to have warnings in Spanish as well as English on the package label and the package insert, with toll-free numbers and/or internet websites so that consumers may obtain additional data or clarification.

(Response) FDA allows manufacturers to print their package label and labeling in languages other than English. However, manufacturers must adhere to certain requirements in 21 CFR 201.15(c)(1), (c)(2), and (c)(3). Thus, FDA permits a dual label, e.g., a

complete English label can be accompanied with a complete label in Spanish, side by side. A package insert can be printed in English on one side, and Spanish on the other. Also, manufacturers may include toll-free numbers and internet websites in product labeling. If a manufacturer wants to include this type of information within the Drug Facts box, it must be done in accordance with § 201.66(c)(9).

III. FDA's Final Conclusions on Warnings and Other Labeling Information for OTC Vaginal Contraceptive and Spermicide Drug Products Containing N9

A. Labeling Requirements

FDA is amending part 201 (21 CFR part 201) by adding § 201.325 entitled "Over-the-counter drugs for vaginal contraceptive and spermicide use containing nonoxynol 9 as the active ingredient; required warnings and labeling information." This section will require new warnings and other labeling information for all OTC vaginal contraceptive and spermicide drug products containing N9 as the active ingredient, whether marketed under a New Drug Application (NDA) or the ongoing OTC drug review. The required warnings must be prominently displayed on the outside container or wrapper of the retail package, or the immediate container label if there is no outside container or wrapper, in accordance with the requirements of § 201.66(c), FDA's labeling regulation (Drug Facts) for OTC drug products. FDA is requiring that the following new warnings be added to the labeling of all marketed OTC vaginal contraceptive/spermicide drug products containing N9:

1. Under the heading "Warnings" the warning "Not for rectal (anal) use" [in

bold type]" will follow the warning "For vaginal use only" [in bold type].

2. Under the heading "Warnings" the warning "Sexually transmitted diseases (STDs) alert [in bold type]: This product does not [this word in bold type] protect against HIV/AIDS or other STDs and may increase the risk of getting HIV from an infected partner".

3. Under the subheading "Do not use," the warning "Do not use [in bold type] if you or your sex partner has HIV/AIDS. If you do not know if you or your sex partner is infected, choose another form of birth control."

4. Under the subheading "When using this product," the warning "When using this product [in bold type][optional, bullet] you may get vaginal irritation (burning, itching, or a rash)".

5. Under the subheading "Stop use and ask a doctor if," the warning "Stop use and ask a doctor if [in bold type][optional, bullet] you or your partner get burning, itching, a rash, or other irritation of the vagina or penis."

FDA is also requiring additional labeling information. This information is to appear either on the outside container or wrapper of the retail package, under the "Other information" section of the Drug Facts labeling in accordance with § 201.66(c)(7), or in a package insert. The only exception is the statement in § 201.325(c) about the correct use of latex condoms, which must appear on the outside container or wrapper of the retail package or the immediate container label if there is no outside container or wrapper, under the "Other information" section of the "Drug Facts" labeling. The additional labeling information is as follows:

- "studies have raised safety concerns that products containing the spermicide nonoxynol 9 can irritate the vagina and rectum. Sometimes this irritation has no symptoms. This irritation may increase

the risk of getting HIV/AIDS from an infected partner".

- "you can use nonoxynol 9 for birth control with or without a diaphragm or condom if you have sex with only one partner who is not infected with HIV and who has no other sexual partners or HIV risk factors".

- "when used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate, the risk of catching or spreading HIV, the virus that causes AIDS. [this information must appear on the outside container or wrapper labeling in the Drug Facts labeling under "Other information"]".

- "use a latex condom without nonoxynol 9 if you or your sex partner has HIV/AIDS, multiple sex partners, or other HIV risk factors".

- "ask a health professional if you have questions about your best birth control and STD prevention methods".

FDA is also recommending that all of the required warnings and other labeling information be included in a package insert. Many marketed OTC vaginal contraceptive and spermicide drug products already have a package insert that contains information on how to use the product, and this new information could readily be incorporated in the package insert.

The following is an example of the Drug Facts labeling (for content purposes only) for a vaginal contraceptive/spermicide drug product containing N9 that incorporates all of the required new warnings and labeling information on the Drug Facts label. The quantity of active ingredient per dosage unit, the font sizes for title, headings, subheadings, condensed text, and bullets, and other graphic features, must be in accordance with § 201.66.

