

March 2005

HHS

Efforts to Research
and Inform the Public
about Nonoxynol-9
and HIV



G A O

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Highlights of [GAO-05-399](#), a report to congressional requesters

Why GAO Did This Study

Preventing the transmission of HIV, the virus that causes AIDS, is an important public health challenge. Researchers have sought to develop a microbicide—a substance to help users protect themselves against HIV. In the mid-1980s, researchers found that Nonoxynol-9 (N-9), a spermicide found in various contraceptive products, showed potential as a microbicide. However, more recent studies raised concerns that N-9 may increase certain users' risk of contracting HIV.

GAO was asked to describe federal agencies' and contraceptive product manufacturers' actions related to N-9 and HIV. In this report, GAO reviewed (1) the efforts by federal agencies and manufacturers of contraceptive products to assess the safety of N-9 and its effectiveness as a microbicide for preventing HIV transmission and (2) the information provided to the public about the safety of N-9 and its effectiveness as a microbicide.

GAO reviewed journal articles, *Federal Register* notices, product packaging, educational materials, and other documents. GAO also interviewed officials from the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and selected manufacturers of N-9 contraceptive products.

www.gao.gov/cgi-bin/getrpt?GAO-05-399.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marjorie Kanof at (202) 512-7114.

HHS

Efforts to Research and Inform the Public about Nonoxynol-9 and HIV

What GAO Found

Federal agencies have undertaken a variety of efforts to research N-9 as a potential microbicide—including conducting, funding, or reviewing studies on the safety and effectiveness of N-9. In the 1990s, CDC and NIH conducted and funded research on the effectiveness and safety of N-9 as a microbicide to prevent HIV infection. For example, in 1996 CDC and others began a 4-year study on the effectiveness of an N-9 vaginal contraceptive product in preventing the transmission of sexually transmitted diseases, including HIV. The results of the research by the agencies during this period were inconsistent—some research indicated that N-9 reduced the incidence of HIV while other research suggested that frequent use of N-9 may increase the risk of contracting the virus. Then in 2000, the preliminary results of a major clinical study suggested more strongly that N-9 vaginal contraceptive products did not prevent HIV infection and may increase the risk of infection among frequent users. As a result of the study, CDC and NIH stopped conducting and funding research on N-9 as a microbicide out of concern for participants' safety. FDA continued to review available research on the safety of N-9 as part of its regulation of vaginal contraceptive products and, in 2003, proposed new warning labels for N-9 vaginal contraceptive products. As of March 2005, FDA was also in the process of developing a proposal for new warning labels for N-9 condoms. As of that date, FDA had not finalized the new warning labels for N-9 vaginal contraceptive products and had not proposed new warning labels for N-9 condoms. Representatives from two manufacturers of N-9 contraceptive products have reviewed research on N-9's safety for the purpose of commenting on FDA's proposed warning labels.

The information CDC and FDA have provided to the public about the use of N-9 as a microbicide has been, at times, inconsistent. In the early 1990s, CDC cautioned that there was insufficient information to conclude that N-9 may prevent HIV transmission. By 1998, in response to new research, the agency informed the public that N-9 vaginal contraceptive products did not prevent HIV. During the same period, FDA also cautioned that N-9 had not been proven to prevent HIV transmission, but in 1999, a brochure posted on its Web site stated that N-9, along with a condom, may be used to prevent HIV transmission. By 2000, CDC had responded to new research findings and had revised its educational publications to state that N-9 may actually increase the risk of contracting HIV when used frequently. In contrast, FDA did not revise the brochure on its Web site that stated that some experts believe N-9 may prevent HIV and suggested using N-9 along with a condom. FDA left this information on its Web site until these statements were deleted in September 2003 when FDA officials realized the information was inconsistent with proposed warning labels.

In commenting on a draft of this report, the Department of Health and Human Services (HHS) provided clarification that GAO incorporated where appropriate.

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Abbreviations

CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
MMWR	<i>Morbidity and Mortality Weekly Report</i>
N-9	Nonoxynol-9
NIH	National Institutes of Health
PPFA	Planned Parenthood Federation of America
STD	sexually transmitted disease
WHO	World Health Organization

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United States Government Accountability Office
Washington, D.C. 20548

March 31, 2005

The Honorable Mark Souder
Chairman
Subcommittee on Criminal Justice, Drug Policy and Human Resources
Committee on Government Reform
House of Representatives

The Honorable Tom Coburn
United States Senate

The Honorable Joseph Pitts
House of Representatives

The Honorable David Weldon
House of Representatives

Preventing the transmission of HIV, the virus that causes AIDS, is an important public health challenge. The Centers for Disease Control and Prevention (CDC) has reported that an estimated 850,000–950,000 HIV positive people live in this country, including 180,000–280,000 who do not know they are infected.¹

Researchers have sought to develop a microbicide² that could be used to prevent HIV transmission. If developed, a microbicide could be a topically applied substance to help users protect themselves against HIV or other sexually transmitted diseases (STD). One of the advantages of a microbicide over other methods of preventing HIV—such as condoms or mutual monogamy—would be that an individual could use the microbicide without the cooperation of a sexual partner.

¹ Centers for Disease Control and Prevention, *Basic Statistics: HIV Estimate*, <http://www.cdc.gov/hiv/stats.htm> (downloaded Jan. 31, 2005).

² A microbicide is any agent that kills microbes such as bacteria, fungi, and parasites. Some microbes are capable of causing disease.

In the mid-1980s researchers found that Nonoxynol-9 (N-9), a widely available spermicide³ found in various over-the-counter⁴ contraceptive products—including some condoms and certain vaginal contraceptive products such as foams and gels—showed promise as a potential microbicide for STDs, including HIV.⁵ In 1988, the Surgeon General, in collaboration with CDC, distributed brochures to 107 million U.S. households that stated that based on laboratory tests, condoms with N-9 may provide additional protection against HIV.⁶ Around this time, it was also widely reported in newspapers and journals that it was advisable to use contraceptive products with N-9 because it might help prevent HIV.⁷ However, more recent studies have raised concerns that N-9 vaginal contraceptive products may not be effective against HIV and may in fact increase certain users' risk of contracting the virus. Public health organizations have also expressed concerns that consumers may use condoms lubricated with N-9 (N-9 condoms) for anal intercourse in order to protect themselves against HIV without knowing the degree to which the use of such condoms may put them at risk. Because of the potential risks involved, the use of N-9 is an important public health issue—one that involves CDC, the Food and Drug Administration (FDA), and the National Institutes of Health (NIH) and their research, regulatory actions, or efforts to educate the public about N-9 and HIV.

You asked us to describe federal agencies' and contraceptive product manufacturers' actions related to N-9 and HIV. This report describes

³ A spermicide is a chemical compound that inactivates sperm by damaging their cell membranes.

⁴ Over-the-counter refers to drug products sold without a prescription.

⁵ For example, N-9, available over-the-counter for almost 50 years, was first demonstrated to be effective against HIV in a laboratory study in 1985. D.R. Hicks, L.S. Martin, J.P. Getchell, et al., "Inactivation of HTLV-III/LAV-Infected Cultures of Normal Human Lymphocytes by Nonoxynol-9 In-vitro," *The Lancet* (1985).

⁶ C.E. Koop, Surgeon General, and Centers for Disease Control, Public Health Service, *Understanding AIDS* (1988).

⁷ For example the *New York Times* reported in 1987 that "Additional protection is gained by applying spermicides containing nonoxynol-9, which kills the AIDS virus." See J.E. Brody, "Personal Health," *New York Times* (Mar. 4, 1987). That same year, the *Journal of the American Medical Association* reported that the Surgeon General recommended that condoms be lubricated with N-9 "which some evidence shows may inhibit the virus." See C.E. Koop, "Physician Leadership in Preventing AIDS," *Journal of the American Medical Association*, vol. 258 (1987).

