Tab B

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 and condoms with spermicidal lubricant containing nonoxynol–9 (condoms with spermicidal lubricant) 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 FDA is proposing the draft guidance document entitled "Class II Special Controls Guidance Document: Labeling for Male Condoms Made of Natural Rubber Latex," as the special control that the agency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.

DATES: Submit written or electronic comments on the proposed rule by [*insert date 90 days after date of publication in the* **Federal Register**]. 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, by any of the following methods:

- 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.
- E-mail: *fdadockets@oc.fda.gov*. Include Docket No. 2004N–0556 in the subject line of your e-mail message.
- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the agency name and Docket No. 2004N–0556 for this rulemaking. All comments received will be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, see section IX, "General Request for Comments" of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents and comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and/or 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 contraceptive protection 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.

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 contraceptive protection 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 protection against STDs.

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). 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 ΦX174 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 study showed that latex condoms are highly effective at preventing passage of even the smallest infectious agents. 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 protection 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 1990's (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 provide protection against STD 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 are consistent with these findings (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 STD transmission, although, as discussed in the following section, the degree of risk reduction varies depending on the route of transmission of the STD. As discussed later in this document, this finding is also supported by review of studies on condom use and STD risk reduction.

C. Plausibility for STD Risk Reduction Attributable to Condoms

FDA evaluated the plausibility of attributing STD 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 STD pathogens and how they are transmitted. Specifically, STD 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 thus reduce the overall risk of STD transmission.

In the evaluation to determine the overall effectiveness of condoms in preventing STD transmission, it is critical to recognize that individual STDs 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 STDs. To determine whether and to what extent it is reasonable, based on available information, to expect a condom to protect against different STDs, FDA considered nine STDs, including those most common in the United States, and their routes of sexual transmission. Table 1 of this document lists each STD considered and its usual route(s) of sexual transmission.

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

STD	Exposure to and From the Head of the Penis	Exposure to Infectious Skin or Mucosa (Excluding the Head of the Penis)
Group I		
HIV/Aquired Immunodeficiency Syndrome (AIDS)	✓	
Neisseria gonorrhea	✓	
Chlamydia trachomatis	✓	
Trichomoniasis	✓	
Hepatitis B Virus	✓	
Group II		
Syphilis	✓	✓
Genital HSV	✓	✓
Genital HPV	✓	✓
Chancroid	✓	✓

Regarding the potential for STD risk reduction attributable to condom use, FDA concluded that the potential for condoms to help prevent STDs that are transmitted from or to the penis (table 1, group I) is greater than the potential risk reduction for STDs 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 STDs transmitted from or to the penis, a condom will provide a physical barrier that helps to prevent STD pathogens contained in penile fluid from reaching the cervico-vaginal or ano-rectal mucosa, thereby reducing the risk of transmission from males with STDs that meet these conditions. It also protects a man's urethra from STD pathogens contained in his partner's secretions. STDs 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 STDs, under its plausibility analysis, FDA concludes that while condoms are likely to provide some risk reduction, the degree of risk reduction may not be as great as that expected for group I STDs. This is because, for group II STDs, the condom provides a barrier in some, but not all, situations that may lead to transmission. Protection against group II STDs depends on the site of the sore/ulcer or infection. Condoms can only protect against tranmission when the ulcers or infections are covered or when susceptible sites are protected by the condom.

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 of STD transmission. The extent of risk reduction varies between two general groups of STDs. 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 Protection Against STDs by Other Federal Agencies

FDA also reviewed evaluations by other federal public health agencies regarding condoms and the protection 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 STDs and came to the following conclusions:

HIV/AIDS: Workshop findings reaffirmed that condoms are highly effective against HIV transmission. From review of a meta-analysis of HIV discordant couples (Ref. 8), it was noted that correct and consistent condom use decreased the risk of HIV/AIDS transmission by approximately 85 percent. Panelists noted that many of the HIV/AIDS studies they reviewed employed better study methodologies than studies of other STDs. 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 STDs.

