Federal Register

# Proposed Rules

Vol. 70, No. 218

Monday, November 14, 2005

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

### 21 CFR Part 884

**[Docket No. 2004N–0556]**

**RIN 0910–AF21**

## Obstetrical and Gynecological Devices; Designation of Special Control for Condom and Condom With Spermicidal Lubricant

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing to amend the classification regulations for condoms to designate a special control for natural rubber latex (latex) condoms with and without spermicidal lubricant. FDA is proposing the draft guidance document entitled "Class II Special Controls Guidance Document: Labeling for Male Condoms Made of Natural Rubber Latex," as the special control that the agency believes will help provide a reasonable assurance of the safety and effectiveness of the devices. Elsewhere in this issue of the **Federal Register**, FDA is announcing a notice of availability of the draft special controls guidance document for public comment.

**Deleted:** and condoms with spermicidal lubricant containing nonoxynol–9 (condoms with spermicidal lubricant)

**DATES:** Submit written or electronic comments on the proposed rule by February 13, 2006. See section IV.C of this document for the proposed effective and compliance dates of a final rule based on this proposal.

**ADDRESSES:** You may submit comments, identified by Docket No. 2004N–0556 and/RIN number 0910–AF21, by any of the following methods:

*Electronic Submissions*

Submit electronic comments in the following ways:

• Federal eRulemaking Portal: *http:// www.regulations.gov*. Follow the instructions for submitting comments.

• Agency Web site: *http:// www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.

*Written Submissions*

Submit written submissions in the following ways:

• FAX: 301–827–6870.

• Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

*Instructions*: All submissions received must include the agency name and Docket No. and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ ohrms/dockets/default.htm*, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

*Docket*: 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, 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, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:**

Colin M. Pollard, Center for Devices and Radiological Health (HFZ-470), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301–594–1180.

**SUPPLEMENTARY INFORMATION:** The preamble to this proposed rule provides an extensive scientific discussion addressing the medical accuracy of condom labeling, as required by Public Law 106–554. This discussion provides the basis for the labeling recommendations that FDA proposes, through this rulemaking, to designate as a special control for latex condoms. (FDA intends to address condoms made from other materials at a future date and solicits comments on possible special controls for such condoms in section VIII of this document.) After reviewing public comments, FDA intends to issue a final rule designating the guidance document as the special control for latex condoms with and without spermicidal lubricant.

## I. Statutory and Regulatory Background

The Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301 *et seq.*), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Public Law 94–295), the Safe Medical Devices Act of 1990 (SMDA) (Public Law 101–629), the Food and Drug Administration Modernization Act (Public Law 105–115), and the Medical Device User Fee and Modernization Act (Public Law 107-250), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, defined by the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513 of the act, FDA refers to devices that were in commercial distribution before May 28, 1976 (the date of enactment of the 1976 amendments), as preamendments devices. FDA classifies these devices after the agency takes the following steps: (1) Receives a recommendation from a device classification panel (an FDA advisory committee); (2) publishes the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) publishes a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution before May 28, 1976, generally referred to as postamendments devices, are classified automatically by statute (section 513(f) of the act) into class III without any FDA rulemaking process. Those devices remain in class III until FDA does the following: (1) Reclassifies the device into class I or II; (2) issues an order classifying the device into class I or II in accordance with section 513(f)(2) of the act; or (3) issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the act, to a legally marketed device that has been classified into class I or class II. The agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the act (21 U.S.C. 360(k)) and regulations at part 807 (21 CFR part 807).

Under the 1976 amendments, class II devices were defined as devices for which there was insufficient information to show that general controls themselves would provide reasonable assurance of safety and effectiveness, but for which there was sufficient information to establish performance standards to provide such assurance. SMDA broadened the definition of class II devices to mean those devices for which the general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but for which there is sufficient information to establish special controls to provide such assurance, including performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, recommendations, and any other appropriate actions the agency deems necessary (section 513(a)(1)(B) of the act).

In addition to the act, as amended, and its implementing regulations, on December 21, 2000, Congress enacted Public Law 106–554, which required that FDA "* * * reexamine existing condom labels" and "* * * determine whether the labels are medically accurate regarding the overall effectiveness or lack of effectiveness of condoms in preventing sexually transmitted diseases, including [human papillomavirus]." Under this mandate, FDA undertook a review of the medical accuracy of condom labeling, which included an extensive review of the scientific information related to condoms. This review is discussed in the following paragraphs. The draft special controls guidance document includes labeling recommendations based on this FDA review.

## II. Regulatory History of the Devices

### *A. Condoms*

Condoms were marketed in the United States for both contraceptive and prophylactic (preventing transmission of sexually transmitted diseases (STDs)) use prior to the enactment of the 1976 amendments. As a preamendments device, the condom was classified along with hundreds of other devices during FDA's original classification proceedings. Based primarily on the clinical expertise and experience of experts on the Obstetrics and Gynecology Device

Classification Panel, FDA classified condoms into class II by regulation published in the **Federal Register** of February 26, 1980 (45 FR 12710). Condoms were identified as "***a sheath which completely covers the penis with a closely fitting membrane. The condom is used for contraceptive and for prophylactic purposes (preventing transmission of venereal disease)*** " (21 CFR 884.5300). This classification regulation includes latex condoms.

At the time that condoms were classified into class II, the statutory definition of that class contemplated the establishment of mandatory performance standards for all class II devices, in accordance with section 514(b) of the act (21 U.S.C. 360d(b)). Because of the complex process associated with issuing mandatory performance standards, the agency did not establish a performance standard for condoms or virtually any other class II device before SMDA provided additional options for special controls for class II devices in 1990. The present rulemaking proposes to designate a special control for latex condoms.

Condoms are also subject to general controls, which include good manufacturing practices (quality system regulation), registration and listing, adverse event reporting, and the prohibitions on adulteration and misbranding. This device is also subject to labeling requirements applicable to all devices, including a statement of principal intended action(s) and adequate directions for use, as described in part 801 (21 CFR part 801).

In addition to the general labeling requirements, latex condoms are subject to specific labeling requirements addressing expiration dating and latex sensitivity (§§ 801.435 and 801.437). FDA established expiration dating requirements in response to information that showed that the effectiveness of latex condoms as a barrier to sexually transmitted diseases, including human immunodeficiency virus (HIV), is dependent upon the integrity of the latex material. The expiration dating regulation addresses the risk of condom deterioration due to product aging and helps ensure that consumers have information regarding the safe use of latex condoms (62 FR 50501, September 26, 1997). The latex sensitivity labeling requirements were added in response to numerous reports of severe allergic reactions and deaths related to a wide range of medical devices containing natural rubber (62 FR 51021 at 51029, September 30, 1997).

*B. Condoms With Spermicidal Lubricant*

Condoms with spermicidal lubricant (containing nonoxynol–9) were classified by statute into class III because they were not in commercial distribution before May 28, 1976 (enactment of the 1976 amendments). In 1982, in response to a reclassification petition, the Center for Devices and Radiological Health (CDRH) reclassified condoms with the spermicide nonoxynol–9 (N–9) in the lubricant from class III to class II. The purpose of N–9 in the lubricant was to provide additional pregnancy risk reduction in the event that semen were to leak or seep into the vagina. At the time of this reclassification, N–9 was already available as an over-the-counter vaginal drug product, used alone or with a cervical cap or diaphragm.

**Comment [PT1]:** The FDA is probably not trying to convey that people would be protected from contraceptives

**Deleted:** contraceptive protection

**Deleted:** contraceptive protection

The petition for reclassification of condoms with N–9 in the lubricant contained evidence demonstrating that N–9 on the condom reduces sperm motility, a key factor in fertilization. Although the petition did not include clinical data to establish the degree of pregnancy risk reduction provided by the N–9 in addition to that provided by the condom, FDA believed that the condom with spermicidal lubricant might provide an increase in use-effectiveness—the level of effectiveness attained by typical users, including those who either fail to use the product correctly or do not use it each time during sexual intercourse—and recognized that clinical studies of the device would be difficult to conduct and may not provide evidence justifying the effort of collecting it (47 FR 18670, April 30, 1982).

To address the limitation of the data, in the agency's reclassification order, FDA stipulated that the labeling for condoms with spermicidal lubricant bear the following contraceptive effectiveness provision:

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

In the preamble to the final rule that codified the reclassification, FDA explained that condoms with spermicidal lubricant were reclassified into class II, provided that the labeling included the contraceptive effectiveness provision and an expiration date statement (47 FR 49021, October 29, 1982). To date, all legally marketed condoms with spermicidal lubricant have included the contraceptive effectiveness provision in the proposed labeling contained in the premarket notification (510(k)) submission that formed the basis for their clearance by CDRH. The condom with spermicidal lubricant is identified as "a sheath which completely covers the penis with a closely fitting membrane with a lubricant that contains a spermicidal agent, N–9. This condom is used for contraceptive and prophylactic purposes (preventing transmission of venereal disease)" (21 CFR 884.5310).

Condoms with spermicidal lubricant were reclassified into class II, mandatory performance standards. As discussed earlier in this document, however, because of the complex process associated with issuing mandatory performance standards, the agency did not establish a performance standard for condoms or virtually any other class II device before 1990, when the enactment of SMDA provided additional options for special controls. Consistent with current statutory authority, the present rulemaking proposes to designate a special control for latex condoms with spermicidal lubricant, as well as latex condoms without spermicidal lubricant. Condoms with spermicidal lubricant are also subject to general controls, including good manufacturing practices (quality system regulation), establishment registration and device listing, adverse event reporting, and the prohibitions on adulteration and misbranding.

This device is also subject to the labeling requirements applicable to all devices, including a statement of principal intended action(s) and adequate directions for use, as described in part 801. In addition to these general labeling requirements, latex condoms with spermicidal lubricant are also subject to the same labeling requirements addressing expiration dating and latex sensitivity as condoms without spermicidal lubricant (§§ 801.435 and 801.437).

**III. Review of the Medical Accuracy of Condom Labeling**

In re-examining condom labeling as directed by Public Law 106–554, and in the development of the draft special controls guidance document, FDA considered the following:

- Physical properties of condoms,
- Condom slippage and breakage during actual use,
- Plausibility for STD-risk reduction attributable to condoms,
- Evaluations of condom effectiveness against STDs by other Federal agencies, and
- Clinical data regarding condom against STDs.

**Comment [p2]:** risk reduction

**Deleted:** protection

Taken together, the information FDA considered and its analysis support the conclusion that condoms reduce the overall risk of STD transmission, although the degree of risk reduction for different types of STDs varies with their routes of transmission.

During the course of its reexamination of the medical accuracy of condom labeling, FDA also considered information on N–9 (section III.F of this document) and recent studies on contraception (section III.G of this document). The following sections summarize FDA's review.