(1) efforts by federal agencies and manufacturers of contraceptive products to assess the safety of N-9 and its effectiveness as a microbicide for preventing HIV transmission, (2) the information federal agencies and manufacturers of contraceptive products have provided to the public about the safety of N-9 and its effectiveness as a microbicide, and (3) decisions by manufacturers and public health organizations that may have affected the availability of N-9 condoms.

To describe the efforts of federal agencies and manufacturers of contraceptive products to assess the safety of N-9 and its effectiveness as a microbicide for preventing HIV transmission, we reviewed reports, journal articles, *Federal Register* notices, agency Web sites, and other documents related to N-9 and HIV. We interviewed officials from CDC, FDA, and NIH. We also interviewed officials from the three largest condom manufacturers in the United States—Armkel, LLC; SSL International; and Ansell Limited—which account for an estimated 98 percent of U.S. condom retail sales; as well as officials from two manufacturers of other N-9 contraceptive products—Apothecus Pharmaceutical Corporation and Johnson & Johnson Consumer Companies, Incorporated. To describe the information federal agencies and manufacturers of contraceptive products have provided to the public about the safety of N-9 and its effectiveness as a microbicide, we reviewed articles, pamphlets, agency and manufacturer Web sites, manufacturer product packaging, and other educational materials related to N-9 and HIV. We also interviewed officials from CDC, FDA, and the manufacturers of contraceptive products. Because concerns about the safety of N-9 in preventing HIV first began to surface around 1990, we focused our review on efforts to research and provide public information on N-9 and HIV from 1990 to the present. To describe decisions by manufacturers and public health organizations that may have affected the availability of N-9 condoms, we interviewed officials from CDC; FDA; NIH; three national reproductive health organizations—Planned Parenthood Federation of America (PPFA), Family Health International, and the Global Campaign for Microbicides; and the three largest condom manufacturers in the United States. We also interviewed a researcher who conducted a key clinical study on N-9 and HIV. We performed our work from October 2003 through March 2004 and August 2004 through March 2005 in accordance with generally accepted government auditing standards.

Results in Brief

Federal agencies have undertaken a variety of efforts to research N-9 as a potential microbicide—including conducting, funding, or reviewing studies on the safety and effectiveness of N-9, and manufacturers have reviewed

research on the safety of N-9. In the 1990s, CDC and NIH conducted and funded research on the effectiveness and safety of N-9 as a microbicide to prevent HIV infection. For example, in 1996 CDC and others began a 4-year study on the effectiveness of an N-9 vaginal contraceptive product in preventing the transmission of STDs, including HIV. In the 1990s, NIH funded a range of laboratory and clinical studies of N-9 as a possible microbicide for HIV. During this time, FDA reviewed research on N-9 as part of its regulatory process for reviewing the safety and effectiveness of N-9 as a vaginal contraceptive. The results of the research conducted, funded, and reviewed by the agencies during this period were inconsistent—some research indicated that N-9 reduced the incidence of HIV while other research suggested that frequent use of N-9 may increase the risk of contracting the virus. Then in 2000, the preliminary results of a major clinical study suggested more strongly that N-9 vaginal contraceptive products did not prevent HIV infection and may increase the risk of infection among frequent users. As a result of the study, CDC and NIH stopped conducting and funding research on N-9 as a microbicide out of concern for participants' safety. FDA continued to review available research on the safety of N-9 as part of its regulation of vaginal contraceptive products and, in 2003, proposed new warning labels for N-9 vaginal contraceptive products. As of March 2005, FDA was also in the process of developing a proposal for new warning labels for N-9 condoms. As of that date, FDA had not finalized the new warning labels for N-9 vaginal contraceptive products and had not proposed new warning labels for N-9 condoms. Representatives from two manufacturers of N-9 contraceptive products have reviewed research on N-9's safety in preparing comments on FDA's proposed warning labels.

The information CDC and FDA have provided to the public about the use of N-9 as a microbicide has been, at times, inconsistent. In the early 1990s, CDC cautioned that there was insufficient information to conclude that N-9 may prevent HIV transmission. By 1998, in response to new research, the agency informed the public that N-9 vaginal contraceptive products did not prevent HIV. For example, CDC's 1993 STD treatment guidelines cautioned that women should not assume that N-9 vaginal contraceptive products protect them against HIV, and the updated 1998 guidelines stated that vaginal contraceptive products offer no protection against HIV infection. During the same period, FDA also cautioned that N-9 had not been proven to prevent HIV transmission, but in 1999, a brochure on its Web site suggested that N-9, along with a condom, may be used to prevent HIV transmission. By 2000, CDC had responded to new research findings and had revised its educational publications to state that N-9 may actually

increase the risk of contracting HIV when used frequently. In contrast, FDA did not revise the brochure on its Web site that stated that some experts believe N-9 may prevent HIV and suggested using N-9 along with a condom. FDA left this information on its Web site until these statements were deleted in September 2003 when FDA officials realized this information was inconsistent with the proposed warning labels for N-9 vaginal contraceptive products. The three largest condom manufacturers have also taken steps to inform the public about N-9 and HIV. For example, one condom manufacturer has informed its consumers that N-9 does not prevent HIV transmission and may increase some users' risk of contracting HIV. In contrast, other manufacturers of contraceptive products that we interviewed have not taken such steps.

In recent years, some key manufacturers and public health organizations have stopped producing, distributing, or promoting N-9 condoms, and the percentage of these condoms on the market is reported to have decreased. In January 2004, one of the three largest condom manufacturers stopped producing N-9 condoms. Similarly, according to representatives from PPFA, the organization stopped manufacturing N-9 condoms in 2002. A representative from PPFA explained that this decision was based on a concern about the safety issues associated with N-9 condoms. Like PPFA, another key public health organization we interviewed has begun to recommend against the use of N-9 condoms.

In commenting on a draft of this report, the Department of Health and Human Services (HHS) provided clarification that GAO incorporated where appropriate.

Background

N-9 was developed as a contraceptive and is the only spermicide available in the United States. It is found in a variety of over-the-counter vaginal contraceptive products—including creams, foams, gels, and suppositories—and on N-9 condoms. Vaginal contraceptive products that contain N-9 have been sold over-the-counter in the United States for almost 50 years. N-9 condoms have been available over-the-counter in the United States since the early 1980s.

Federal Agency Responsibilities

Three federal agencies within HHS—CDC, NIH, and FDA—have responsibilities that affect the public's use of N-9 contraceptive products.

CDC CDC is responsible for conducting and reviewing research related to public health issues and disseminating this information to state public health agencies, medical professionals, and the public. CDC shares information, for example, on diseases such as HIV and uses a variety of means to do this, including publications such as the *Morbidity and Mortality Weekly Report* (MMWR)⁸ and treatment guidelines. It also provides information through its Web site and in letters issued directly to state health departments and other public health professionals.

NIH NIH, which comprises 27 separate institutes and centers, conducts research in its own laboratories and funds research in universities, medical schools, hospitals, and other research institutions. Some of this research investigates drugs used to prevent and treat various diseases, including HIV. In order to provide information to the public on various health issues, NIH may post the results of its research on its Web site and sometimes publishes summary reports on various research topics.

FDA FDA is responsible, among other things, for regulating the manufacture and sale of drugs and medical devices sold in the United States. FDA also regulates the labeling information provided by manufacturers of drugs and medical devices. FDA also seeks to educate the public about the products it regulates and uses a variety of means, including pamphlets, Web site information, and the *FDA Consumer* magazine⁹ to do this. Within FDA, two centers are involved in the review of N-9 contraceptive products—the Center for Drug Evaluation and Research (CDER), which oversees vaginal contraceptive drug products, and the Center for Devices and Radiological Health (CDRH), which oversees condoms, including N-9 condoms.