Gonorrhea: Studies reviewed showed that correct and 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 protection 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:[1] The report stated that the scientific literature did not allow an accurate assessment

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[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*). (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**.) FDA has similarly included this STD in table 1 as a group I STD 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 STD. Neither FDA's prior labeling recommendations nor its proposed special control guidance recommend making specific claims for condom effectiveness against trichomoniasis.

of the degree of potential protection offered against these STDs 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 STDs were considered in the summary conclusions on STD 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 STDs 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 STDs, and 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. ~~With respect to condom effectiveness, the report 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."~~ 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. ~~Condoms~~ 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

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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:

> [g]iven 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.

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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."

CDC is that ~~condoms~~ condom use reduce 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). Insert C

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E. Systematic Reviews Regarding Condom Protection Against STDs

The agency also analyzed the following sources of clinical data regarding condom protection against STDs:

- 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 STDs where such reviews were available; and
- Individual clinical studies for STDs where systematic reviews were not identified.

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

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

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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."

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 protection 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 protection 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 protection 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 correct and 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 STDs, which are transmitted by exposure of the cervico-vaginal, urethral, or rectal mucosa to penile fluids or cervico-vaginal secretions.

2. Group II

Syphilis: FDA is not aware of any systematic reviews of the condom literature regarding protection 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 significant protective effect for condoms against syphilis transmission. Although data are limited, this infomation also supports the conclusion that correct and consistent condom use can reduce the risk of syphilis.

Genital Herpes: FDA is aware of one systematic review of the condom literature regarding protection 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 reivew, was a prospective study among discordant couples that found condom use during more than 25 percent of sex acts was associated with protection against HSV-2 acquisition for women but not for men (Ref. 17). More recent prospective studies showed that condom use was 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. Certain strains of genital HPV cause genital warts, while others are asymptomatic. The majority of genital HPV infections spontaneously regress and do not lead to clinical disease. Less commonly, genital HPV infection is

persistent and leads to cellular abnormalities of the cervix that may progress to cervical cancer. (Ref. 34) FDA

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). ~~A 2002~~ Insert D OMB

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 correctly and consistently, can be effective in reducing the risk of

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

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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.

transmission of group II STDs. The degree of risk reduction would be expected to be less than that for group I STDs.

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 scientific evidence that N–9-lubricated condoms provide any additional protection against pregnancy or STDs 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 STD 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 STDs. 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 STD 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 latex condoms containing N–9 in the lubricant. FDA is aware of only one study specifically examining the effect on STD 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 STDs, 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.

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 STD 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.

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 protection provided by condoms, nor undervalues overall STD risk reduction provided by condom use.

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 diseases," 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.

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 reduced protection condoms offer against transmission of certain STDs, 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 STD transmission can lead to better choices by individuals who seek to protect themselves against these infections and potentially to reduced transfer of STDs.

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 protection provided by condoms against unintended pregnancy and against various types of STDs, 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 STD 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 STD transmission, the issue of incorrect and inconsistent use (which undermines

the effectiveness of the condom in protecting against unintended pregnancy and STD 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. Although latex condoms can greatly reduce the risk of unintended pregnancy, 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 protection 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 protection 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 STDs

The other principal intended use of latex condoms is protection against the transmission of STDs. In developing the special control, FDA examined the plausibility of STD risk reduction and other scientific evidence, explained previously in section III of this document. This body of evidence indicates that as an overall matter, latex condoms are effective at reducing the risk of STD transmission, but that differences exist in the level of risk reduction provided by latex condoms with respect to two general groups of STDs, distinguished by 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 STD transmission by explaining the effectiveness of latex condoms with regard to this use. The draft guidance recommends that the labeling explain that latex condoms can greatly reduce, but not eliminate, the risk of acquiring or transmitting (catching or spreading) HIV. The guidance also recommends labeling to inform users that STDs 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 latex condoms can reduce the risk of STDs that are spread to or from the penis by direct contact with the vagina and genital fluids, such as gonorrhea and chlamydia. It further recommends labeling that indicates that some STDs, such as genital herpes and HPV, may also be transmitted by contact with infectious skin or mucosa not covered by the condom, and that condoms provide less protection against these STDs. Labeling should clarify that, even for these STDs, however, 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. OMB

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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 STD 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 STD 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 STD 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 STD prevention.

Specifically, as explained in the previous sections, based on its review of the available scientific evidence, FDA concludes that N–9 kills sperm;

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The guidance for condom labeling does not recommend including information about other ways to prevent the transmission of STDs 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 STD 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 STDs. The guidance does recommend that condom users consult health care professionals or seek additional information about STDs 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.