*A. Physical Properties of Condoms*

Condoms are designed to work in accordance with a straightforward premise—condoms provide a physical barrier to sperm and to STD pathogens, and thus can reduce the likelihood of conception or STD transmission, which depend on the passage of those agents. (In the case of condoms containing N–9 in the lubricant, with respect to contraception, this physical barrier is supplemented by a spermicide.) To assess this premise, and in particular to determine what condom labels should communicate, FDA considered several sources of information about the physical properties of condoms.

1. Condom Barrier Property (Viral Penetration Assay)

To test the hypothesis that a condom inherently acts as a barrier to passage of very tiny particles, Lytle et al., conducted an in vitro study of nine different brands of latex condoms commercially available in the United States (470 samples), with and without spermicidal lubricant containing N–9. This study, later characterized as a viral penetration assay, used the bacteriophage FX174 as a surrogate for a pathogenic human virus (Ref. 1). This surrogate bacteriophage is only 27 nanometers (nm) in size, and is smaller than any pathogens that cause STDs. (By way of comparison, most bacteria are 1,000 nm or larger; HIV and herpes simplex virus (HSV) are on the order of 100 nm, and human papillomavirus (HPV) is about 53 nm. The test bacteriophage is also much smaller than sperm, which are 5–10 μm (cell body), i.e., 5,000–10,000 nm.) Of the 470 condoms tested, 12, or 2.6 percent, exhibited some viral penetration. Only two of the 470 condoms (0.43 percent) exhibited significant viral penetration.

This in vitro study showed that latex condoms are highly effective at preventing passage of even the smallest infectious agents.

**Deleted:** . This supports the conclusion expressed later in this document that condoms are effective in reducing transmission of any STD to which they provide a mechanical barrier, namely, any STD that is spread to or from the penis, the area covered by the condom.

2. Presence/Absence of Holes (Water Leak Test)

Another physical property important to condom performance is the presence or absence of tiny pinholes that might occur in some condoms, even under optimal manufacturing conditions, but which are too small to see without magnification. As the viral penetration assay (Ref. 1) illustrated, passage of a virus or bacterium requires concomitant passage of the fluid medium in which the pathogens are suspended. Consequently, to operate as effective barriers, condoms should not have holes, even tiny holes, that might permit passage of fluid. The notion that condoms should not have holes is intuitive, and condom manufacturers have for years used tests for detection of tiny holes in the condom as a product release quality control measure, on a lot-by-lot basis. Likewise, FDA has pursued legal actions against manufacturers of condoms that have holes. See, e.g., *Dean Rubber Manufacturing Co.* v. *United States*, 356 F.2d 161 (8th Cir. 1966) (condoms labeled for prevention of venereal disease were adulterated where some had tiny pinholes, detectable through water leak test).

One way to test for the presence of tiny pinholes is by a standard water leak test that requires filling the condom with 300 milliliters (ml) of water and inspecting for leakage. Current consensus standards (American Society for Testing Materials (ASTM) D 3492 and International Standards Organization (ISO) 4074) address test methodology and acceptance criteria, and the agency has recognized both of these standards in accordance with section 514(c) of the act. (Interested parties can search for FDA-recognized standards by accessing the following Web site: *http:// www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm.*)

The agency believes that condom test methods and acceptance criteria regarding barrier properties specified in either of these two recognized standards are appropriate for use by manufacturers in the implementation of good

manufacturing practices (GMPs) under the quality system regulations (21 CFR part 820) for their condom manufacturing operations. During inspections to monitor compliance with the quality system regulation, FDA confirms that condoms manufactured for the U.S. market are subject to appropriate acceptance testing to demonstrate compliance with their performance specifications, including testing to address the detection of pinholes. FDA also performs a check of all imported condom shipments, using the water leak test described previously in this document, to determine whether they meet an acceptable quality level.

3. Air Burst Properties Besides being made of material that inherently serves as a barrier to sperm and microscopic STD pathogens, and being manufactured through processes that minimize the occurrence of tiny holes in finished product, other physical properties of a condom important to its effectiveness include air burst properties, such as burst pressure and burst volume. Such properties have previously been correlated with breakage during use (Ref. 2). In developing standards that specify minimum values that manufacturers use as specifications for their condoms, FDA and standards development organizations considered data from studies of air burst testing combined with data from manufacturers' experience with this test methodology. On April 5, 1994, FDA issued a letter to condom manufacturers requesting that they adopt ISO air burst testing as part of their finished device testing to provide increased assurance of risk reduction from sexually transmitted diseases, including HIV. Following the issuance of this letter and FDA's recognition of the ISO, ASTM, and similar standards, manufacturers of latex condoms legally distributed in the United States have established and implemented air burst test requirements as part of their GMP procedures.

4. Packaging and Shelf Life In collaboration with the Centers for Disease Control and Prevention (CDC) and state level health departments, FDA sponsored a large, multi-year shelf-life study testing the physical properties of marketed condoms over time under a variety of test conditions during the 1990s (Ref. 3). This study also highlighted the importance of quality packaging of the condom to prevent product deterioration. Using the results of this study, FDA issued a new labeling regulation in 1997 to address expiration dating for condoms made from natural rubber latex and the shelf life testing that must support it (§ 801.435). A similar provision is now contained in
the international standard for latex condoms (ISO 4074).

*B. Condom Slippage and Breakage During Actual Use*

Because condoms must be in place and intact to form an effective barrier and thus help prevent pregnancy and reduce risk of STI transmission, condoms should be designed to avoid slippage and breakage during actual use. As discussed later in this document, the National Institutes of Health (NIH) convened a workshop on condom effectiveness against STDs in June 2000 (the June 2000 Workshop). The June 2000 Workshop panelists looked at the question of condom slippage and breakage during use. The report from the June 2000 Workshop, based on the best available studies at the time, concluded that the condom breakage rate during use ranges from 0.4 percent to 2.3 percent, with a comparable rate for condom slippage (Ref. 4). Key factors affecting breakage include lack of experience, use of lubricant, and condom size. Since the June 2000 Workshop, we are aware of three additional, prospective studies that show breakage and slippage rates of 1% – 4% (Refs. 5, 6, and 7).

These data, when considered together with condom barrier properties and plausibility information (discussed in the following paragraphs), also support the conclusion that condoms reduce the risk of STI transmission, although, as discussed in the following section, the degree of risk reduction varies depending on the route of transmission of the STI. As discussed later in this document, this finding is also supported by review of studies on condom use and STI risk reduction.

*C. Plausibility for STI Risk Reduction Attributable to Condoms*

FDA evaluated the plausibility of attributing STI risk reduction to regular condom use by integrating the preceding information about the condom's barrier properties with information about general condom design (e.g., how the condom is donned and how it covers the penis) and about the clinical microbiology of STI pathogens and how they are transmitted. Specifically, STI transmission requires contact between a pathogen source from an infected individual (e.g., semen, mucus, or lesion) and a recipient site of an uninfected partner (e.g., vaginal or cervical mucosa of a woman, the urethra of a man, genital skin of either a man or a woman). For the reasons explained in the following paragraphs, the agency concludes that condoms can limit this contact, and that they may reduce the overall risk of STI transmission.

In the evaluation to determine the overall effectiveness of condoms in preventing STI transmission, it is critical to recognize that individual STIs vary with respect to routes of transmission (e.g., via penile fluid or exposure to infectious skin) and infectivity (e.g., how many viral or bacterial particles must be transmitted for infection to occur). Based on these factors, FDA evaluated the extent to which a condom, which only covers the shaft and head of the penis, can provide an effective physical barrier to transmission of different STIs. To determine whether and to what extent it is reasonable, based on available information, to expect a condom to protect against different STIs, FDA considered nine STIs, including those most common in the United States, and their routes of sexual transmission. Table 1 of this document lists each STI considered and its usual route(s) of sexual transmission.

**Deleted:** protection

**Deleted:** provide protection

**Deleted:** against

**Deleted:** STD

**Comment [PT3]:** And we are aware of a French study [Messiah, 1997] that shows breakage and slippage rates of 1.4% – 7.5%, inversely proportional to experience.

**Deleted:** are consistent with these findings

**Deleted:** STD

**Deleted:** STD

**Deleted:** STD

**Deleted:** *STD*

**Deleted:** STD

**Deleted:** STD

**Deleted:** STD

**Deleted:** thus

**Deleted:** STD

**Deleted:** STD

**Deleted:** STD

**Deleted:** STD

**Deleted:** STD

**Deleted:** STD

**Deleted:** STD

TABLE 1.—STIS AND USUAL ROUTE(S) OF TRANSMISSION TABLE 1.—STIS AND USUAL ROUTE(S) OF TRANSMISSION—Continued

| STI | Exposure to and From the Head of the Penis | Exposure to Infectious Skin or M cluding the Head of the Penis) |
|---|---|---|
| Group I | | |
| HIV/Aquired Immunodeficiency Syndrome (AIDS) | | |

| STI | Exposure to and From the Head of the Penis | Exposure to Infectious Skin or M cluding the Head of the Penis) |
|---|---|---|
| Neisseria gonorrhea | | |
| Chlamydia trachomatis | | |
| Trichomoniasis | | |
| Hepatitis B Virus | | |
| Group II | | |
| Syphilis | | |
| Genital HSV | | |
| Genital HPV | | |
| Chancroid | | |

Regarding the potential for STI risk reduction attributable to condom use, FDA concluded that the potential for condoms to help prevent STIs that are transmitted from or to the penis (table 1, group I) is greater than the potential risk reduction for STIs that are also transmitted by contact with infectious skin or mucosa not covered by the condom (table 1, group II). This risk reduction is a result of the condom's ability to serve as a barrier to help prevent contact between the genital fluids and the potentially susceptible mucosa. For STIs transmitted from or to the penis, a condom will provide a physical barrier that helps to prevent STI pathogens contained in penile fluid from reaching the cervico-vaginal or ano-rectal mucosa, thereby reducing the risk of transmission from males with STIs that meet these conditions. It also protects a man's urethra from STI pathogens contained in his partner's secretions. STIs that meet these conditions include HIV, gonorrhea, chlamydia, trichomoniasis, Hepatitis B, and are listed in group I, in table 1 of this document.

For group II STIs, under its plausibility analysis, FDA concludes that while condoms may provide some risk reduction, the degree of risk reduction may not be as great as that expected for group I STIs. This is because, for group II STIs, the condom provides a barrier in some, but not all, situations that may lead to transmission. Risk reduction for group II STIs depends on the site of the sore/ulcer or infection. Condoms can only reduce the risk of transmission when the ulcers or infections are covered by the condom.

The extent of risk reduction varies between two general groups of STIs. Risk reduction is greater for those transmitted exclusively through contact with the penis. Risk reduction is not as great for those that may be transmitted both through such contact and through contact with infectious skin or mucosa not covered by the condom.

*D. Evaluations of Condom Risk Reduction Against STIs by Other Federal Agencies*

FDA also reviewed evaluations by other federal public health agencies regarding condoms and the risk reduction they provide against sexually transmitted diseases.