FDA reviews the active ingredients in specific categories of drugs that were sold over-the-counter in the United States prior to 1975 through a process known as the “monograph process.”¹⁰ Under the monograph process, FDA establishes the conditions under which specific categories of drugs, rather than specific products, are generally recognized as safe and effective and

⁸ CDC’s MMWR is a series of articles on public health issues that are based on reports sent to CDC by state and territorial health departments.

⁹ *FDA Consumer* is a publication intended to educate the public as well as health care providers about products that FDA regulates.

¹⁰ FDA also refers to the monograph process as the Over-the-Counter Drug Review.

not misbranded.¹¹ Examples of categories of drugs subject to the monograph process include antacids and certain cold and cough remedies. When FDA completes the monograph process, it issues a final monograph that describes labeling indications, warnings, and directions for use, among other things. Prior to the issuance of a final monograph, FDA policies allow over-the-counter drugs to stay on the market. However, FDA may pursue regulatory actions against these drugs—such as requiring labeling changes—if the agency determines that the failure to act poses a potential health hazard to consumers.¹²

Since N-9 was available over-the-counter prior to 1975, it is the subject of a monograph review for a category of drugs called vaginal contraceptive drug products.¹³ As of March 2005, FDA had not issued a final monograph for this category of drugs.¹⁴ Although some condoms on the market are lubricated with N-9, these N-9 condoms are not subject to the monograph review process for vaginal contraceptive products because FDA regulates these products as medical devices.¹⁵

¹¹ In the first step of the three-step monograph process, an Advisory Review Panel of nongovernment experts reviews data on active ingredients and provisionally classifies the ingredients as Category I (safe and effective), Category II (not safe and effective), or Category III (more data needed). The panel's report is published as an advance notice of proposed rule making in the *Federal Register*. In the second step, FDA publishes a tentative final monograph or proposed rule for the particular category of drugs. In the third step, FDA publishes a final monograph or final rule containing FDA's final conclusions. See 21 C.F.R. § 330.10.

¹² FDA Compliance Guide No. 7132b.15, March 1995.

¹³ In the rest of this report, we refer to FDA's category of "vaginal contraceptive drug products" as vaginal contraceptive products.

¹⁴ The first step of the monograph process for this category of drugs occurred in 1980 when FDA published the report of the Advisory Review Panel on over-the-counter contraceptives and other vaginal drug products, which provisionally classified N-9 as safe and effective as a contraceptive. See 45 Fed. Reg. 82014 (Dec. 12, 1980). The second step occurred in 1995, when FDA issued a proposed rule that required additional clinical research to determine the contraceptive effectiveness for different formulations of N-9. See 60 Fed. Reg. 6892 (Feb. 3, 1995). According to FDA officials, the issuance of the final monograph is pending its review of a large contraceptive efficacy study that was published in March 2004. FDA is allowing the continued marketing of vaginal contraceptive products pending completion of this review.

¹⁵ See 21 C.F.R. § 884.5300 and 21 C.F.R. § 884.5310.

Federal Agencies Have Researched the Safety and Effectiveness of N-9 as a Microbicide, While Manufacturers Reviewed Its Safety

Federal agencies have undertaken a variety of efforts to research the safety and effectiveness of N-9 as a microbicide. This research included funding, conducting, or reviewing studies on the safety and effectiveness of N-9 as a microbicide. It was largely conducted until 2000, when the preliminary results of a major clinical study prompted CDC and NIH to halt further research on N-9 as a microbicide because of safety concerns. FDA—as part of its regulation of vaginal contraceptive products—continued to review research on the safety of N-9 and proposed new warning labels for vaginal contraceptive products in 2003. Manufacturers reviewed the safety of N-9 for the purpose of commenting on the proposed warning labels.

Federal Agencies Researched the Safety and Effectiveness of N-9 as a Microbicide until 2000

During the 1990s, three federal agencies—CDC, NIH, and FDA—funded, conducted, or reviewed medical research to determine whether N-9 was safe and effective as a microbicide. CDC, as part of its public health efforts to prevent the spread of HIV, conducted and funded research involving N-9. For example, in 1996, CDC and others began a major 4-year study on the effectiveness of N-9 vaginal contraceptive products in preventing the transmission of STDs, including HIV, among female sex workers located in four countries. In addition, CDC compiled a bibliography of research on potential microbicides conducted through September 1996.¹⁶ Containing abstracts of over 55 safety and effectiveness studies and other reviews of N-9 vaginal contraceptive products and N-9 condoms, the bibliography was intended as a resource for clinicians, researchers, and public health specialists interested in microbicide research.

Like CDC, NIH conducted and funded research during the 1990s on N-9's safety and effectiveness as a microbicide. Within NIH, two institutes were primarily responsible for most of its N-9 research—the National Institute of Allergy and Infectious Diseases and the National Institute of Child Health and Human Development. NIH's research ranged from laboratory studies of

¹⁶ Centers for Disease Control and Prevention, *Guide to Microbicide Research and Development: HIV Infection, Selected Bibliography through September 1996*.

N-9's effect on animal tissue to randomized clinical trials that measured the effect of various N-9 vaginal contraceptive products in preventing HIV transmission among women.¹⁷

Although the FDA did not conduct or fund research on N-9, the agency reviewed research on N-9 vaginal contraceptive products as part of its monograph process. The agency convened an advisory committee meeting in 1996 to review available research on the safety and effectiveness of N-9 as both a contraceptive and a microbicide.¹⁸ This meeting included presentations on a wide variety of published and unpublished research, including laboratory studies of N-9 and clinical studies on N-9 vaginal contraceptive products. The meeting also included discussion about the implications of this research and identified guidelines for the design of future studies to address concerns about dosage and formulation differences in the research available at the time, among other things.

The results of the research on N-9 that federal agencies conducted, funded, and reviewed during the 1990s were inconsistent. For example, among the studies compiled in CDC's bibliography on microbicide research, some found that the use of N-9 vaginal contraceptives reduced the incidence of HIV as well as other STDs, while other studies indicated that frequent use of N-9 vaginal contraceptives may have irritated subjects' vaginal tissue, which may result in subjects being more susceptible to HIV infection. Throughout the 1990s, various reviews in clinical journals also characterized the results of research on N-9 as inconsistent.¹⁹ For example, a 1995 review in the journal *AIDS* noted the existence of "substantially

¹⁷ Laboratory testing is conducted to determine whether a drug has an effect on a disease in animals and whether it is reasonably safe for initial testing in humans. Randomized clinical trials are studies designed to determine the safety and effectiveness of a drug in humans by comparing the outcomes for a group using the drug to the outcomes for a similar group using a placebo or a standard therapy.

¹⁸ The meeting included representatives from the FDA advisory committees for anti-infective drugs, antiviral drugs, reproductive health drugs, and nonprescription drugs. FDA advisory committees are composed of academicians, clinicians, consumer group representatives, industry representatives, and patients or their caregivers. The committees provide independent advice to FDA in order to contribute to the quality of the agency's regulatory decision making.

¹⁹ Most of the reviewed research involved N-9 vaginal contraceptives.

different opinions” about the safety and effectiveness of N-9 when used for HIV prevention.²⁰ Similarly, a 1999 commentary in the *American Journal of Public Health* noted that epidemiologic studies on N-9 were conflicting.²¹

During the 1990s, reviewers of studies involving N-9 observed that several factors may have accounted for the inconsistency of the research results. For example, studies varied in terms of the dosage of N-9 and the chemical formulation of the contraceptive product used.^{22,23} Additionally, the different populations studied may have affected the outcomes of the research. For example, some studies were based on the experience of sex workers, who used N-9 vaginal contraceptive products with relatively higher frequency than the populations in other studies. Studies were also not always comparable to the extent that they varied in their sample sizes.