BILLING CODE 6111-01-S

Sample Drug Facts

Drug Facts	
Active ingredient	Purpose
nonoxynol 9	Vaginal contraceptive
Use prevents pregnancy	
Warnings	
<ul style="list-style-type: none"> ▪ For vaginal use only ▪ Not for rectal (anal) use 	
Sexually transmitted diseases (STDs) alert: This product does not protect against HIV/AIDS or other STDs and may increase the risk of getting HIV from an infected partner	
Do not use if you or your sex partner has HIV/AIDS. If you do not know if you or your sex partner is infected, choose another form of birth control.	
When using this product	
<ul style="list-style-type: none"> ▪ you may get vaginal irritation (burning, itching, or a rash) 	
Stop use and ask a doctor if	
<ul style="list-style-type: none"> ▪ you or your partner get burning, itching, a rash or other irritation of the vagina or penis 	
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.	
Directions	
<ul style="list-style-type: none"> ▪ [product dependent] 	
Other information	
<ul style="list-style-type: none"> ▪ studies have raised safety concerns that products containing the spermicide nonoxynol 9 can irritate the vagina and rectum. Sometimes this irritation has no symptoms. This irritation may increase the risk of getting HIV/AIDS from an infected partner. ▪ you can use nonoxynol 9 for birth control with or without a diaphragm or condom if you have sex with only one partner who is not infected with HIV and who has no other sexual partners or HIV risk factors ▪ when used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate, the risk of catching or spreading HIV, the virus that causes AIDS ▪ use a latex condom without nonoxynol 9 if you or your sex partner has HIV/AIDS, multiple sex partners, or other HIV risk factors ▪ ask a health professional if you have questions about your best birth control and STD prevention methods 	
Inactive ingredients [product dependent]	
Questions or comments?	[product dependent]

BILLING CODE 6111-01-C

B. Statement About Warnings

Mandating warnings in an OTC drug product regulation does not require a finding that any or all of the OTC drug products covered by the regulation actually caused an adverse event, and FDA does not so find. Nor does FDA's requirement of warnings repudiate the prior OTC drug monographs and regulations under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the act. This judgment balances the benefits of these drug products against their potential risks. (See 21 CFR 330.10(a).)

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort

action (*Glastetter v. Novartis Pharmaceuticals Corp.*, 252 F.3d 986,991 (8th Cir. 2001)). To mandate warnings, or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see the December 6, 2002 (67 FR 72555), final rule entitled "Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use."

IV. Analysis of Impacts

In accordance with Executive Order 12866, FDA has previously analyzed the potential economic effects of this final rule. As announced in the proposal, the agency has determined that the rule is not a significant regulatory action as defined by the Order. The agency has not received any new information or comments that would alter its previous determination.

FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes this final rule is not a significant regulatory action under Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the one-time costs to comply with this rule are small, the agency certifies that the final rule will not have a significant economic impact

on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$127 million, using the most current (2006) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

The purpose of this final rule is to require additional labeling for OTC vaginal contraceptive and spermicide drug products containing N9. The labeling includes new warnings and other important information about using these products. These products are currently packaged in an outer carton that should have sufficient space to accommodate this additional labeling. FDA is aware that most of the currently marketed products already include a consumer package insert. Therefore, to allow firms greater flexibility, FDA is allowing some of the new information to appear in the package insert. There are a limited number of products currently marketed that will be affected by this final rule, and the incremental one-time costs are minimal. The one-time costs include designing the new carton, designing a new package insert, and the inventory loss of any unused current labeling. FDA assumes the same weighted average cost to relabel, inflated to reflect current dollars, that it estimated for the final rule requiring uniform label formats of OTC drug products (64 FR 13254 at 13279 to 13281) (i.e., $\$3,600 \times 1.164^1$ (\$4,190) per stock keeping unit (SKU) (individual products, packages, and sizes)). Inventory loss was estimated using data from a study supporting the previously mentioned rule. With a 6-month implementation period, inventory loss was estimated to be between \$582 and \$3,492 per SKU, depending on product sales, for an estimated weighted average inventory loss of \$2,386. The inventory

loss and redesign costs for the package insert are estimated to be about \$1,606 per SKU².

FDA's Drug Listing System identifies 15 manufacturers and distributors of OTC vaginal contraceptive and spermicide drug products containing N9 that together produce approximately 40 SKUs. At a relabeling cost of \$4,190 per SKU and an inventory loss of \$2,386 per SKU, estimated total one-time cost of relabeling would be \$263,040 ($40 \times (\$4,190 + \$2,386)$)³. Even if all required wording is revised on the outer carton, manufacturers may revise their package inserts as well to conform to the revised language. This adds another \$64,240 ($40 \times \$1,606$) to the one-time cost, for an estimated total of \$327,280⁴.