1. The June 2000 Workshop: Scientific Evidence on Condom Effectiveness

In June 2000, the National Institutes of Health (NIH) convened a workshop with other federal public health agencies and outside expert panelists. The June 2000 Workshop entitled "Scientific Evidence on Condom Effectiveness for Sexually Transmitted Disease (STD) Prevention" involved other federal agencies, including FDA, CDC, and the U.S. Agency for International Development. The report issuing from the June 2000 Workshop was based on consideration of approximately 138 papers, the majority of which were published before December 1999, mostly in peer-reviewed journals (*http:// www.niaid.nih.gov/dmid/stds/ condomreport.pdf*). (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**.) During its deliberations, the June 2000 Workshop panelists considered whether condoms can prevent infection by eight different STIs and came to the following conclusions:

*HIV/AIDS.* From review of a meta-analysis of HIV discordant couples (Ref. 8), it was noted that consistent condom use decreased the risk of HIV/AIDS transmission by approximately 85 percent. Panelists noted that many of the

**Comment [p4]:** US-based
**Deleted:** STD
**Deleted:** STD
**Comment [p5]:** Divide table up into mode of transmission mentioned in NIH report: genital fluids genital ulcer other (HPV)
**Deleted:** STD
**Deleted:** STD
**Deleted:** STD
**Deleted:** STD
**Deleted:** STD
**Deleted:** STD
**Deleted:** STD
**Deleted:** STD
**Deleted:** STD
**Deleted:** STD
**Comment [p6]:** may
**Deleted:** STD
**Deleted:** are likely to
**Deleted:** STD
**Deleted:** STD
**Deleted:** Protection against
**Deleted:** STD
**Deleted:** protect
**Deleted:** against transmission
**Comment [PT7]:** Since the epidemiological (in vivo) data do ... [1]
**Deleted:**
**Deleted:** or when susceptible sit ... [2]
**Comment [p8]:** risk reduction
**Comment [p9]:** provided by co ... [3]
**Deleted:** In summary, consideri ... [4]
**Deleted:** STD
**Deleted:** *Protection*
**Deleted:** *STD*
**Deleted:** protection
**Comment [PT10]:** the Worksh ... [5]
**Deleted:** STD
**Comment [p11]:** only reduce ... [6]
**Comment [PT12]:** the term "h ... [7]
**Comment [PT13]:** did not eva ... [8]
**Deleted:** Workshop findings ... [9]
**Deleted:** correct and

HIV/AIDS studies they reviewed employed better study methodologies than studies of other STIs. For example, HIV/AIDS studies were prospective, measured exposure for discordant couples (i.e., one partner is infected and the other is not infected), and were more likely to measure the effect of correct and consistent condom use. The primary outcome measure for these studies was typically condom effectiveness against transmission of HIV. Such study design features represent a relative strength of the HIV/ AIDS condom literature compared with condom literature for other STIs.

*Gonorrhea*: Studies reviewed showed that consistent condom use would reduce the risk of gonorrhea for men. However, the report stated that limitations in study methodology did not allow an assessment of the degree of risk reduction in women.

*Genital HPV*: The report issuing from the Workshop concluded that most of the reviewed studies did not obtain sufficient information on condom use to allow careful evaluation of the association between condom use and HPV infection or disease. The report also concluded that there was no epidemiologic evidence that condom use reduced the risk of HPV infection, but that condom use might afford some protection in reducing the risk of HPV-associated diseases, including warts in men and cervical neoplasia (cervical cancer precursors and invasive cancer) in women.

*Chlamydia, Syphilis, Genital HSV, Chancroid, and Trichomoniasis*: The

[1] Trichomoniasis was addressed by the June 2000 Workshop organized by NIH, the report of which is cited in Ref. 4, as well as in a CDC fact sheet discussed later in this document (*http:// www.cdc.gov/nchstp/od/latex.htm*). (F DA has

report stated that the scientific literature did not allow an accurate assessment of the degree of potential protection offered against these STIs by correct and consistent condom use.

Although the panel acknowledged the available laboratory data on physical performance of condoms, as well as data from clinical studies on condom use patterns and condom slippage and breakage during use, neither these factors nor the plausibility of condom protection against the various STIs were considered in the summary conclusions on STI risk reduction described previously in this document, which reflected solely the assessment of clinical studies. As already explained, FDA's approach in the present rulemaking has considered all of these factors, in addition to the clinical data.

The June 2000 Workshop Summary also included an FDA analysis that looked at how different possible condom failure modes can affect the expected volume of semen exposure. Workshop panelists concluded that this analysis showed that, even in the event of condom breakage, leakage or slippage, condom use would still result in greatly reduced exposures because the amount of semen is reduced by orders of magnitude when compared to not using a condom at all.

2. CDC Fact Sheet "Male Latex Condoms and Sexually Transmitted Diseases"

In December 2002, CDC developed a fact sheet for public health personnel entitled "Male Latex Condoms and Sexually Transmitted Diseases," with information on condom protection against HIV/AIDS, gonorrhea, chlamydia, trichomoniasis, HSV, syphilis, chancroid, and HPV (*http:// www.cdc.gov/nchstp/od/latex.htm*). (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**.) CDC's fact sheet addressed the same eight STIs considered by the June 2000 Workshop. The CDC Fact Sheet was based on laboratory studies, the theoretical basis for protection for condoms to reduce risk for STIs, and

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** ) FDA has similarly included this STI in table 1 as a group 1 STI on the basis of its route of transmission. This rulemaking does not consider any additional information regarding trichomoniasis, however, because there is no significant new information on this STI. Neither FDA's prior labeling recommendations nor its proposed special control guidance recommend making specific claims for condom effectiveness against trichomoniasis.

results of clinical studies. Based on review of these items, the fact sheet concluded:

Latex condoms, when used consistently and correctly, are highly effective in preventing transmission of HIV, the virus that causes AIDS. In addition, correct and consistent use of latex condoms can reduce the risk of other sexually transmitted diseases (STDs), including discharge and genital ulcer diseases. While the effect of condoms in preventing human papillomavirus (HPV) infection is unknown, condom use has been associated with a lower rate of cervical cancer, an HPV-associated disease.

3. CDC Report to Congress entitled "Prevention of Genital Human Papillomavirus Infection"

CDC included a systematic literature review of condoms and HPV and HPV-associated diseases in its January 2004 report to Congress entitled "Prevention of Genital Human Papillomavirus Infection." This report describes the epidemiology of genital HPV infection and its transmission, and summarizes strategies to prevent infections with genital HPV and HPV-associated diseases. The report cited three studies (not included in the June 2000 Workshop report) that showed a statistically significant reduction in risk of HPV infection attributable to condoms, but noted that most studies did not show this effect (Refs. 31, 32, 33). The report stated that "all published epidemiologic studies have significant methodologic limitations which make the effect of condoms in prevention of HPV infection unknown." The report continued:

Given these observations, as well as the facts that laboratory studies show that latex condoms provide a barrier to HPV and that most genital HPV in men is located on areas of the skin covered by a condom, the cumulative body of available scientific evidence suggests that condoms may provide some protection in preventing transmission of HPV infections but that protection is partial at best. The available scientific evidence is not sufficient to recommend condoms as a primary prevention strategy for the prevention of genital HPV infection. There is evidence that the use of condoms may reduce the risk of cervical cancer.

**Deleted:** STD

**Deleted:** STD

**Comment [PT14]:** did not evaluate correct use

**Deleted:** correct and

**Deleted:** protection

**Comment [p15]:** risk reduction

**Comment [p16]:** It should be noted that this Workshop considered only articles related to reduction of STI transmission during vaginal intercourse.

**Deleted:** STD

**Deleted:** STD

**Deleted:** STD

**Deleted:** STD

**Deleted:** STDs

**Deleted:** STD

**Deleted:** STD

**Deleted:** STD

**Comment [PT17]:** This factsheet reports no ranges for effectiveness for risk reduction against STIs and lists no citations

**Comment [PT18]:** A review of these studies shows that only one study (Kjaer, 2000 [31]) has statistically significant results

**Comment [p19]:** A review of these three articles quoted by the CDC, show only one study (Kjaer, 2000) to be statistically significant while the other two (Katloff, 1996, Mayaud, 2001) were not (confidence intervals of risk reduction including 1.0).

The summary section of the report addressed strategies to prevent HPV infection and stated "[w]hile available scientific evidence suggests that the effect of condoms in preventing HPV is unknown, condom use has been associated with lower rates of the HPV-associated diseases of genital warts and cervical cancer." The CDC report offered two possible explanations about how condoms might reduce the risk of genital warts and cervical cancer when the effect of condoms in preventing HPV infection is unknown. Condom use could reduce the quantity of HPV transmitted or the likelihood of re-exposure to HPV, thereby decreasing the risk of developing clinical disease. Another possible explanation offered by CDC is that condom use reduces the risk of exposure to a possible cofactor for cervical cancer, such as chlamydia or genital herpes, thereby reducing the risk of developing cervical cancer (Ref. 9). The summary section went on to state that "[r]egular cervical cancer screening for all sexually active women and treatment of precancerous lesions remains the key strategy to prevent cervical cancer."

*E. Systematic Reviews Regarding Condom Risk Reduction Against STIs*

The agency also analyzed the following sources of clinical data regarding condom risk reduction against STIs:

- Systematic reviews (meaning reviews of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from studies that are included with the review) for STIs where such reviews were available; and
- Individual clinical studies for STIs where systematic reviews were not identified.

In the following analysis of clinical studies regarding condom risk reduction against STIs, the STIs have been grouped according to plausibility for risk reduction attributable to condom use, discussed previously. The STIs transmitted primarily to or from the head of the penis (HIV, gonorrhea, chlamydia, and HBV) are discussed first (group I STIs). STIs that are also transmitted by exposure to infectious skin or mucosa excluding the head of the penis are discussed second (group II STIs). FDA believes this body of literature illustrates both the limitations and the benefits of condom use for risk reduction against STIs.

1. Group I *HIV*: In a recent meta-analysis (Ref. 10), Weller and Davis selected 14 clinical studies for final analysis based on exemplary study design. These prospective cohort studies of discordant heterosexual couples showed that correct and consistent use of condoms resulted in an overall 80 percent reduction in HIV incidence. Other reviews (Ref. 11) also have shown risk reduction against HIV associated with correct and consistent condom use. Consistent with the NIH Workshop

findings, these reviews support the conclusion that correct and consistent condom use is highly effective in reducing the transmission of HIV infection.

*Gonorrhea*: FDA is aware of one systematic review of the condom literature regarding risk reduction against gonorrhea. This systematic review of 42 epidemiological studies reported in 2004 evaluated condom effectiveness for preventing gonorrhea, chlamydia, and pelvic inflammatory disease and found that in the vast majority of studies condom use was associated with a reduced risk of gonorrhea in women and men (Ref. 12).

*Chlamydia*: FDA is aware of one systematic review of the condom literature regarding risk reduction against chlamydia (Ref. 12). The 2004 epidemiology review cited in the previous discussion of gonorrhea found that the vast majority of studies showed that correct and consistent condom use reduces the risk of chlamydia for both men and women.