In 2000, after the preliminary results of a major clinical study—known as the COL-1492 study—were reported, CDC and NIH stopped conducting and funding research on N-9 as a microbicide out of concern for participants’ safety.²⁴ Compared to the results of earlier studies, the preliminary results of the COL-1492 study suggested more strongly that N-9 did not prevent HIV infection and, in addition, that N-9 may increase the risk of infection among frequent users.²⁵ The COL-1492 study compared the use of an N-9 vaginal contraceptive gel called COL-1492 to a vaginal moisturizer without N-9 among 892 sex workers in Benin, Cote d’Ivoire, South Africa, and

²⁰ C. Elias and L.L. Heise, “Nonoxynol-9: The Need for Policy in the Face of Uncertainty,” *AIDS*, vol. 9, no. 3 (1995).

²¹ P. Feldblum, S. Weir, and W. Cates, “The Protective Effect of Condoms and Nonoxynol-9 Against HIV Infection,” *American Journal of Public Health*, vol. 89, no. 1 (1999).

²² Since the monograph process for over-the-counter drugs evaluates the active ingredients in categories of drugs rather than specific products, N-9 vaginal contraceptive products on the market may vary in formulation and dosage.

²³ See, for example, R.L. Cook and M.J. Rosenberg, “Do Spermicides Containing Nonoxynol-9 Prevent Sexually Transmitted Infections? A Meta-Analysis,” *Sexually Transmitted Diseases*, vol. 25, no. 3 (March 1998).

²⁴ Although NIH stopped conducting and funding research on N-9 as a microbicide, it continued research on the effectiveness of N-9 as a contraceptive product.

²⁵ This study was conducted primarily in locations with a high prevalence of HIV infection and among sex workers, who typically have multiple partners and were, therefore, considered high risk. The risk of becoming infected with HIV increases with the number of sexual partners, whether or not condoms are used, and the local prevalence of infection.

Thailand. The preliminary results of this study indicated that the incidence of HIV infection among users of the N-9 vaginal contraceptive gel was 48 percent higher than among users of the moisturizer without N-9. Moreover, the study showed there was little effect of N-9 vaginal contraceptive use on the incidence of certain other STD infections, such as gonorrhea and chlamydia. After the preliminary results of the COL-1492 study became available, officials at CDC and NIH decided to discontinue researching N-9 as a possible microbicide for HIV.

After 2000, FDA Continued to Review Research on the Safety of N-9 as Part of Its Regulation of N-9 Contraceptive Products

Although federal agencies stopped conducting and funding research on N-9 as a potential microbicide in 2000, FDA continued to review research on the safety of N-9 as part of the agency's regulation of vaginal contraceptive products under the monograph process. During this review, FDA considered, among other things, the recommendations of two key public health reports,²⁶ published in 2002 by CDC and by the World Health Organization (WHO) in collaboration with the CONRAD Program.²⁷ The reports recommended that N-9 not be used to prevent HIV transmission and warned that frequent use of N-9 vaginal contraceptive products may cause genital lesions, which may increase the risk of HIV infection in persons at high risk for HIV. The reports also recommended that N-9 condoms not be promoted because there was no published scientific evidence that N-9-lubricated condoms provide any additional protection against STDs compared with other condoms.²⁸ The reports also recommended that N-9 contraceptive products, including both N-9 condoms and vaginal contraceptive products, should not be used during anal intercourse. The WHO/CONRAD report concluded that for women at

²⁶ Centers for Disease Control and Prevention, "Nonoxynol-9 Spermicide Contraception Use – United States, 1999," *Morbidity and Mortality Weekly Report*, vol. 51, no. 18 (May 2002). World Health Organization/CONRAD, *WHO/CONRAD Technical Consultation on Nonoxynol-9: Summary Report* (June 2002).

²⁷ The CONRAD Program, which is a nonprofit organization, supports the development of methods to prevent pregnancy and STDs, including HIV/AIDS. Funded primarily by the Agency for International Development, the program offers both financial support as well as technical assistance for the various stages of product development.

²⁸ CDC did not advise against using previously purchased N-9 condoms. However, because of their shorter shelf life, higher cost, association with urinary tract infections in women, and lack of apparent benefit compared with other lubricated condoms, CDC recommended against purchasing any additional N-9 condoms.

low risk for HIV infection, the use of N-9 vaginal contraceptives remained a viable option.

Based on its review of this and other information, including the published results of the COL-1492 study,²⁹ FDA determined that the use of N-9 vaginal contraceptive products may pose a potential health hazard to consumers and proposed new warning labels for N-9 vaginal contraceptive products in January 2003.³⁰ Specifically, FDA proposed adding warning labels that indicate that vaginal contraceptive products with N-9 do not protect against HIV or other STDs and that frequent use, such as more than once a day, of N-9 can increase vaginal irritation, which may increase the risk of contracting HIV from infected partners. The proposed warnings also indicate that the labeled products are for vaginal use only.

As of March 2005, FDA was in the process of finalizing the rule for new warning labels for vaginal contraceptive products containing N-9. According to FDA officials, a draft of the final rule had been completed, and the rule had begun the clearance process within HHS. Officials told us that they expected the clearance process to be completed by September 2005, after which the final rule would be published. According to FDA officials, the rule-making process used to establish new warning labels typically takes more than 2 years.

As part of the process for establishing new warning labels for N-9 vaginal contraceptive products, FDA reviewed more than 150 comments submitted in response to the proposed warning labels. These comments ranged from concerns that the proposed language was not strong or specific enough to comments indicating that FDA had gone too far in its proposed warning. FDA officials also stated that 10 specific issues brought up in the public comments on the proposed warning labels required extensive review,

²⁹ While there were some differences between the published study and the preliminary results reported in 2000, the conclusions of the published study were consistent with those of the preliminary results. The published study reported that “nonoxynol-9 increased the risk of HIV infection compared with the placebo.” It also stated that “risk was especially high in women who used the study drug more than 3.5 times per day.” See L. Van Damme, et al., “Effectiveness of COL-1492, a Nonoxynol-9 Vaginal Gel, On HIV-1 Transmission in Female Sex Workers: A Randomised Controlled Trial,” *The Lancet*, vol. 360 (September 2002).

³⁰ FDA policy states that FDA may pursue regulatory action against over-the-counter drugs prior to the adoption of a final monograph if the agency determines that the failure to act would pose a potential health hazard to consumers. See FDA Compliance Guide No. 7132b.15, March 1995.

including comments that the labels should specifically warn against using vaginal contraceptive products for anal intercourse and concerns that the proposed warning labels might discourage women who are at low risk for HIV from using N-9 as a contraceptive.³¹

FDA officials told us they also plan to issue guidance and proposed new warning labels for condoms—including warnings for N-9 condoms. They said they expect a draft to be issued for public comment in 2005. These officials noted that they considered new warning labels for N-9 condoms in the context of a larger initiative started in 2001 to review condom labeling for medical accuracy with respect to the overall effectiveness of condoms against STDs.³² FDA officials told us that officials from CDRH and CDER collaborated to ensure that the new labeling proposals for N-9 condoms and N-9 vaginal contraceptive products will be consistent.³³ As of March 2005, an HHS official told us that HHS had completed its review of the draft guidance and labels. After this review, FDA officials told us the draft would be sent to the Office of Management and Budget for review before being issued for public comment. FDA officials said that FDA expects to be able to issue the draft guidance and condom warning labels by May 2005.