As FDA is providing the language of the labeling to be used, all firms should have the necessary skills and personnel to perform the required relabeling either in-house or by contractual arrangement. The final rule does not require any new reporting or recordkeeping activities. No additional professional skills are needed.

About 9 firms affected by this final rule meet the Small Business Administration's definition of a small entity (fewer than 750 employees). The actual impact on these firms will vary depending on the number and nature of the products they manufacture or distribute. All nine entities market additional types of products and have only one or two SKUs affected by this final rule. The average incremental cost per SKU to comply with this final rule is estimated to be \$8,182 ($\$327,280/40$ SKUs). Actual costs to the small entities will likely be lower because distributors of low sales volume OTC drug products usually market their products in packaging that costs less than the industry average.

While the costs to individual manufacturers to relabel their products are minimal, the potential benefits to consumers who use these products are substantial. FDA considers it essential that users be aware that these products do not protect against the AIDS virus (HIV) or other STDs. The monetary benefit of potentially preventing any cases of AIDS or STDs is significant compared to the minor cost of relabeling these products to provide the new required information.

²The original values from the uniform label formats rule (64 FR 13254), inventory loss between \$500 and \$3,000 and a weighted average of \$2,050, were inflated by 16.4 percent.

³In the proposal for this rule, the estimated total one-time cost of relabeling was reported in error as \$266,000, the actual value should have been \$226,000.

⁴In the proposed rule this value was reported as \$321,000, but should have been \$281,200.

FDA considered but rejected several labeling alternatives: (1) A shorter or longer implementation period, and (2) an exemption from coverage for small entities. FDA considers it important that this information appear in product labeling as soon as possible, but acknowledges that implementation in a timeframe any less than 6 months would be very difficult for affected manufacturers. However, because of the importance of this new labeling information, FDA considers a period of 12 months too long to implement this new labeling. FDA rejected an exemption for small entities because the new labeling is also needed by consumers who purchase products marketed by those entities.

The analysis shows that this final rule is not economically significant under Executive Order 12866 and that FDA has considered the burden to small entities. Based on this analysis, FDA does not believe manufacturers will incur a significant economic impact. Therefore, FDA certifies that the final rule will not have a significant economic impact on a substantial number of small entities. No further analysis is required under the Regulatory Flexibility Act (5 U.S.C. 605(b)).

V. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the labeling statements are a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

VI. Environmental Impact

FDA has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule will have a preemptive effect on State law. Section 4(a) of the Executive order requires agencies to "construe * * * a Federal statute to preempt State law only where the statute contains an express

¹ The annual PPI for pulp, paper, and allied products (the major cost driver for labeling) rose by 16.4 percent between 1998 and 2005 (from 174.1 to 202.6) <http://data.bls.gov/cgi-bin/survey/most>, extracted December 5, 2006. (FDA has verified the Web site address, but we are not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**.)

preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute." Section 751 of the the act (21 U.S.C. 379r) is an express preemption provision. Section 751(a) of the act (21 U.S.C. 379r(a)) provides that: "* * * no State or political subdivision of a State may establish or continue in effect any requirement— * * * (1) that relates to the regulation of a drug that is not subject to the requirements of section 503(b)(1) or 503(f)(1)(A); and (2) that is different from or in addition to, or that is otherwise not identical with, a requirement under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 *et seq.*), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 *et seq.*)."

Currently, this provision operates to preempt States from imposing requirements related to the regulation of nonprescription drug products. (See section 751(b) through (e) of the act for the scope of the express preemption provision, the exemption procedures, and the exceptions to the provision.) This final rule would establish new warning statements and other labeling for all OTC vaginal contraceptive drug products. Although this final rule would have a preemptive effect, in that it would preclude States from promulgating requirements related to labeling for OTC vaginal contraceptive drug products that are different from or in addition to, or not otherwise identical with a requirement in the final rule, this preemptive effect is consistent with what Congress set forth in section 751 of the act. Section 751(a) of the act displaces both State legislative requirements and State common law duties. We also note that even where the express preemption provision is not applicable, implied preemption may arise. See *Geier v. American Honda Co.*, 529 US 861 (2000).