This information also supports the conclusion that correct and consistent condom use can reduce the risk of chlamydia in both men and women.

*Hepatitis B*: FDA is not aware of any systematic reviews of the condom literature regarding risk reduction against Hepatitis-B (HBV). Although data are limited, FDA identified one study that addressed this issue. This was a cross-sectional study (Ref.13), that showed that consistent condom use was significantly associated with lower prevalence of HBV.

In summary, the previously discussed information shows that condoms, when used correctly and consistently, can be effective in reducing the risk of transmission of group I STIs, which are transmitted by exposure of the cervico-vaginal, urethral, to penile fluids or cervico-vaginal secretions.

2. Group II

*Syphilis*: FDA is not aware of any systematic reviews of the condom literature regarding risk reduction against syphilis. However, FDA identified two prospective studies that have examined this question. A prospective cohort analysis of female "sex workers" in Bolivia (Ref. 14), showed that condom use was associated with a 61 percent reduction in the risk of syphilis. A secondary analysis of a prospective study (Ref. 15) also found a statistically significant risk reduction (29%) for condoms against syphilis transmission. Although data are limited, this information also supports the conclusion that consistent condom use can reduce the risk of syphilis.

*Genital Herpes*: FDA is aware of one systematic review of the condom literature regarding risk reduction against herpes. A literature review published in 2002 (Ref. 16) found that condom use appeared to reduce the risk of HSV-2 infection for women; an important study, cited in that review, was a prospective study among discordant couples that found condom use during more than 25 percent of sex acts was associated with risk reduction against HSV-2 acquisition for women but not for men (Ref. 17). More recent prospective studies showed that condom use was

**Comment [p20]:** This factsheet reports no ranges of effectiveness for risk reduction against different STIs, and lists no references.

**Deleted:** *Protection*

**Deleted:** *STDs*

**Deleted:** protection

**Deleted:** STDs

**Deleted:** STDs

**Deleted:** STDs

**Deleted:** protection

**Deleted:** STDs

**Deleted:** STDs

**Deleted:** STDs

**Deleted:** STDs

**Deleted:** STDs

**Deleted:** STDs

**Deleted:** protection

**Deleted:** STDs

**Deleted:** protection

**Comment [PT21]:** These guidelines should not be based on non-peer reviewed abstracts. Reference should be made to Holmes, et al. Bulletin of World Health Organization. 2004;82(6)

**Deleted:** protection

**Comment [PT22]:** These guidelines should not be based on non-peer reviewed abstracts. Reference should be made to Holmes, et al. Bulletin of World Health Organization. 2004;82(6)

**Deleted:** protection

**Deleted:** correct and

**Deleted:** STDs

**Comment [PT23]:** No data provided for anal intercourse

**Deleted:** or rectal mucosa

**Comment [p24]:** (29% risk reduction)

**Deleted:** protection

**Deleted:** protective effect

**Deleted:** correct and

**Comment [p25]:** risk reduction

**Deleted:** protection

**Deleted:** protection

associated with a reduced risk of HSV-2 for men and women (Refs. 18 and 19).

*HPV*: Genital HPV is a common infection in sexually active persons. Some strains of HPV are associated with genital warts; others are associated with cervical cancer. Most strains cause no immediate symptoms. The majority of genital HPV infections spontaneously regress and do not lead to clinical disease. Less commonly, HPV infection may persist and lead to cancer of the cervix, penis, anus, or tonsils.

FDA is aware of two systematic reviews of the scientific literature on HPV infection and condom use. The previously described 2004 CDC Report to Congress concluded that "* * * the effect of condoms in preventing HPV infection is unknown, [but] condom use has been associated with lower rates of the HPV-associated diseases of genital warts and cervical cancer" (Ref. 9). CDC concluded that the available scientific evidence is not sufficient to recommend condoms as a primary prevention strategy for the prevention of genital HPV infection, but that it does indicate that use of condoms may reduce the risk of cervical cancer. A separate review of 20 studies in 2002 found that, while condoms may not prevent HPV infection, they can reduce the risk of genital warts, cervical intraepithelial neoplasia II or III, and invasive cervical cancer (Ref. 20). This supports the conclusion that condoms can reduce the risk of genital warts, cervical intraepithelial neoplasia II or III, and invasive cervical cancer, which are caused by HPV.

*Chancroid*: FDA was unable to identify any systematic review articles on whether condom use reduces the risk of chancroid. Although data are limited, FDA is aware of one prospective cohort study (Ref. 21) of condom use for prevention of genital ulcer disease (presumed to be chancroid) that was conducted among prostitutes in Kenya. This study reported that condom use was associated with a significantly reduced risk of genital ulcer disease. It is important to note that the incidence of chancroid in the United States is extremely low.[2] In 1999, only 143 new cases were reported to the CDC (Ref. 22).

In summary, the previously discussed information suggests that condoms, when used consistently, can be effective in reducing the risk of transmission of group II STIs. The degree of risk reduction would be expected to be less than that for group I STIs.

*F. Nonoxynol-9 (N-9)*

Because N-9 kills HIV in vitro, some researchers in the early 1990s hypothesized that N-9 might help prevent or reduce the risk of HIV transmission in humans. This benefit, however, has not been demonstrated and was never included on the labeling of either drugs or devices, including condoms lubricated with N-9. Further, recent clinical data demonstrate that N-9 does not protect against HIV transmission, and frequent use can cause vaginal irritation, which may increase the risk of transmission of HIV from infected partners.

A study of "sex workers" in South Africa, Benin, Cote d'Ivoire, and Thailand who used a vaginal N-9 gel formulation reported higher HIV incidence than women who used a placebo formulation (without N-9) (Ref. 23). The study did not control for covariates such as condom use or anal sex, but 16 percent of women converted from HIV negative to HIV positive in the N-9 gel arm, compared to 12 percent of women who converted from HIV negative to HIV positive in the placebo group (p=.047). The study also showed that for the 32 percent of participants who reported use of a mean of more than 3.5 applications of vaginal gel per working day, the risk of HIV-1 infection in N-9 users was almost twice that in women who used the placebo gel. Researchers found that women who used N-9 had more vaginal lesions and vaginal lesions with epithelial breach, which might have facilitated the HIV transmission through the vaginal mucosa.

On June 25, 2002, the United Nation's World Health Organization (WHO) issued a report from a meeting it held in October 2001 to assess the available scientific information regarding the safety and effectiveness of N-9 when used for contraceptive purposes and to provide advice to Member States on the use of N-9. (Ref. 24). The WHO report concluded that there was no published

[2] Neither FDA's prior labeling recommendations nor the agency's proposed special control guidance recommend making specific claims for condom effectiveness against chancroid.

scientific evidence that N-9-lubricated condoms provide any additional risk reduction against pregnancy or STIs compared with condoms lubricated with other products . In view of this finding and because adverse effects due to the addition of N-9 to condoms were possible, the WHO recommendation to the Member States was that condoms lubricated with N-9 should no longer be promoted for use in their condom distribution programs. However, the WHO report also concluded that "*** it is better to use N-9-lubricated condoms than no condoms."

Prompted by this information, FDA conducted an exhaustive review of available literature on N-9 related to STI transmission for the purpose of evaluating over-the-counter (OTC) vaginal contraceptive drug products containing N-9. Based on this review, FDA concluded that N-9 does not protect against HIV/AIDS and other STIs. Furthermore, FDA identified potential new risks regarding HIV/AIDS associated with N-9 use. On January 16, 2003, FDA published a notice of proposed rulemaking that proposed to add warnings on the labeling for over-the-counter vaginal contraceptive drug products that contain N-9 (68 FR 2254, January 16, 2003) to address this information. FDA believes that, with the additional warnings, consumers can safely use these OTC drug products for their intended use as contraceptives. The preamble for this proposed drug labeling rule discusses in detail FDA's scientific review and conclusions regarding N-9 and STI transmission, which the agency likewise considered in its present evaluation.

The study of "sex workers" discussed previously in this document and others discussed in the preamble to the proposed labeling rule for vaginal contraceptive drugs containing N-9 were conducted using N-9 drug products, not

**Comment [PT26]:** Update to published article by same author

**Deleted:** Certain strains of genital HPV cause genital warts, while others are asymptomatic.

**Deleted:** genital

**Deleted:** is persistent and leads to cellular abnormalities of the cervix that may progress to cervical cancer (Ref. 34)

**Comment [p27]:** no data provided for anal intercourse

**Deleted:** correctly and

**Deleted:** STDs

**Deleted:** STDs

**Comment [p28]:** (This reference should be updated to the published paper by the same author).

**Comment [p29]:** may persist and lead to cancer of the cervix, penis, anus, or tonsils.

**Deleted:** protection

**Deleted:** STDs

**Deleted:** STD

**Deleted:** STDs

**Deleted:** STD

latex condoms containing N–9 in the lubricant. FDA is aware of only one study specifically examining the effect on STI risk of N–9 in condom lubricant (Ref. 25). The study found no additional protective effect for gonorrhea and chlamydia. In addition, FDA believes the literature regarding N– 9 vaginal contraceptive drug products establishes that N–9 does not protect against HIV/AIDS or other STIs, and also indicates that vaginal irritation can result from exposure to N–9, including in amounts similar to that found on N– 9 lubricated condoms. That literature also indicates that such irritation presents a potential increased risk of HIV/AIDS transmission if a user is subsequently exposed to genital secretions from an infected partner.

Deleted: STD

Deleted: STDs

In addition to the information regarding vaginal irritation and subsequent increased risk of HIV transmission associated with N–9 use, recent scientific studies also provide evidence indicating that N–9 damages rectal tissue and may increase transmission of infectious agents through the rectum. In animal studies comparing N–9 rectal lubricant against lubricant that is N–9 free, shortened time until infection occurred in animals pretreated with the N–9 product (Ref. 26).

Histologic abnormalities were more common on rectal biopsy following N– 9 use compared to placebo lubricant (89 percent vs. 69 percent) (Ref. 27). In a different study, rectal lavage following application of N–9 gel showed sheets of exfoliated epithelium 15 minutes following product application. No sheets of cells were observed 15 minutes following application of the control product. Finally, no sheets of cells were noted 8 to 12 hours following application of either product (Ref. 28).

FDA is not aware of studies that have been conducted expressly to determine whether use of N–9 during anal intercourse increases the risk of HIV acquisition in humans. However, FDA believes that the evidence described previously in this document regarding the increased likelihood of HIV acquisition attributable to vaginal N–9 exposure, combined with the evidence of anal tissue disruption from N–9, suggests a similar risk in that context.

*G. Contraception*

As stated earlier in this document, condoms are also used to help prevent unintended pregnancy. The effectiveness of condoms as a contraceptive has been well established for years, as indicated in FDA's 1980 classification regulation and reaffirmed by recently published contraceptive studies on commercially available condoms (Refs. 5, 6, 29, and 30). These studies show that the typical use pregnancy rate after 6 month's reliance on condoms is 5.4 percent to 7.9 percent. These studies also show that correct and consistent use can significantly lower the failure (pregnancy) rate. Many of the same caveats that apply to use of a condom for STI risk reduction are equally important to condom use for preventing unintended pregnancy, e.g., correct and consistent use and factors that affect slippage and breakage (experience, lubrication, condom size). Attention to these factors is important to maximize condom protection.