³¹ Among the more than 150 comments, FDA received a range of comments from 15 health and research organizations—such as the American College of Obstetricians and Gynecologists and Family Health International. The majority of these organizations supported FDA's labeling proposal, and half of them recommended that the FDA go even further than saying “for vaginal use only,” either by warning that N-9 vaginal contraceptives should not be used for anal intercourse or by notifying consumers that there is an increased risk when used for anal intercourse. Four organizations stated that the warnings should be more specific in assuring women at low risk for HIV that N-9 can be safe and effective as a contraceptive. In addition to comments from health and research organizations, FDA received comments from two manufacturers of contraceptive products containing N-9. These manufacturers indicated that the proposed warning labels went too far in suggesting that N-9 may lead to increased HIV transmission and might discourage women who are at low risk for HIV from using N-9 as a contraceptive.

³² The Consolidated Appropriations Act of 2001 required FDA to examine condom labeling. See Pub. L. No. 106-554, App. A, § 516(b), 114 Stat. 2763, 2763A-73 (2000).

³³ Officials also noted that in the past, FDA had not permitted condom labeling to claim that N-9 provided any additional protection against HIV or other STDs.

Manufacturers of N-9 Contraceptive Products Have Researched the Safety of N-9

Two manufacturers of N-9 contraceptive products that we interviewed have researched the safety of N-9. Specifically, they reviewed the research literature on the safety of N-9 in order to prepare comments in response to the language of FDA's proposed warning labels for vaginal contraceptive products. For example, one manufacturer concluded that FDA's proposed labeling—that implied a link between the use of N-9 vaginal contraceptive products and an increased risk of HIV transmission—was not sufficiently supported by the scientific literature. However, no manufacturers we interviewed have conducted research on N-9's effectiveness as a microbicide. Manufacturers would only be required to conduct such research if they were to seek approval from FDA to use N-9 vaginal contraceptives for a new indication—such as HIV prevention. However, FDA officials reported that no manufacturers sought approval for a new indication for N-9.

The Information Provided to the Public about the Use of N-9 as a Microbicide Has Been, at Times, Inconsistent

The information CDC and FDA provided the public about the use of N-9 as a microbicide has been, at times, inconsistent. In the early 1990s, CDC cautioned that there was insufficient information to conclude that N-9 may prevent HIV transmission. By 1998, in response to new research, CDC informed the public that N-9 vaginal contraceptive products did not prevent HIV. During the same period, FDA also cautioned that N-9 had not been proven to prevent HIV transmission, but in 1999, a brochure on its Web site stated that N-9, along with a condom, may be used to prevent HIV transmission. By 2000, CDC stated that N-9 may actually increase the risk of contracting HIV when used frequently. FDA, in contrast, did not revise the brochure on its Web site that stated some experts believe N-9 may prevent HIV and suggested using N-9 along with a condom. Some manufacturers we interviewed have also taken steps to inform the public about N-9 and HIV, while others have not. (See app. I for a timeline of selected events and publications related to N-9's potential use as a microbicide.)

At Times, CDC and FDA Provided Inconsistent Information about the Use of N-9 to Prevent HIV

In the early 1990s, based on the information that was available at the time, CDC cautioned that there was insufficient information to conclude that N-9 may prevent HIV transmission.³⁴ According to CDC's 1993 STD treatment guidelines,³⁵ "protection of women against HIV infection should not be assumed from the use of vaginal spermicides, vaginal sponges, or diaphragms." This document also stated, "No data exist to indicate that condoms lubricated with spermicides are more effective than other lubricated condoms in protecting against the transmission of HIV infection...." This document recommended the use of condoms, with or without a spermicide in order to protect against STDs, including HIV.³⁶ Similarly, an article in a 1993 issue of CDC's MMWR cautioned that there was no evidence that N-9 prevents HIV transmission. According to this issue of MMWR, "No reports indicate that nonoxynol-9 used alone without condoms is effective for preventing sexual transmission of HIV." This document also repeated the recommendation to use condoms with or without a spermicide.³⁷

By 1998, in response to new research, CDC informed the public that N-9 should not be used as a microbicide because it does not protect against HIV and revised its STD treatment guidelines to state that "vaginal spermicides offer no protection against HIV infection, and spermicides are not recommended for HIV prevention."³⁸ At this time, CDC did not revise its recommendation to use condoms with or without spermicide.

³⁴ Before 1990, CDC published three articles in MMWR stating that based on information from laboratory studies, additional protection against HIV and other STDs might be obtained from using spermicides in conjunction with condoms.

³⁵ CDC's STD treatment guidelines include information for the treatment of patients who have STDs. The guidelines were developed after consultation with a group of professionals knowledgeable in the field of STDs. These guidelines are periodically updated as new information becomes available.

³⁶ Centers for Disease Control and Prevention, "1993 Sexually Transmitted Diseases Treatment Guidelines," *Morbidity and Mortality Weekly Report*, vol. 42, no. RR-14 (September 1993).

³⁷ Centers for Disease Control and Prevention, "Update: Barrier Protection Against HIV Infection and Other Sexually Transmitted Diseases," *Morbidity and Mortality Weekly Report*, vol. 42, no. 30 (August 1993).

³⁸ Centers for Disease Control and Prevention, "1998 Guidelines for Treatment of Sexually Transmitted Diseases," *Morbidity and Mortality Weekly Report*, vol. 47, no. RR-1 (January 1998).

FDA's educational publications during the 1990s also cautioned that N-9 had not been proven to prevent HIV transmission, but in some cases, the agency suggested that N-9, along with a condom, may be used to prevent HIV transmission. For example, a 1990 article published in the magazine *FDA Consumer* stated, "Although it has not been scientifically proven, it is possible that Nonoxynol-9 may reduce the risk of transmission of the AIDS virus during intercourse as well. Using a spermicide along with a latex condom is therefore advisable, and is an added precaution in case the condom breaks.... Some experts think that even if a condom with spermicide is used, additional spermicide in the form of a jelly, cream or foam should be added."³⁹ In 1998, an *FDA Consumer* article stated that N-9 may reduce the risk of transmitting certain STDs, but cautioned that it has not been proven to prevent sexual transmission of HIV.⁴⁰ Another 1998 *FDA Consumer* article stated that spermicides alone do not give adequate protection against HIV.⁴¹ However, in 1999, FDA indicated to the public that N-9 may protect them against HIV transmission. An FDA brochure posted to the Web site and titled *Condoms and Sexually Transmitted Diseases...Especially AIDS* stated, "Some experts believe nonoxynol-9 may kill the AIDS virus during intercourse, too. So you might want to use a spermicide along with a latex condom as an added precaution...."⁴²

In response to the preliminary results of the COL-1492 study that were released at the 2000 International AIDS Conference, CDC revised its earlier position on N-9. CDC had previously cautioned that N-9 used alone without a condom offered no protection against HIV infection and was not recommended for HIV prevention. However, by 2000 CDC's educational publications had included the statement that N-9 may increase the risk of transmission when used frequently. In an August 2000 letter to health care providers and public health personnel, CDC reported that the preliminary results of the COL-1492 study demonstrated that N-9 did not protect against

³⁹ Food and Drug Administration, "Latex Condoms Lessen Risks of STDs," *FDA Consumer* (1990).

⁴⁰ Food and Drug Administration, "Condoms: Barriers to Bad News," *FDA Consumer* (1998).

⁴¹ Food and Drug Administration, "On the Teen Scene: Preventing STDs," *FDA Consumer* (1998).

⁴² This Web site posting was of a brochure originally issued in 1990. The document stated that the information was current as of December 2, 1999. See Food and Drug Administration, *Condoms and Sexually Transmitted Diseases...Especially AIDS* (Rockville, Md.: 1990).