FDA believes that the preemptive effect of the final rule would be consistent with Executive Order 13132. Section 4(e) of the Executive order provides that "when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings." FDA provided the States with an opportunity for appropriate participation in this rulemaking when it sought input from all stakeholders through publication of the proposed rule in the **Federal Register** of January 16, 2003 (68 FR

2254). FDA received comments from three State groups on the proposal and considered those comments in drafting this final rule.

In addition, on May 12, 2006, FDA's Division of Federal and State Relations provided notice via fax and email transmission to elected officials of State governments and their representatives of national organization. The notice provided the States with further opportunity for input on the rule. It advised the States of the publication of the proposed rule and encouraged State and local governments to review the notice and to provide any comments to the docket (Docket No. 1980N-0280 (formerly Docket No. 80N-0280)), opened in the January 16, 2003, **Federal Register** proposed rule, by a date 30 days from the date of the notice (i.e., by June 12, 2006), or to contact certain named individuals. FDA received no comments in response to this notice. The notice has been filed in the above numbered docket.

In conclusion, the agency believes that it has complied with all of the applicable requirements under the Executive order and has determined that the preemptive effects of this rule are consistent with Executive Order 13132.

VIII. References

The following references are on display in the Division of Dockets Management, 5630 Fishers Lane, rm 1061, Rockville, MD 20852, under Docket No. 1980N-0280, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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4. Sansgiry, S. S., P. S. Cady, and S. Patil, "Readability of Over-the-Counter Medication Labels," *Journal of the American Pharmaceutical Association*, NS37(5):522-528, 1997.
5. A National Survey of Consumers and Health Professionals: "Attitudes and Beliefs About the Use of Over-the-Counter Medicines: A Dose of Reality," prepared for The National Council on Patient Information and Education (NCPPIE), www.harrisinteractive.com, 2002.
6. 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*, 360:971-977, 2002.

7. Kreiss, J. et al., "Efficacy of Nonoxynol 9 Contraceptive Sponge Use in Preventing Heterosexual Acquisition of HIV in Nairobi Prostitutes," *Journal of the American Medical Association*, 268:477-482, 1992.

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10. FDA, Draft Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Labeling for Male Condoms Made of Natural Rubber Latex, Center for Devices and Radiological Health (CDRH), 2005.

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12. Bounds, W. et al., "The Diaphragm With and Without Spermicide: A Randomized, Comparative Efficacy Trial," *Journal of Reproductive Medicine*, 40:11:764-774, 1995.

13. Richwald, G. A. et al., "Effectiveness of the Cavity-Rim Cervical Cap: Results of a Large Clinical Study," *Obstetrics and Gynecology*, 74:2:143-148, 1989.

14. Bernstein, G., "Use-Effectiveness Study of Cervical Caps: Final Report," Washington, DC: National Institute of Child Health and Human Development, contract no. NO1-HD-1-2804, 1986.

15. Gross, M. et al., "Rectal Microbicides for U.S. Gay Men. Are Clinical Trials Needed?," *Sexually Transmitted Diseases*, 25:6:296-302, 1998.

16. Mansergh, G. et al., "Rectal Use of Nonoxynol-9 Among Men Who Have Sex With Men," *AIDS*, 17:6:905-909, 2003.

17. Phillips, D. M. and V. R. Zacharopoulos, "Nonoxynol-9 Enhances Rectal Infection by Herpes Simplex Virus in Mice," *Contraception*, 57:341-348, 1998.

18. Patton, D. et al., "Rectal Applications of Nonoxynol-9 Cause Tissue Disruption in a Monkey Model," *Sexually Transmitted Diseases*, 29:581-587, 2002.

19. Phillips, D. et al., "Nonoxynol-9 Causes Rapid Exfoliation of Sheets of

Rectal Epithelium,” *Contraception*, 62:149–154, 2002.

20. Phillips, D. M. et al., “Lubricants Containing N–9 May Enhance Rectal Transmission of HIV and Other STIs,” *Contraception*, 70:107–110, 2004.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 201 is amended as follows:

PART 201—LABELING

■ 1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

■ 2. Section 201.66 is amended by adding paragraph (c)(5)(ii)(H) to read as follows:

§ 201.66 Format and content requirements for over-the-counter (OTC) drug product labeling.

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- (c) * * *
- (5) * * *
- (ii) * * *

(H) Sexually transmitted diseases (STDs) warning for vaginal contraceptive and spermicide drug products containing nonoxynol 9 set forth in § 201.325(b)(2). This warning shall follow the subheading “Sexually transmitted diseases (STDs) alert:”

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■ 3. Section 201.325 is added to subpart G to read as follows:

§ 201.325 Over-the-counter drugs for vaginal contraceptive and spermicide use containing nonoxynol 9 as the active ingredient; required warnings and labeling information.