**Comment [PT30]: use typical use failure rate over a period of year and use Hatcher, 2004 reference**

Deleted: STD

**IV. Proposed Rule**

FDA reviewed the previously stated information as part of our reexamination of condom labeling directed by Public Law 106–554. In light of the agency's findings from our review, FDA is proposing to amend the classification regulations for condoms. The proposed regulatory changes, discussed in the following paragraphs, are intended to help ensure that condoms are used safely and effectively by providing labeling conveying a concise, accurate message that neither exaggerates the degree of overall risk reduction provided by condoms, nor undervalues overall STI risk reduction provided by condom use.

Deleted: protection

Deleted: STD

*A. Overview of Regulatory Changes*

First, FDA is proposing to amend the identification sections of the classification regulations for condoms with and without spermicidal lubricant to change the wording "venereal disease" to "sexually transmitted infections," to reflect current medical terminology. These identification sections will continue to encompass condoms made of all materials, including natural membrane (skin) and synthetics, as well as latex. Second, FDA is proposing to add classification sections to each of the regulations, segregating the subset of condoms in each classification that are made of latex. Finally, FDA is proposing to designate a special controls guidance document with labeling recommendations for latex condoms.

Deleted: diseases

As previously noted, latex condoms with and without spermicidal lubricant were classified into class II prior to the effective date of the SMDA provisions that broadened the definition of class II devices to establish special controls beyond mandatory performance standards. Developing a special controls guidance document as the means to provide reasonable assurance of the safety and effectiveness of condoms was not a regulatory option at the time of their original classification. Under the authority provided by SMDA, FDA is now able to propose the designation of a guidance document as a special control the agency believes will, together with the general controls, reasonably assure the safety and effectiveness of these devices. FDA has developed a draft special controls guidance entitled "Class II Special Controls Guidance Document: Labeling for Male Condoms Made of Natural Rubber Latex." This draft guidance document describes means by which latex condoms with and without spermicidal lubricant may comply with the requirement of special controls for class II devices. The draft guidance document identifies the issues associated with these devices and recommends addressing these issues through labeling.

The current voluntary guidance recommendations for condom labeling do not address some of the important information FDA has identified in this proposed rule. In particular, current labeling does not provide specific

information about the limited risk reduction condoms offer against transmission of certain STIs, such as HPV, that can be transmitted through contact with infected skin outside the area covered by the condom. In addition, current labeling does not provide specific information about the potential risks associated with the use of the spermicidal lubricant nonoxynol-9 (N–9) in condoms. FDA believes that providing consumers with this additional information on condom labeling can improve the safe and effective use of condoms. More accurate information about the risks and benefits of condom use with respect to STI transmission can lead to better choices by individuals who seek to protect themselves against these infections and potentially to reduced transfer of STIs.

The labeling recommendations in the draft guidance are intended to provide information to users of latex condoms with and without spermicidal lubricant. The draft special controls guidance recommends labeling to inform users about the extent of risk reduction provided by condoms against unintended pregnancy and against various types of STIs, as well as information about possible risks associated with exposure to N–9 contained in the spermicidal lubricant of some condoms. The labeling recommendations provide important information for condom users to assist them in determining whether latex condoms are appropriate for their needs and, if so, to determine whether a condom with or without N–9 lubricant is most suitable. Many of the labeling recommendations are similar to statements in existing condom labeling, but are being updated to reflect current information. The labeling recommendations related to N–9 are more comprehensive than existing labeling.

FDA believes that this draft guidance is an appropriate special control to help provide reasonable assurance of the safety and effectiveness of latex condoms and latex condoms with spermicidal lubricant containing N–9. The following section discusses the issues requiring special controls and how FDA's proposed special control guidance document, announced elsewhere in this issue of the **Federal Register**, recommends addressing them.

*B. Issues Requiring Special Controls*

From its general knowledge of condoms and its specific review of the scientific evidence regarding the overall effectiveness of condoms in preventing STI transmission, FDA has identified several issues associated with the use of latex condoms that require special controls to provide reasonable assurance of safety and effectiveness. As addressed in more detail in the following paragraphs, the draft guidance document provides labeling recommendations that address the risks of unintended pregnancy and of STI transmission, the issue of incorrect and inconsistent use (which undermines the effectiveness of the condom in protecting against unintended pregnancy and STI transmission), and the risks and limited benefits presented by N–9, which is used in latex condoms with spermicidal lubricant.

1. Unintended Pregnancy

One of the principal intended uses of latex condoms is contraception. Consistent use of latex condoms can reduce the risk of pregnancy by 85%; however, they cannot eliminate this risk. In addition, as discussed elsewhere in this document, N–9, which is used in the lubricant of some condoms, kills sperm, but the degree of additional contraceptive risk reduction that it adds to the condom has not been measured.

The draft special controls guidance document recommends that the labeling indicate that, when used correctly, latex condoms can greatly reduce, but do not eliminate, the likelihood of pregnancy. The draft guidance also recommends that the labeling include a comparative contraceptive effectiveness table with pregnancy rates for barrier contraceptives. This table is provided in the draft guidance and is intended to enable contraceptive users to compare alternatives and make appropriate choices.

The draft special controls guidance document also includes a recommendation that the labeling for latex condoms with N–9 state that the pregnancy risk reduction that N–9 provides has not been measured. If the proposed rule designating a special control and the accompanying guidance become final, the new statement will supersede the provision originally included in the order reclassifying latex condoms with N–9 from class III to class II (47 FR 49201).

2. Transmission of STIs

The other principal intended use of latex condoms is reduction of STI transmission. In developing the special control, FDA examined the plausibility of STI risk reduction and other scientific evidence, explained previously in section III of this document. This evidence suggests that consistent use of latex condoms reduces the risk of transmission for some, but not all, of the common STIs. Differences in the level of risk reduction provided by consistent use of latex condoms is primarily related to their means of transmission.

Consistent with FDA's findings in the scientific review described previously in this document, the draft special controls guidance provides specific labeling recommendations addressing the risks of STI transmission by explaining the effectiveness of latex condoms with regard to this use. The draft guidance recommends that the labeling explain that consistent use of latex condoms significantly reduces, but does not eliminate, the risk of acquiring or transmitting (catching or spreading) HIV. The guidance also recommends labeling to inform users that STIs can be transmitted in various ways, including transmission to or from the penis and transmission by other types of sexual contact. The guidance recommends labeling to explain that consistent use of latex condoms reduces risk (50% - 60%) for STIs such as gonorrhea and chlamydia, that are transmitted through genital fluids during penile-vaginal sex.

**Deleted:** reduced
**Deleted:** protection
**Deleted:** STDs
**Deleted:** STD
**Deleted:** STDs
**Deleted:** protection
**Deleted:** STDs
**Deleted:** STD
**Deleted:** STD
**Deleted:** STD
**Comment [p31]:** 85%
**Deleted:** Although l
**Deleted:** can greatly
**Deleted:** unintended
**Deleted:** ,
**Deleted:** protection
**Deleted:** protection
**Formatted** ... [10]
**Formatted** ... [11]
**Deleted:** STDs
**Comment [p32]:** reducing the risk
**Deleted:** protection
**Deleted:** against the transmissi ... [12]
**Deleted:** STD
**Deleted:**
**Deleted:** body of
**Deleted:** indicates that as an ov ... [13]
**Deleted:** are effective at
**Deleted:** ing
**Deleted:** STD
**Deleted:** transmission, but that d
**Deleted:** exist
**Deleted:** condoms
**Deleted:** with respect to two g ... [14]
**Comment [p33]:** (85%, if us ... [15]
**Deleted:** STD
**Deleted:** can
**Deleted:** greatly
**Deleted:** STDs
**Deleted:** can
**Deleted:** the
**Deleted:** of STDs
**Deleted:** spread to or from the ... [16]

It further recommends labeling that indicates that some STIs, such as genital herpes and HPV, may also be transmitted by contact with infectious skin or mucosa not covered by the condom. In other words, consistent condom use provides considerably less risk reduction for herpes and HPV than for HIV, chlamydia, and gonorrhea. Labeling should clarify that, even for herpes and HPV, there may be some benefits from correct and consistent use, such as a lower risk of catching or spreading herpes infection and a lower risk of developing some HPV-related diseases, such as genital warts and cervical cancer.

The guidance for condom labeling does not recommend including information about other ways to prevent the transmission of STIs or to reduce the adverse clinical outcomes associated with these infections. There is important additional public health information about strategies to prevent transmission of HPV and to reduce serious clinical outcomes. These strategies include abstinence for men and women and regular cervical screening for women. However, the agency believes its primary role in this area is its jurisdiction over labeling for latex condoms and that its main goal must be to ensure that such labeling supports the safe and effective use of latex condoms by users who have chosen latex condoms for protection. At this time, the agency has concluded that it would not be useful to include in condom labeling additional educational information about social behaviors or public health programs that can reduce the risk and consequences of STI transmission. Additional information in condom labeling may confuse condom purchasers or cause them to overlook important messages. However, providing this information through other mechanisms not under FDA's jurisdiction may be beneficial.

FDA believes the message it has crafted in its labeling recommendations is a balanced recognition of the benefits and limits of condoms for reducing STIs. The guidance does recommend that condom users consult health care professionals or seek additional information about STIs from reputable governmental agencies. FDA's recommended labeling is also likely to be a springboard for new initiatives to inform and educate public health officials, health educators, and—in the end—potential condom users. FDA fully expects to partner with Federal, State, and local public health officials to help develop such informational and educational materials.

Later in this proposal, FDA is specifically requesting comments from the public about the value of adding additional information to condom labeling about other ways to prevent the spread of HPV and the clinical outcomes that may develop from that infection.

3. Incorrect or Inconsistent Use In order for latex condoms to achieve a protective effect against the risks identified above, they must be used correctly and consistently. Incorrect use can undermine the effectiveness of the condom against the likelihood of unintended pregnancy and risks of STI transmission. Inconsistent use, for example, not using a condom with every act of intercourse, can also diminish the effectiveness of the condom against the risks of unintended pregnancy and STI transmission. The draft special controls guidance document recommends that the labeling include appropriate precautions to help reduce the incorrect and inconsistent use of latex condoms. The draft guidance recommends specific precautions on using, storing, and lubricating latex condoms.

4. Issues Associated With N–9 in Condoms With Spermicidal Lubricant

As discussed previously in this document, since 1982, condoms with N–9 in the lubricant have been required to bear a statement addressing the contraceptive effectiveness of N–9 in order to be classified under § 884.5310. No claims relating N–9 to the effectiveness of condoms in preventing STI transmission have been permitted on condom labeling. Subsequently, new information has been developed that demonstrates that there are risks associated with N–9 that may outweigh its benefits as a spermicidal lubricant for certain users and that confirms that N–9 provides no benefit for STI prevention.