HIV infection and may have caused more transmission. This letter also stated that N-9 should not be recommended as an effective means of HIV prevention and that the use of N-9 for HIV prevention may be harmful to certain users. This warning was also published in an August 2000 issue of MMWR.⁴³ Similarly, in 2002 when CDC revised its STD treatment guidelines,⁴⁴ it included information indicating that spermicides containing N-9 were not effective in preventing HIV infection and that frequent use had been associated with genital lesions, which may be associated with an increased risk of HIV transmission. These revised STD treatment guidelines further stated that condoms lubricated with spermicides are no more effective than other lubricated condoms in preventing HIV transmission, and also stated that “purchase of any additional condoms lubricated with the spermicide N-9 is not recommended.”⁴⁵ This information also appeared in an article in a May 2002 issue of MMWR.⁴⁶

⁴³ Centers for Disease Control and Prevention, “Notice to Readers: CDC Statement on Study Results of Product Containing Nonoxynol-9,” *Morbidity and Mortality Weekly Report*, vol. 49, no. 31 (August 2000).

⁴⁴ Since 1990, CDC has revised its STD treatment guidelines three times—in 1993, 1998, and 2002.

⁴⁵ Centers for Disease Control and Prevention, “Sexually Transmitted Diseases Treatment Guidelines 2002,” *Morbidity and Mortality Weekly Report*, vol. 51, no. RR-6 (May 2002).

⁴⁶ Centers for Disease Control and Prevention, “Nonoxynol-9 Spermicide Contraception Use – United States, 1999,” *Morbidity and Mortality Weekly Report*, vol. 51, no. 18 (May 2002).

While CDC was informing the public that N-9 was not effective in preventing HIV and that frequent use of N-9 may increase the risk of HIV transmission, the public would have obtained different information from FDA. An FDA official told us that the agency has not disseminated any new educational materials related to N-9 and HIV transmission since 2000. However, FDA left its brochure—which stated that some experts believe that N-9 may prevent HIV transmission—on its Web site until this information was deleted in September 2003 when FDA officials realized the information in the brochure on the Web site was inconsistent with the proposed warning labels for N-9 vaginal contraceptive products.⁴⁷ According to one FDA official, documents on the agency’s Web site were updated in an “ad hoc” manner, rather than through an official process.⁴⁸

Some Manufacturers Have Taken Steps to Inform Consumers about N-9 and HIV

The three largest condom manufacturers have taken steps to inform the public about N-9 and HIV. In particular, one condom manufacturer has taken multiple steps to inform its consumers that N-9 does not prevent HIV transmission and may increase some users’ risk of contracting HIV. This large manufacturer of condoms has added warning labels to N-9 condom packaging that indicate that N-9 is not effective in protecting against HIV. This manufacturer has also published pamphlets and used similar language on its Web site to explain to consumers the risks associated with N-9. In addition, two other large manufacturers of condoms added warnings to their Web sites about the use of N-9. In contrast, officials from major manufacturers of vaginal contraceptive products that we interviewed told us they have not disseminated such information. One of these manufacturers reported that its review of research on N-9 suggested that the link between the use of N-9 and an increased risk of HIV infection was speculation.

⁴⁷ In January 2003, FDA proposed adding warning labels that indicate that vaginal contraceptive products with N-9 do not protect against HIV or other STDs and that frequent use, such as more than once a day, of N-9 can increase vaginal irritation, which may increase the risk of contracting HIV from infected partners.

⁴⁸ An official from FDA’s Office of Public Affairs stated that the office is responsible for updating information available on the FDA Web site.

Some Manufacturers and Public Health Organizations Have Stopped Producing and Distributing N-9 Condoms

In recent years, there have been several changes in the production, distribution, and promotion of N-9 condoms. In January 2004, the condom manufacturer SSL International announced that it was halting production of its Durex brand condoms that are lubricated with N-9 because of a decrease in sales to public health agencies and because of an anticipated decrease in retail sales. SSL International representatives attributed this decrease in sales to safety concerns raised by the 2002 release of the WHO/CONRAD report. Another large manufacturer of condoms reported that the percentage of N-9 condoms sold on the retail market declined from 2000 to 2003.

Like SSL International, PPFA and a leading distributor—Mayer Laboratories—have also stopped manufacturing and distributing N-9 condoms. A representative from PPFA told us that the organization stopped manufacturing N-9 condoms in June 2002 because of safety concerns based on published scientific studies indicating that N-9 does not protect against HIV and that frequent N-9 use may actually increase HIV transmission. In addition, a representative from PPFA stated that its decision to halt production of N-9 condoms was influenced by the release of the conclusions of the WHO/CONRAD report and the outcome of a meeting with public health entities organized by the Global Campaign for Microbicides.⁴⁹ Another public health organization, the Gay Men’s Health Clinic in New York, has also begun to recommend that clients not use N-9 condoms. As of early in 2003, a distributor—Mayer Laboratories—stopped distributing N-9 condoms. Information from Mayer Laboratories stated that this decision was based on a concern about the safety of N-9 condoms.

Concluding Observations

CDC’s and NIH’s efforts to research N-9’s potential use as a microbicide ended in 2000, when the preliminary results of a major clinical trial indicated that N-9 may actually increase the risk of contracting HIV. CDC has warned that N-9 may increase the risk of HIV transmission when used frequently, and some manufacturers of N-9 condoms have taken steps to either add their own warning labels or remove their N-9 condoms from the market, while other manufacturers have not taken such steps. FDA has proposed requiring new warning labels that indicate that N-9 vaginal

⁴⁹ The Global Campaign for Microbicides is an organization that works to accelerate microbicide development, facilitate widespread access and use, and protect the needs and interests of users through advocacy, policy analysis, and social science research.

contraceptive products do not protect against HIV or other STDs and that frequent use, such as more than once a day, may increase the risk of contracting HIV. FDA is also developing proposed warning labels for N-9 condoms. While FDA expects to issue the final rule for the new warning labels for vaginal contraceptive products by September 2005, it has not yet issued proposed warning labels for N-9 condoms, and it has not indicated a target date to issue the final warning labels for N-9 condoms. Since FDA is still in the process of completing warning label changes for N-9 vaginal contraceptive products and condoms, the public may be left in doubt about the appropriate uses of these products until FDA finalizes these warnings. Further, the public may be at risk if the products are used inappropriately.

Agency Comments

HHS provided written comments on a draft of this report. (See app. II).

In its written comments, HHS stated that the final sentence in the draft report—that said the public may be at risk until FDA finalizes the warning labels for N-9 vaginal contraceptive products and N-9 condoms—may unintentionally undermine efforts to inform the public of the protection provided by condoms. HHS suggested we modify this to say that consumers may be left in doubt about the appropriate uses of these products. We have revised the conclusion to acknowledge that until FDA finalizes its warning labels, consumers may be left in doubt about the appropriate uses of these products. However, the conclusion also states that the public may be at risk if the products are used inappropriately.

In its written comments, HHS stated that the draft did not indicate that FDA had never permitted condom labeling to claim that N-9 provides any additional protection against HIV or other STDs. To ensure clarity on this issue, we have added this statement to the report. HHS's written comments also stated that it is important to make clear that the barrier features of condoms provide the primary protection against STDs and the primary contraceptive protection. While this is an important fact in educating consumers about methods to protect themselves against STDs, the objectives of this report were focused on N-9 and its potential as a microbicide.

HHS's written comments also stated that FDA's primary means of public health communication is through product labeling oversight and that FDA has, on occasion, provided supplementary information through consumer outreach efforts. The draft report noted the role FDA has in labeling oversight and described FDA's proposed warning labels for N-9 vaginal

contraceptive products and its efforts to develop proposed warning labels for N-9 condoms. The draft report also described the information FDA provided to the public through a brochure that it posted to its Web site and through *FDA Consumer* magazine articles. HHS's written comments also stated that the supplementary statements FDA provided to the public through consumer outreach efforts always acknowledged the scientific uncertainty concerning the effectiveness of N-9 as a protection against STDs. Examples of FDA's acknowledgement of scientific uncertainty were provided in the draft report.