(a) Studies indicate that use of vaginal contraceptive drug products containing nonoxynol 9 does not protect against infection from the human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS), or against the transmission of other sexually transmitted diseases (STDs). Studies also indicate that use of vaginal contraceptive drug products containing nonoxynol 9 can increase vaginal irritation, such as the disruption of the vaginal epithelium, and also can cause epithelial disruption when used in the rectum. These effects may increase the risk of transmission of the AIDS virus (HIV) from an infected partner. Therefore, consumers should be warned

that these products do not protect against the transmission of the AIDS virus (HIV) or other STDs, that use of these products can increase vaginal and rectal irritation, which may increase the risk of getting the AIDS virus (HIV) from an HIV infected partner, and that the products are not for rectal use. Consumers should also be warned that these products should not be used by persons who have HIV/AIDS or are at high risk for HIV/AIDS.

(b) The labeling of OTC vaginal contraceptive and spermicide drug products containing nonoxynol 9 as the active ingredient, whether subject to the ongoing OTC drug review or an approved drug application, must contain the following warnings under the heading “Warnings,” in accordance with 21 CFR 201.66.

(1) “[bullet] For vaginal use only [bullet] Not for rectal (anal) use” [both warnings in bold type].

(2) “Sexually transmitted diseases (STDs) alert [in bold type]: This product does not [word “not” in bold type] protect against HIV/AIDS or other STDs and may increase the risk of getting HIV from an infected partner”.

(3) “Do not use” [in bold type] if you or your sex partner has HIV/AIDS. If you do not know if you or your sex partner is infected, choose another form of birth control”.

(4) “When using this product [in bold type] [optional, bullet] you may get vaginal irritation (burning, itching, or a rash)”.

(5) “Stop use and ask a doctor if [in bold type] [optional, bullet] you or your partner get burning, itching, a rash, or other irritation of the vagina or penis”.

(c) The labeling of this product states under the “Other information” section of the Drug Facts labeling in accordance with § 201.66(c)(7), “[bullet] when used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate, the risk of catching or spreading HIV, the virus that causes AIDS.

(d) The labeling of this product includes the following statements either on the outside container or wrapper of the retail package, under the “Other information” section of the Drug Facts labeling in accordance with § 201.66(c)(7), or in a package insert:

(1) “[bullet] studies have raised safety concerns that products containing the spermicide nonoxynol 9 can irritate the vagina and rectum. Sometimes this irritation has no symptoms. This irritation may increase the risk of getting HIV/AIDS from an infected partner”.

(2) “[bullet] you can use nonoxynol 9 for birth control with or without a diaphragm or condom if you have sex

with only one partner who is not infected with HIV and who has no other sexual partners or HIV risk factors”.

(3) “[bullet] use a latex condom without nonoxynol 9 if you or your sex partner has HIV/AIDS, multiple sex partners, or other HIV risk factors”.

(4) “[bullet] ask a health professional if you have questions about your best birth control and STD prevention methods”.

(e) Any drug product subject to this section that is not labeled as required and that is initially introduced or initially delivered for introduction into interstate commerce after June 19, 2008, is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352), is a new drug under section 505 of the act (21 U.S.C. 355), and is subject to regulatory action.

Dated: December 10, 2007.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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DEPARTMENT OF STATE

22 CFR Part 124

[Public Notice 6031]

Amendment to the International Traffic in Arms Regulations: Regarding Dual and Third Country Nationals

AGENCY: Department of State.

ACTION: Final rule.

SUMMARY: The Department of State is amending the text of the International Traffic in Arms Regulations (ITAR) to allow access to defense articles and services for dual and third country nationals of certain countries through revisions in procedures for technical assistance agreements and manufacturing licensing agreements. This regulatory change will reduce the burden on exporters of defense articles and on foreign parties to the agreements by reducing the number of individual Non Disclosure Agreements (NDA’s) which must be executed and maintained on file.

DATES: *Effective Date:* This rule is effective December 19, 2007.

ADDRESSES: Interested parties may submit comments at any time by any of the following methods:

- *E-mail:*

DDTCResponseTeam@state.gov with an appropriate subject line.

- *Mail:* Department of State, Directorate of Defense Trade Controls, Office of Defense Trade Controls Policy, ATTN: Regulatory change, ITAR