Specifically, as explained in the previous sections, based on its review of the available scientific evidence, FDA concludes that N–9 kills sperm; however, the additional pregnancy risk reduction provided by N–9 has not been measured. This limited contraceptive benefit clearly does not apply when a condom is used for anal sex. Furthermore, N–9 on the condom does not protect against HIV/AIDS or other STIs. FDA also concludes that N– 9 can irritate the vagina, which may increase the risk of HIV/AIDS transmission from an infected partner. Additionally, clinical data demonstrate that N–9 can irritate the cells lining the rectum, a finding that, in combination with other information about the transmissibility of HIV, indicates that N–9 may increase the risk of HIV transmission from an infected partner when used for anal sex. Given these factors, for some users, risks associated with N–9 may outweigh the benefits of using a condom containing N–9 in the spermicidal lubricant. The recommended labeling in the draft special controls guidance instructs such users to choose a latex condom without N–9.

From discussions with condom manufacturers, FDA's understanding is that a large proportion of couples using condoms with N–9 are using them primarily for contraception and are at low risk for HIV/AIDS infection. To provide reasonable assurance of safe and effective use, however, users need to know about the increased risk of HIV acquisition from an infected partner that might be associated with exposure to N–9, including exposure resulting from use of condoms containing N–9 in the lubricant, as well as understand the scope of benefits provided by latex condoms lubricated with N–9. Through the proposed designation of the special controls guidance document, FDA seeks to provide decisionmaking information and cautions that should permit users to determine whether a latex condom with spermicidal lubricant is appropriate for their needs.

Specifically, FDA's draft special controls guidance document recommends that the labeling for latex condoms with spermicidal lubricant state that the product contains the spermicide N–9, which kills sperm, but that the pregnancy risk

**Comment [p34]:** Risk reduction ranges from 50-60% with consistent use.

**Deleted:** STDs

**Deleted:** , and that condoms provide less protection against these STDs.

**Deleted:** these STDs, however,

**Comment [PT35]:** Labeling should include a table showing % risk reduction associated with consistent condom use for each of the common STIs (HIV, chlamydia, gonorrhea, syphilis, trichomoniasis, HPV, herpes, and HBV)

**Comment [PT36]:** Labeling should also include a recommendation for routine STI screening for nonmonogamous condom users

**Comment [p37]:** Labeling should include a table showing consistent condom use effectiveness for risk reduction against various STIs.

**Deleted:** STDs

**Deleted:** STD

**Deleted:** STDs

**Deleted:** STDs

**Deleted:** STD

**Deleted:** STD

**Comment [p38]:** risk reduction

**Deleted:** STD

**Deleted:** STD

**Deleted:** protection

**Deleted:** STDs

**Comment [PT39]:** Shouldn't the FDA look at scientific studies on this issue, rather than rely on anecdotal information from manufacturers?

**Deleted:** ve

**Deleted:** protection

**Deleted:** protection

reduction provided by N–9 has not been measured. The draft guidance also recommends that the labeling state that the N–9 lubricant on the condom does not protect against HIV/AIDS or other STIs. Including this information permits potential users of condoms with N–9 to evaluate the benefits that this particular type of condom may offer, particularly in relation to other latex condoms. As discussed in FDA's proposed rule on OTC vaginal contraceptive drug products containing N–9, information currently available to the general public creates the misperception that N–9 might help decrease the risk of becoming infected with HIV and other STIs (68 FR 2254). Addressing the lack of STI risk reduction provided by N–9 is therefore necessary to help assure safe and effective use of condoms with N–9 because the public may mistakenly believe that N–9 does provide this benefit.

In addition, the draft special controls guidance document recommends that condom labeling inform users that use of N–9 can irritate the vagina and that this may increase the risk of getting HIV/AIDS from an infected partner. Labeling should also inform users that if they or their partner have HIV/AIDS, or if their infection status is unknown, they should choose a latex condom without N–9. In addition, given that use of N–9, which is intended solely for contraceptive effect, offers no benefit for anal intercourse, and that rectal use of N–9 may increase the risk of HIV/AIDS transmission, the proposed labeling warns that N–9 can irritate the rectum and that condoms with N–9 should not be used for anal sex.

FDA believes that the designation of this special control, which addresses the information developed since the 1982 reclassification of condoms with spermicidal lubricant into class II, together with general controls, should reasonably assure the safety and effectiveness of these devices. Crafting labeling for these devices does present unique difficulties, however. Unlike OTC vaginal contraceptive drugs containing N–9, latex condoms (both with and without N–9) are intended for STI prevention as well as contraception. While the N–9 lubricant provided on some condoms is intended to support only the contraceptive use of the condom, this N–9 lubricant component may also unintentionally increase the risk of transmission of HIV if a person were exposed to an infected partner's secretions after first being exposed to the N–9 lubricant on the condom. For example, this increased risk scenario could occur if a person had sex using a condom with N–9 and then subsequently had sex with an infected partner who did not use any condom. At the same time, for reasons explained in the prior sections, latex condoms with N–9 are effective barrier devices, and it is this barrier effectiveness that is the source of their risk reduction against HIV/ AIDS and other STIs.

For these reasons, the proposed labeling in the draft special controls guidance document indicates that latex condoms (both with and without spermicidal lubricant containing N–9), when used correctly every time you have sex, greatly reduce, but do not eliminate, the risk of catching or spreading HIV, while also indicating that persons who may be at risk of HIV exposure should choose latex condoms without N–9. We welcome comments on this labeling and on any means of improving it to minimize confusion. In addition, in section VIII of this document, FDA specifically requests comments on whether this special control is sufficient to provide a reasonable assurance of the safety and effectiveness of latex condoms with spermicidal lubricant containing N–9, or whether there are other special controls that FDA should consider. FDA also requests comments on whether special controls alone are sufficient to provide a reasonable assurance of the safety and effectiveness of latex condoms with spermicidal lubricant containing N–9 or whether the risks of N–9 outweigh the potential contraceptive benefits the spermicide adds to the barrier protection of condoms.

At this time, FDA is not proposing to designate a special control for any condoms made of natural membrane (skin) or synthetic materials. Discussions with the condom industry indicate that condoms made from natural rubber latex represent nearly 98 percent of the U.S. retail market for condoms. The agency understands that all condoms distributed by public health and other organizations are also made from natural rubber latex, based on the agency's discussions with manufacturers. The agency believes, therefore, that the recommendations in the draft special controls guidance document address the vast majority of condoms distributed in the United States. However, at a future date, FDA also intends to address condoms made from other materials that are not specifically addressed by this guidance. Until FDA provides further specific guidance for these products, manufacturers of synthetic condoms may consult Part C of FDA's guidance document entitled "Testing Guidance for Male Condoms Made From New Material (June 25, 1995)," available at:
*http://www.fda.gov/cdrh/ode/ oderp455.html*, and manufacturers of natural membrane condoms may consult the guidance document entitled "Guidance for Industry-Uniform Contraceptive Labeling (July 23, 1998)," available at: *http://www.fda.gov/cdrh/ ode/contrlab.html*.

FDA believes, however, that most of the recommendations contained in the draft special controls guidance document for latex condoms regarding labeling to address N–9 are also applicable to nonlatex condoms containing N–9, and encourages manufacturers to follow those aspects, as noted in the draft guidance itself. We also specifically solicit comment in section VIII of this document on whether the recommendations in the proposed draft guidance that address issues related to N–9 should be proposed as a special control for all condoms with spermicidal lubricant, regardless of material.

*C. Implementation and Proposed Effective and Compliance Dates*

After reviewing public comments on this proposed rule and draft guidance document, FDA intends to finalize the guidance document and to issue a final rule for condoms with and without spermicidal lubricant, which will make that guidance document effective as the special control for latex condoms with and without spermicidal lubricant. FDA proposes to implement any such final rule as follows. We propose that any final rule based on this proposal become effective 30 days after the date of its publication in the **Federal Register**. We propose that latex condoms cleared for

**Deleted:** STDs

**Deleted:** STDs

**Deleted:** STD

**Deleted:** protection

**Deleted:** STD

**Deleted:** protection

**Deleted:** STDs

**Comment [PT40]:** Known risks *always* outweigh unknown potential benefits

marketing on or after this effective date (but submitted in 510(k)s filed before the effective date) comply with the requirement of special controls by following the recommendations in the special control or providing equivalent assurances of safety and effectiveness no more than 60 days after the effective date of any final rule based on this proposal. Premarket notification submissions (510(k)s) for new latex condoms with or without spermicidal lubricant, filed after the effective date of any final rule based on this proposal, must address the issues covered in the special controls guidance document when the 510(k) is submitted. However, the firm submitting a 510(k) needs only to show that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness.

FDA proposes that latex condoms legally marketed before the effective date of any final rule resulting from this proposal comply with the requirement of special controls by following the recommendations in the special controls guidance document or in some other way providing equivalent assurances of safety and effectiveness within 12 months after the date of publication of the final rule based on this proposal in the **Federal Register** (11 months after the effective date of the final rule based on this proposal). If the issues requiring special controls are addressed by labeling as recommended in the special controls guidance document, no new premarket notification (510(k)) or other report need be filed to address the changes made. (However, if a manufacturer chooses to satisfy the requirement of special controls by making other changes to the device that trigger the submission of a new 510(k) in accordance with § 807.81(a)(3), a new submission will be required.)

This dual compliance date proposal is intended to allow depletion of stocks of condoms with existing labeling, as well as production of condoms with new labeling. Based on discussion with major manufacturers, we believe that the majority of latex condoms reach final users well within 12 months of leaving manufacturer control. We welcome comment on our estimate and on the proposed implementation strategy in general.

## V. Environmental Impact

The agency has determined under 21 CFR 25.34(b) 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.

## VI. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and 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 that this proposed rule is consistent with the principles identified in Executive Order 12866. The Office of Management and Budget (OMB) has determined that this proposed rule is a significant regulatory action as defined by the Executive order and so is subject to OMB review.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. FDA does not believe that the proposed rule will have a significant economic impact on a substantial number of small entities, but recognizes the uncertainty of its estimates. Because the agency acknowledges that many affected entities are small entities, the analysis presented below, along with this preamble, constitutes the agency's Initial Regulatory Flexibility Analysis, and the agency specifically solicits comments on its estimates and analysis of the impact of the rule on those 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 $115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

### *A. Background*

The purpose of this proposed rule is to amend the classification regulations for condoms and condoms with spermicidal lubricant to designate a labeling guidance as a special control for latex condoms within either classification. (FDA intends to address condoms made from other materials at a future date.) As discussed earlier in this preamble, condoms and condoms with spermicidal lubricant have been previously classified into class II in accordance with section 513 of the act. The draft special controls guidance identifies particular issues associated with these devices and recommends labeling to address those issues. The current voluntary guidance recommendations for condom labeling do not address some of the important risk information FDA has identified in this proposed rule. In particular, current labeling does not provide specific information about the reduced risk reduction condoms offer against transmission of certain STIs, such as HPV, that can be transmitted through

**Deleted:** STDs

contact with infected skin outside the area covered by the condom. In addition, current labeling does not provide specific information about the potential risks associated with the use of the spermicidal lubricant nonoxynol-9 (N–9) in condoms. FDA believes that providing consumers with this additional information on condom labeling can improve the safe and effective use of condoms. More accurate information about the risks and benefits of condom use with respect to STI transmission can lead to better choices by individuals who seek to protect themselves against these infections and potentially to reduced transfer of STIs.