HHS also commented that the timeline in appendix I should begin with the 1988 CDC brochure *Understanding AIDS*, which advised that N-9, when used with a condom, might provide additional protection against HIV. We mentioned this brochure in the introduction to the draft report when we stated that in the mid-1980s N-9 showed promise as a potential microbicide for STDs, including HIV. However, as we stated in the scope and methodology section of the draft report, we focused our review on efforts to research and provide public information on N-9 and HIV from 1990 to the present because concerns about the safety of N-9 in preventing HIV first began to surface in about 1990. Further, HHS commented that the timeline should make clear that the first indication that N-9 presented added risks did not emerge until 2000 (the COL-1492 study). However, this study was not the first indication that N-9 presented added risks, and the draft report discussed earlier concerns.

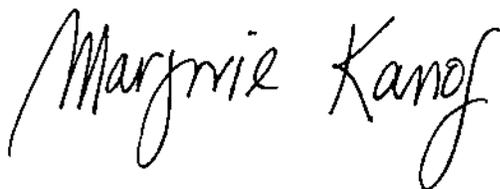
HHS's written comments also made a number of other suggestions to clarify the draft report, which we incorporated. First, HHS suggested that we clearly indicate in the report when we are discussing vaginal contraceptive products containing N-9, condoms with N-9, or both. We have reviewed the report for clarity and made changes where necessary. Second, HHS's comments stated that much of the research discussed in the report was restricted to vaginal contraceptive products and that these studies did not involve N-9 condoms. We have clarified this point in the report. Finally, HHS's comments stated that the 1999 FDA brochure *Condoms and Sexually Transmitted Diseases . . . Especially AIDS* was an Internet posting of a brochure initially issued in 1990. We clarified the text of our report to note that the Web site posting was of a brochure originally issued in 1990 and that the document stated the information was current as of December 2, 1999. We also added the 1990 brochure to the timeline in appendix I.

HHS included several other comments. First, HHS stated that we should be clear that N-9 condoms are regulated as medical devices not through the monograph process. This information was discussed in the background section of the draft report. Second, HHS's written comments stated that the report should recognize that some manufacturers stopped selling condoms with N-9 because of economic considerations and not safety concerns. This information was included in the draft report and we noted further that one manufacturer attributed the decrease in sales of N-9 condoms to the safety concerns raised by the 2002 release of the WHO/CONDRAD report. Third, HHS raised concerns that the draft report had not explained the significance of the actions of manufacturers. This information was included in the draft report. Finally, HHS's comments said we should note that the report on the COL-1492 study was published in 2002 and the information available prior to that time could be considered only preliminary. This information was also reflected in the draft report and in the timeline in appendix I.

HHS's comments are reprinted in appendix II. HHS also provided technical comments, which we incorporated into the report as appropriate.

As we agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from its date. We will then send copies to others who are interested and make copies available to others who request them. In addition, this report will be available at no charge on GAO's Web site at <http://www.gao.gov>.

If you or your staff have any questions about this report, please call me at (202) 512-7114. Another contact and key contributors are listed in appendix III.



Marjorie Kanof
Managing Director, Health Care

Timeline of Selected Events and Publications Related to N-9's Potential Use as a Microbicide, 1990–2004

1990s		2000s	2000s
	<p>1990: An FDA brochure, <i>Condoms and STDs... Especially AIDS</i>, stated that "Some experts believe nonoxynol-9 may kill the AIDS virus during intercourse, too. So you might want to use a spermicide along with a latex condom as an added precaution...."</p> <p>1990: An FDA Consumer magazine article, "Latex Condoms Lessen the Risk of STDs," stated that "Although it has not been scientifically proven, it is possible that nonoxynol-9 may reduce the risk of transmission of the AIDS virus during intercourse...."</p> <p>1993: "CDC Update: Barrier Protection Against HIV Infection and Other Sexually Transmitted Diseases" in MMWR stated that "No reports indicate that nonoxynol-9 used alone without condoms is effective for preventing sexual transmission of HIV.... No data exist to indicate that condoms lubricated with spermicides are more effective than other lubricated condoms in protecting against the transmission of HIV infection.... Therefore, latex condoms with or without spermicides are recommended."</p> <p>1993: CDC's 1993 STD treatment guidelines stated that "protection of women against HIV infection should not be assumed from the use of vaginal spermicides, vaginal sponges, or diaphragms."</p> <p>1997: CDC publication <i>What We Know About Nonoxynol-9 for HIV and STD Prevention</i> stated that "CDC does not recommend using spermicide alone to prevent HIV infection."</p> <p>1998: CDC's 1998 STD treatment guidelines stated that "vaginal spermicides offer no protection against HIV infection, and spermicides are not recommended for HIV prevention ... the consistent use of condoms, with or without spermicidal lubricant or vaginal application of spermicide is recommended."</p> <p>1998: An FDA Consumer magazine article, "Condoms: Barriers to Bad News," stated that "The spermicide nonoxynol-9, used in some condoms, has been shown to be effective as a contraceptive, and may reduce the risk of transmitting certain STDs. But the spermicide has not been proven to prevent sexual transmission of HIV."</p>	<p>1998: An FDA Consumer magazine article, "On the Teen Scene: Preventing STDs," stated that "... spermicides alone ... do not give adequate protection against HIV and other STDs."</p> <p>1999: An FDA brochure on its Web site and titled <i>Condoms and STDs... Especially AIDS</i> continued to include the statement "Some experts believe nonoxynol-9 may kill the AIDS virus during intercourse, too. So you might want to use a spermicide along with a latex condom as an added precaution...."</p> <p>2000: Preliminary results of a major clinical study among high-risk female sex workers were presented at the International AIDS conference in Durban, South Africa. The results indicate that N-9 is not effective as a microbicide against HIV and may increase certain users' risk of contracting the virus.</p> <p>2000: NIH and CDC reported that the agencies halted all studies actively pursuing N-9's use as a microbicide between 2000 and 2001.</p> <p>2000: A CDC letter issued to health care providers and public health personnel stated that because N-9 has been shown to be ineffective against HIV and may increase HIV risk among certain user groups, N-9 should not be recommended for HIV prevention.</p> <p>2001: WHO, in collaboration with CONRAD, convened a meeting to review the available literature regarding N-9's safety and effectiveness as a spermicide and a microbicide.</p> <p>2002: The final results of the presentation at the International AIDS conference held in Durban, South Africa, were published in <i>The Lancet</i>.</p> <p>2002: CDC published a report in MMWR stating, "Sexually active women should consider their individual HIV/STD infection risk when choosing a method of contraception. Providers of family planning services should inform women at risk for HIV/STDs that N-9 contraceptives do not protect against these infections."</p>	<p>2002: CDC's 2002 STD treatment guidelines stated that "Recent evidence has indicated that vaginal spermicides containing nonoxynol-9 (N-9) are not effective in preventing ... HIV infection. Thus, spermicides alone are not recommended for STD/HIV prevention. Frequent use of spermicides containing N-9 ... may be associated with an increased risk of HIV transmission Purchase of any additional condoms lubricated with the spermicide N-9 is not recommended...."</p> <p>2002: WHO and CONRAD published the summary report of their consultation on the available literature regarding N-9's safety and effectiveness as a spermicide and a microbicide.</p> <p>2002: PPFA halted production and distribution of N-9 condoms.</p> <p>2003: Mayer Laboratories halted distribution of N-9 condoms.</p> <p>2003: FDA proposed warning labels for vaginal contraceptive drug product packaging. The proposed warning stated that vaginal contraceptive products with N-9 do not protect against HIV or other STDs and that frequent use of N-9 can increase vaginal irritation, which may increase the risk of contracting HIV or other STDs. The warnings also indicated that the labeled products were for vaginal use only.</p> <p>2004: SSL International halted production of its Durex brand condoms that were lubricated with N-9 because of a decrease in sales to public health outlets and a projected decrease in retail sales.</p>

Source: GAO.

Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

MAR 22 2005

Ms. Marjorie Kanof
Managing Director, Health Care
U.S. Government Accountability Office
Washington, DC 20548

Dear Ms. Kanof:

Enclosed are the Department's comments on the U.S. Government Accountability Office's (GAO's) draft report entitled, "HHS—Efforts to Research and Inform the Public About Nonoxynol-9's Safety and Effectiveness in Preventing HIV" (GAO-05-399). The comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

The Department provided several technical comments directly to your staff.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely,

A handwritten signature in cursive script that reads "Daniel R. Levinson".

Daniel R. Levinson
Acting Inspector General

Enclosure

The Office of Inspector General (OIG) is transmitting the Department's response to this draft report in our capacity as the Department's designated focal point and coordinator for U.S. Government Accountability Office reports. OIG has not conducted an independent assessment of these comments and therefore expresses no opinion on them.

Appendix II
Comments from the Department of Health
and Human Services

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES
ON THE U.S. GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT:
"HHS—EFFORTS TO RESEARCH AND INFORM THE PUBLIC ABOUT
NONOXYNOL-9'S SAFETY AND EFFECTIVENESS IN PREVENTING HIV"
(GAO-05-399)

The Department of Health and Human Services (HHS) appreciates the opportunity to comment on the U.S. Government Accountability Office's (GAO's) draft report.

Key Points

Condom labeling. GAO's draft does not include any discussion of a key feature of the HHS, Food and Drug Administration's (FDA) regulation of condoms with spermicidal lubricant containing Nonoxynol-9 (N-9). FDA has *never permitted* condom labeling to claim that N-9 provides any additional protection against human immunodeficiency virus (HIV) or other sexually transmitted diseases (STDs). The only claims that may be made in condom labeling concerning N-9 relate to its use as a spermicide which some believe provides the condom with additional contraceptive protection. It is also important to make clear that the *barrier* features of condoms provide the primary protection against STDs and the primary contraceptive protection.

Public health message. HHS is concerned that the final sentence of the draft report (page 26) may unintentionally undermine efforts to inform the public of the protection provided by condoms. If the choice is to use a condom with N-9 or to have unprotected sex in a potentially risky situation, an N-9 condom is by far the better choice. GAO's language may leave some consumers to believe that the reverse is true, because "the public may be at risk." We suggest GAO modify the sentence to read, "**Until FDA completes the rules making changes to the labels for N-9 vaginal contraceptive products and condoms with N-9, consumers may be left in doubt concerning the appropriate uses of these products.**" FDA recognizes the importance of making these labeling changes, and is committed to completing them as rapidly as possible.

General Comments

The report would be improved, and would be more accurate, if it clearly indicated when it is discussing *both* vaginal contraceptive products containing N-9 (regulated as drugs) and condoms with N-9 (regulated as devices), and when it is discussing *only* vaginal contraceptive products or *only* condoms. The report would also be improved if it separately discussed FDA's role in product labeling and FDA's public communications concerning N-9 products.

With regard to public communications, FDA's primary means of public health communication is through product labeling oversight. FDA has on occasion provided supplementary information through consumer outreach efforts, and those supplementary statements have always acknowledged the scientific uncertainty concerning the effectiveness of N-9 as a protection against STDs. With regard to labeling, as discussed above, FDA has never permitted condom

Appendix II
Comments from the Department of Health
and Human Services

labeling to claim that N-9 provides any additional protection against HIV or other STDs, and GAO's report should make this clear.

How Devices Are Regulated

FDA previously provided GAO a short discussion of how medical devices, including condoms with N-9, are regulated; this discussion has been omitted from the draft report. The report discusses the monograph process used to approve drugs, but many readers may not understand that condoms with N-9 are regulated as medical devices and are cleared through the 510(k) premarket notification process, not the monograph process. If GAO needs further information about the 510(k) process, or clarification of the information previously provided, FDA would be glad to help.

Limits of Reported Research

GAO needs to make clear that much of the research discussed in the report was restricted to vaginal contraceptive products, and that these studies did not involve condoms with N-9. For example, the completed arm of the COL-1492 study was confined to very narrow circumstances (sex workers using N-9 vaginal contraceptive products three or more times a day) and *did not* involve condoms with N-9.

Actions by Manufacturers

GAO should recognize that some of the manufacturers' actions discussed were prompted by economic considerations, not by safety concerns. One manufacturer informed FDA that it stopped selling condoms with N-9 simply because there was insufficient consumer demand for their condoms with N-9. Although some manufacturers have decided not to manufacture condoms with N-9, other manufacturers still see market demand from low-risk couples who want the additional contraceptive protection an N-9 condom may offer.

Additional information on Durex cessation of marketing of condoms with N-9. FDA has provided a letter dated January 12, 2004, from Durex to its customers explaining why it would no longer market condoms with N-9. Durex did not cite safety concerns as a reason it would no longer market these products; the reason cited was an anticipated "reduction in demand for spermicidally-lubricated condoms."

The draft report at times mentions that manufacturers have taken some action, but does not explain the significance, if any, of that action. For example, page 6, paragraph 1, last sentence states: "Representatives from two manufacturers . . . reviewed research . . . in preparing comments on FDA's proposed warning labels." What did these manufacturers conclude, and how did those conclusions affect their comments? (This language is also on the Highlights page, last sentence of the paragraph "What GAO found.") In other instances, actions by manufacturers are discussed, but the discussion does not link clearly to the immediately preceding or surrounding content. For example, the last three sentences of the first partial paragraph on page 7

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Comments from the Department of Health
and Human Services

appear to belong to a separate paragraph. One of the examples given in these last three sentences also states that the manufacturer has informed its consumers, and it would be useful to include information on those actions.

It may be useful for GAO to consolidate its discussion of manufacturer actions in a separate section of the report, particularly since the major focus of the report is on actions taken by HHS agencies.

The “1999 Brochure”

A review of the 1990 FDA brochure, *Condoms and Sexually Transmitted Diseases . . . especially AIDS*, and the 1999 Internet posting with the same title will show that the two documents are identical, except the Internet posting omits graphics, corrects two single-letter typos, and omits a short paragraph about the (hardcopy) booklet (“This Booklet will answer many of your questions about condoms. . .”). FDA believes that the “1999 Brochure” is better called the “1999 Internet posting” throughout the report and that the posting should not be described as “updated” (for example, as in the Timeline). The “1990 Brochure” and the “1999 Internet posting” should be shown as separate items in the Timeline.

Appendix 1, Timeline

The timeline should begin with the 1988 Centers for Disease Control brochure, *Understanding AIDS*, which advised that N-9, when used with a condom, might provide additional protection against HIV. The brochure reflected the prevalent scientific view at that time: “Condoms are the best preventive measure against AIDS besides not having sex and practicing safe behavior.” That statement is as true today as it was in 1988. However, the brochure continues, “A condom with a spermicide may provide additional protection [against HIV]. Spermicides have been shown in laboratory tests to kill the virus.” Later research slowly eroded the scientific underpinnings of this belief.

The timeline should make clear that the first indication that N-9 presented added risks did not emerge until 2000 (the COL-1492 study). However, that evidence was confined to very narrow circumstances (sex workers using N-9 vaginal contraceptive products three or more times a day) and *did not* involve or implicate condoms with N-9. Also, it would be appropriate to note that the definitive report on the COL-1492 study was published in 2002; the information available prior to that time could be considered only preliminary.

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