*Other options the agency considered.* One option the agency considered was to publish its conclusions as a regular guidance document, rather than as a special controls guidance document. This approach would have made the information available to the public through agency publication, but it would not have required that manufacturers address the labeling issues FDA has identified. Unlike a regular guidance, which imposes no requirements, a special controls guidance requires that manufacturers address the issues identified in the guidance, either by following the recommendations in the guidance or by some other means that provides equivalent assurances of safety and effectiveness. Although FDA believes that many manufacturers would incorporate significant portions of the new recommendations voluntarily, as they have in the past with respect to other recommendations for condom labeling, FDA concluded that a purely voluntary approach did not ensure sufficient compliance or consistency to adequately convey this important information to the public.

The benefit of the option the agency has chosen is that establishing the labeling guidance as a special control means that manufacturers will be required to address the concerns identified in the guidance, although they will not be bound to use the particular language FDA is recommending. Since the passage of the Safe Medical Devices Act of 1990, FDA has been permitted to establish "special controls" as a way to ensure that a manufacturer of a Class II device will be able to establish the safety and effectiveness of that device. In addition to all the general controls that apply to all classes of devices (such as adverse event reporting and good manufacturing practices), a "special control" provides an additional and necessary level of assurance that the risks associated with a Class II device can be addressed by the manufacturer.

Special control guidances have become one of the most important ways that FDA ensures the safety and effectiveness of Class II medical devices. While a special control guidance remains a "guidance" because there is no requirement to comply with the specific recommendations the guidance sets forth, the special control guidance places an obligation upon the manufacturer to address the issues and concerns identified in that guidance. As a practical matter, most manufacturers do follow the recommendations in a special controls guidance because it is frequently the least burdensome way for that manufacturer to make sure that his Class II product will meet the necessary standards of safety and effectiveness. However, the manufacturer can address the issues identified in the guidance by following the recommendations in the guidance or by some other means that provides equivalent assurances of safety and effectiveness. In this way, issuing a special controls labeling guidance for condoms ensures that manufacturers will provide consumers with the information they need to make an informed decision regarding the use of condoms. The special control guidance helps ensure that information provided to consumers does not exaggerate the degree of overall risk reduction provided by condoms, nor undervalues the overall STI risk reduction provided by condom use. The agency believes this special control will, together with the general controls, provide reasonable assurance of the safety and effectiveness of those devices.

No comment on the deleted text

**VIII. Specific Request for Comments**

FDA welcomes comments on all aspects of the proposed regulation, but particularly invites comments on the following issues:

As discussed in more detail in section IV of this document, FDA specifically requests comments on whether its labeling recommendations for condoms should include more detailed information on the prevention of genital HPV infection, and information on different approaches for prevention of cervical cancer.

In addition, as discussed in section IV of this document, FDA specifically requests comments on whether this special control is sufficient to provide a reasonable assurance of the safety and effectiveness of latex condoms with spermicidal lubricant containing N–9, or whether there are other special controls that FDA should consider. FDA also requests comments on whether special controls alone are sufficient to provide a reasonable assurance of the safety and effectiveness of latex condoms with spermicidal lubricant containing N–9 or whether the risks of N–9 outweigh the potential contraceptive benefits the spermicide adds to the **barrier protection** of condoms.

Finally, as discussed in section IV of this document, the current special control proposal applies only to latex condoms. FDA acknowledges, however, that concerns regarding N–9 in condoms with spermicidal lubricant would appear to be very similar for all condoms, nonlatex as well as latex. For purposes of making a future proposal, FDA solicits comment on possible special controls for nonlatex (including both skin and synthetic) condoms containing N–9. FDA solicits comments on whether the guidance currently proposed as a special control only for latex condoms, insofar as it addresses risks associated with N–9, should be proposed as that special control. FDA also welcomes comments suggesting alternative special controls for nonlatex condoms with N–9. Moreover, FDA also welcomes comments on

**Deleted:** STD

**Deleted:** STDs

**Comment [p44]:** manufacturers should not be allowed to write their own health statements de novo. The FDA should provide several options to manufacturers.

**Deleted:** The agency also considered rulemaking that would mandate specific new language on all condom labeling to address the concerns FDA has identified. The agency rejected this option because a labeling rule deprives manufacturers of any flexibility with respect to the way they provide the information to consumers and because a labeling rule is difficult to change or amend as new scientific information becomes available to update the public health message. ¶

**Deleted:** STD

**Formatted:** Default, Line spacing: single

**Formatted:** Font: 12 pt

**Formatted:** Font: 12 pt, Not Bold

**Comment [PT42]:** Known risks *always* outweigh potential benefits

potential special controls for nonlatex condoms without N–9.

## IX. General Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

## X. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but we are not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**.)


1. 1. Lytle, C. D., L. B. Routson, G. B. Seaborn, et al., "An In Vitro Evaluation of Condoms as Barriers to a Small Virus," *Sexually Transmitted Diseases*, 1997: 24:3:161–164.
2. 2. Steiner, M. J., R. Foldesy, D. Cole, et al., "Study to Determine the Correlation Between Condom Breakage in Human Use and Laboratory Test Results," *Contraception*, 1992:46:3:279–288.
3. 3. Free, M. J., V. Srisamang, J. Vail, et al., "Latex Rubber Condoms: Predicting and Extending Shelf Life," *Contraception*, 1996:53:4:221–229.
4. 4. National Institute of Allergy and Infectious Diseases, Workshop Summary: Scientific Evidence on Condom Effectiveness for Sexually Transmitted Disease (STD) Prevention, July 2001.
5. 5. Walsh, T. L., R. G. Frezieres, K. Peacock, et al., "Evaluation of the Efficacy of a Nonlatex Condom: Results From a Randomized, Controlled Clinical Trial,"

*Perspectives on Sexual and Reproductive Health*, 2003:35:2:79–86.

1. 6. Steiner, M. J., R. Dominik, R. W. Rountree, et al., "Contraceptive Effectiveness of Polyurethane Condom and a Latex Condom: A Randomized Controlled Trial." *Obstetrics and Gynecology*, 2003:101:3:539– 547. see 69117
2. 7. Potter, W. D. and M. de Villemeur, "Clinical Breakage, Slippage and Acceptability of a New Commercial Polyurethane Condom: A Randomized, Controlled Study," *Contraception*, 2003:68:1:39–45.
3. 8. Davis, K. R. and S. C. Weller, "The Effectiveness of Condoms in Reducing Heterosexual Transmission of HIV," *Family Planning Perspectives*, 1999: 31:6:272–279.
4. 9. Centers for Disease Control and Prevention, Department of Health and Human Services, Report to Congress: Prevention of Genital Human Papillomavirus Infection, 18, January 2004.

1. 10. Weller, S. and K. Davis, "Condom Effectiveness in Reducing Heterosexual HIV Transmission (Cochrane Review)," In: *The Cochrane Library Issue 3*, 2002, Oxford: Update Software.
2. 11. Pinkerton, S. D., P. R. Abramson, Effectiveness of Condoms in Preventing HIV Transmission, *Social Science and Medicine*, 1997, May; 44(9):1303–12.
3. 12. Warner, D. L., K. M. Stone, and J. W. Buchler, Using Epidemiology to Understand Condom Effectiveness for Preventing Gonorrhea, Chlamydia, and Pelvic Inflammatory Disease [abstract P116], 2004, National STD Prevention Conference, March 8 to 11, 2004, Philadelphia, PA.
4. 13. Sanchez, J., E. Gotuzzo, J. Escamilla, et al., "Sexually Transmitted Infections in Female Sex Workers: Reduced by Condom Use but Not Limited by a Periodic Examination Program," *Sexually Transmitted Diseases*, 1998:25:2:82–89.
5. 14. Levine, W. C., R. Revollo, V. Kaune, et al., "Decline in Sexually Transmitted Disease Prevalence in Female Bolivian Sex Workers: Impact of an HIV Prevention Project," *AIDS*, 1998 Oct 1;12(14):1899–1906.
6. 15. Ahmed, S., T. Lutalo, M. Wawer, et al., "HIV Incidence and Sexually Transmitted Disease Prevalence Associated with Condom Use: A Population Study in Rakai, Uganda," *AIDS*, 2001 Nov 9; 15(16):2171–9.
7. 16. Casper, C. and A. Wald, "Condom Use and the Prevention of Genital Herpes Acquisition," *Herpes*, 2002:9:1:10–4.
8. 17. Wald A., A. G. M. Langenberg, K. Link, et al., "Effect of Condoms or Reducing the Transmission of Herpes Simplex Virus Type 2 From Men to Women," *Journal of American Medical Association*, 2001:285:3100–3106.
9. 18. Wald A., A. Langenberg, E. Kexel, et al., "Condoms protect Men and Women Against Herpes Simplex Virus Type 2 (HSV–2) Acquisition [abstract B9E]. Presented at the 2002 National STD Prevention Conference," March 4–7, San Diego, CA.
10. 19. Gottlieb, S. L., J. M. Douglas , M. Foster, et al., "Incidence of Herpes Simplex Virus Type 2 Infection in Five Sexually Transmitted Disease Clinics and the Effect of HIV/STD Risk Reduction Counseling," *Journal of Infectious Diseases*, 2004:190:1059–1067.
11. 20. Manhart, L. E. and L. A. Koutsky, "Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta analysis," *Sexually Transmitted Diseases*, 2002:29:11:725–735.
12. 21. Cameron, D. W., E. N. Ngugi, A. R. Ronald, et al., "Condom Use Prevents Genital Ulcers in Women Working as Prostitutes," *Sexually Transmitted Diseases*, 1991:18:3:188–191.
13. 22. Centers for Disease Control and Prevention, Tracking the Hidden Epidemics 2000, Trends in STDs in the United States, Chancroid (*http://www.cdc/gov/nchstp/dstd/ Stats_Trends/Trends2000.pdf*).
14. 23. Van Damme, L., G. Ramjee, M. Alary, 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*, 2002: 360; 9338: 971–977.
15. 24. WHO/CONRAD Technical Consultation on Nonoxynol-9: Summary Report, World

Health Organization, Geneva, 9–10 October, 2001, pp. 1– 27
1. 25. Roddy R. E., M. Cordero, K. A. Ryan, et al., "A Randomized Controlled Trial Comparing Nonoxynol-9 Lubricated Condoms With Silicone Lubricated Condoms for Prophylaxis," *Sexually Transmitted Infections*, 1998: 74:116–119.
2. 26. Phillips, D., "Nonoxynol-9 Enhances Rectal Infection by Herpes Simplex Virus in Mice," *Contraception*, 1998:57:341–348.
3. 27. Tabet, S. R., C. Surawicz, S. Horton, et al., "Safety and Toxicity of Nonoxynol-9 Gel as a Rectal Microbicide," *Sexually Transmitted Diseases*, 1999:26:10:564–571.
4. 28. Phillips, D. "Nonoxynol-9 Causes Rapid Exfoliation of Sheets of Rectal Epithelium," *Contraception*, 2000: 62:3:149–154.
5. 29. Frezieres, R. G., T. L. Walsh, A. L. Nelson, et al., "Evaluation of the Efficacy of a Polyurethane Condom: Results From a Randomized, Controlled Clinical Trial," *Family Planning Perspectives*, 1999:31:2:81–
6. 87.

1. 30. Gallo, M. F., D. A. Grimes, and K. F. Schulz, "Nonlatex vs. Latex Male Condoms for Contraception: A Systematic Review of Randomized Clinical Trials," *Contraception*, 2003:68:5:319–236.
2. 31. Kjaer, S. K., E. I. Svare, A. M. Worm, et al., "Human Papillomavirus Infection in Danish Female Sex Workers: Decreasing Prevalence With Age Despite Continuously High Sexual Activity," *Sexually Transmitted Diseases*, 2000: 27(8):438–445.
3. 32. Kotloff K. L., S. S. Wasserman, K. Russ, et al., "Detection of Genital Human Papillomavirus and Associated Cytologic Abnormalities Among College Women," *Sexually Transmitted Diseases*, 1998:25(5):243–250.
4. 33. Mayaud P., D. K. Gill, H. A. Weiss, et al., "The Interrelation of HIV, Cervical Human Papillomavirus, and Neoplasia Among Antenatal Clinic Attenders in Tanzania," *Sexually Transmitted Infections*, 2001:77(4):248–254.
5. 34. 11th Report on Carcinogens, National Toxicology Program, January 31, 2005, (FactSheet).

**List of Subjects in 21 CFR Part 884**

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 884 be amended as follows:

## PART 884—OBSTETRICAL AND GYNECOLOGICAL DEVICES

1. The authority citation for 21 CFR part 884 continues to read as follows:

**Authority:** 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Section 884.5300 is revised to read as follows:

**§ 884.5300 Condom.**

(a) *Identification.* A condom is a sheath which completely covers the penis with a closely fitting membrane. The condom is used for contraceptive and for prophylactic purposes (preventing transmission of sexually transmitted diseases). The device may also be used to collect semen to aid in the diagnosis of infertility.

.(b) *Classification.* (1) Class II (special controls) for condoms made of materials other than natural rubber latex, including natural membrane (skin) or synthetic.

.(2) Class II (special controls) for natural rubber latex condoms. The guidance document entitled "Class II Special Controls Guidance Document: Labeling for Male Condoms Made of Natural Rubber Latex" will serve as the special control. See § 884.1(e) for the availability of this guidance document.

3. Section 884.5310 is revised to read as follows:

**§ 884.5310 Condom with spermicidal lubricant.**

.(a) *Identification.* A condom with spermicidal lubricant is a sheath which completely covers the penis with a closely fitting membrane with a lubricant that contains a spermicidal agent, nonoxynol–9. This condom is used for contraceptive and for prophylactic purposes (preventing transmission of sexually transmitted diseases).

.(b) *Classification.* (1) Class II (special controls) for condoms made of materials other than natural rubber latex, including natural membrane (skin) or synthetic.

.(2) Class II (special controls) for natural rubber latex condoms. The guidance document entitled "Class II Special Controls Guidance Document: Labeling for Male Condoms Made of Natural Rubber Latex" will serve as the special control. See § 884.1(e) for the availability of this guidance document.

Dated: June 21, 2005.

**Jeffrey Shuren,**

*Assistant Commissioner for Policy.*

[FR Doc. 05–22611 Filed 11–10–05; 8:45 am]

BILLING CODE 4160–01–S

**DEPARTMENT OF THE INTERIOR**

**Minerals Management Service**

**30 CFR Parts 250, 251, and 280**

**RIN 1010–AD23**

## Oil, Gas, and Sulphur Operations and Leasing in the Outer Continental Shelf (OCS)—Recovery of Costs Related to the Regulation of Oil and Gas Activities on the OCS

**AGENCY:** Minerals Management Service (MMS), Interior.

**ACTION:** Proposed rule.

**SUMMARY:** MMS is proposing regulations which impose new fees to process certain plans, applications, and permits. The proposed service fees would offset MMS's costs of processing these plans, applications, and permits.

**DATES:** MMS will consider all comments received by January 13, 2006. MMS will begin reviewing comments and may not fully consider comments received after January 13, 2006.

**ADDRESSES:** You may submit comments on the proposed rule by any of the following methods listed below. Please use the regulatory identifier number (RIN) 1010-AD23 as an identifier in your message. See also Public Comment Procedures under Procedural Matters.

- Federal e-Rulemaking Portal: *http://www.regulations.gov.* Follow the instructions on the website for submitting comments.
- E-mail MMS at *rules.comments@mms.gov.* Use the RIN in the subject line.
- Fax: 703–787–1546. Identify with the RIN.
- Mail or hand-carry comments to the Department of the Interior; Minerals Management Service; Attention: Rules Processing Team (RPT); 381 Elden Street, MS–4024; Herndon, Virginia 20170–4817. Please reference "Recovery of Costs Related to the Regulation of Oil and Gas Activities on the OCS–AD23" in your comments.

You may also send comments on the information collection aspects of this rule directly to the Office of Management and Budget (OMB) via: OMB e-mail: (*OIRA_DOCKET@omb.eop.gov*); mail or hand carry to the Office of Information and Regulatory Affairs, OMB Attention: Desk Officer for the Department of the Interior (1010–AD23) or by fax (202) 395–6566. Please also send a copy to MMS.

**FOR FURTHER INFORMATION CONTACT:**

Martin Heinze, Program Analyst, Office of Planning, Budget and International Affairs at (703) 787–1010.

**SUPPLEMENTARY INFORMATION:**

### Background

Federal agencies are generally authorized to recover the costs of providing services to non-federal entities through the provisions of the Independent Offices Appropriation Act of 1952 (IOAA), 31 U.S.C. 9701. The Act requires implementation through rulemaking. There are several policy documents that provide MMS guidance on the process of charging applicants for service costs. The governing language concerning cost recovery can be found in OMB Circular No. A–25 which states in part, "The provisions of this Circular cover all federal activities that convey benefits to recipients beyond those accruing to the general public. * * * When a service (or privilege) provides special benefits to an identifiable recipient, beyond those that accrue to the general public, a charge would be imposed (to recover the full costs to the Federal Government for providing this specific benefit, or the market price).
* * * The general policy is that user charges will be instituted through the promulgation of regulations." The Department of the Interior (DOI) Manual mirrors this policy (330 DM 1.3 A.).

In this rulemaking, "cost recovery" means reimbursement to MMS for its costs of performing a service by charging a fee to the identifiable applicant/beneficiary of the service. Further guidance is provided by Solicitor's Opinion M–36987, "BLM's Authority to Recover Costs of Minerals Document Processing" (December 5, 1996). As explained in that Solicitor's Opinion, some costs, such as the costs of programmatic environmental studies and programmatic environmental assessments in support of a general agency program are not recoverable because they create an "independent public benefit" rather than a specific benefit to an identifiable recipient. Id. at 9–10.

On March 25, 2005, MMS published an Advance Notice of Proposed Rulemaking (ANPR) in the **Federal Register** titled, "Recovery of Costs Related to the Regulation of Oil and Gas Activities on the Outer Continental Shelf," (70 FR 15246). (The cost recovery fees MMS is addressing in this proposed rule are for different activities than those addressed in the recently promulgated final rule issued on August 25, 2005 (70 FR 49871)). Through the ANPR, MMS alerted the public that we seek to recover the costs of processing certain permits and applications through the rulemaking process. MMS believes that cost recovery for the MMS-provided service of reviewing and

**Page 6: [1] Comment [PT7]** **Patricia Thickstun** **2/8/2006 6:27:00 PM**

Since the epidemiological (in vivo) data do not support this conclusion, results of in vitro studies are irrelevant.

**Page 6: [2] Deleted** **Patricia Thickstun** **2/8/2006 6:19:00 PM**

or when susceptible sites are protected

**Page 6: [3] Comment [p9]** **pthickstun** **2/8/2006 6:27:00 PM**

provided by correct and consistent use of condoms

**Page 6: [4] Deleted** **Patricia Thickstun** **2/8/2006 6:20:00 PM**

In summary, considering the means of transmission of STDs and the extensive information on the physical characteristics and performance of condoms, FDA believes there is strong support for the conclusion that condoms are effective in reducing the overall risk [p1] of STD transmission.

**Page 6: [5] Comment [PT10]** **Patricia Thickstun** **2/8/2006 6:48:00 PM**

the Workshop considered articles related only to the reduction of STI transmission during **penile-vaginal** intercourse (not anal or oral intercourse)

**Page 6: [6] Comment [p11]** **pthickstun** **2/8/2006 6:27:00 PM**

only reduce risk of transmission when the ulcers or infections are covered by the condom

**Page 6: [7] Comment [PT12]** **Patricia Thickstun** **2/8/2006 6:38:00 PM**

the term "highly effective" in the NIH report refers only to in vitro studies by FDA scientists

**Page 6: [8] Comment [PT13]** **Patricia Thickstun** **2/8/2006 6:39:00 PM**

did not evaluate correct use

**Page 6: [9] Deleted** **Patricia Thickstun** **2/8/2006 6:38:00 PM**

Workshop findings reaffirmed that condoms are highly effective against HIV transmission.

**Page 11: [10] Formatted** **Patricia Thickstun** **2/9/2006 10:26:00 AM**

Font: 12 pt

**Page 11: [11] Formatted** **Patricia Thickstun** **2/9/2006 10:26:00 AM**

Default, Indent: First line: 0"

**Page 11: [12] Deleted** **Patricia Thickstun** **2/8/2006 5:16:00 PM**

against the transmission of STDs

**Page 11: [13] Deleted** **Patricia Thickstun** **2/9/2006 10:28:00 AM**

indicates that as an overall matter,

**Page 11: [14] Deleted** **Patricia Thickstun** **2/9/2006 10:31:00 AM**

with respect to two general groups of STDs, distinguished by

**Page 11: [15] Comment [p33]** **pthickstun** **2/8/2006 6:27:00 PM**

(85%, if used consistently,)

**Page 11: [16] Deleted** **Patricia Thickstun** **2/9/2006 10:37:00 AM**

spread to or from the penis by direct contact with the vagina and genital fluids, such as gonorrhea and chlamydia.