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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.

however, the additional pregnancy protection 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 STDs. 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 contraceptive protection 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 protection 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 STDs. 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 STDs (68 FR 2254). Addressing the lack of STD protection 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 STD 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 protection against HIV/AIDS and other STDs.

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 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, 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 $110 million. 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 protection condoms offer against transmission of certain STDs, 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 STD transmission can lead to better

choices by individuals who seek to protect themselves against these infections and potentially to reduced transfer of STDs.

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 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.

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, promulgating 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 protection provided by condoms, nor undervalues the overall STD 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.

B. Affected Entities and Scope of Effect

The proposed rule would affect the persons responsible for the labeling of latex condoms, which, in most cases, would be manufacturers of the vast majority of condoms, including repackagers. If a final rule is issued, manufacturers of condoms, including repackagers, will need to address the issues identified in the special controls guidance document. The firm need only show that its device meets the recommendations of the guidance document or in some other way provides equivalent assurances of safety and effectiveness. To meet the recommendations of the special controls guidance document, wording on the retail package, including the principal display panel, the primary condom package (individual foil), and package insert would most likely need changes to conform to the guidance document.

Agency records show that approximately 35 entities that manufacture or repackage latex condoms would be affected by this proposed rule. FDA does not track the number of different product and package combinations or stockkeeping units (SKUs) on the market. Based on data we received from industry, we estimate that currently there are between 500 and 1,000 SKUs on the market that would need labeling changes. If the products are sold with a retail package, the wording on each of these SKUs would need to be changed. Because manufacturers can often use the same individual foil and package inserts across their product lines, the number of versions of this labeling that would require changes would be less than the number of SKUs.

Based on the agency's experience with the industry and anecdotal information from manufacturer and retail Web sites, we estimate that there would be a total of 802 to 1,605 labeling changes to retail packages, individual foils, and package inserts. We assumed that 95 percent of the SKUs (475 to 950) are marketed with 3 levels of labeling (a retail package, individual foil, and package insert), and the remaining 5 percent have 2 levels (a foil and package insert). For the SKUs with three levels of labeling, we further assumed that for every three retail package redesigns there would be one foil label redesign, and for every four retail package redesigns, there would be one package insert redesign. We based these assumptions on our knowledge that a single condom type is often sold in several retail packages containing different numbers of condoms, in which case retail packages would be different for each SKU but package inserts and foil labels would be shared by multiple SKUs. The distribution of the different labeling that would need to be redesigned is listed in table 2 of this document and includes 475 to 950 retail packages, 183 to 367 foils, and 144 to 288 inserts. (Sample calculation: (500 x 0.95 / 3) + (500 x 0.05) foils and (500 x 0.95 / 4) + (500 x 0.05) inserts.)

C. Costs of Implementation

Frequent package changes or redesigns are standard business practice in the consumer healthcare products market. Manufacturers with products intended for retail sales will have established routines for product relabeling and employees with the technical expertise to implement labeling changes. The cost to relabel a product can be broken into three basic components: regulatory, graphics, and manufacturing. The regulatory component includes determining what changes are necessary, drafting the wording for the new labeling, and coordinating the review and revisions. The graphics component

includes preparing the layouts, proofs, and printing. Finally, the manufacturing component includes incorporating the new labeling into the manufacturing system, discarding old labeling inventory, and making any changes to the packaging line to accommodate the new labeling, if necessary.

The proposed rule designates a special controls guidance document that recommends changes to wording and some additional text. 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. In general, these changes should not require major changes in the design or layout of existing labeling and we believe that, in most cases, the changes could be incorporated without having to increase the dimensions of any of the labeling.

The itemized cost estimates used in this analysis were derived from a study performed for FDA by Eastern Research Group, Inc. (ERG), an economic consulting firm, to estimate the economic impact of the 1999 Over-the-Counter Human Drug Labeling Requirements final rule (64 FR 13254, March 17, 1999).[3] Because the packaging requirements for condoms are similar to those of many OTC drugs, we believe the cost to redesign and print the labeling for OTC drugs is an appropriate proxy for the estimated costs to redesign and print condom labeling. For this analysis, cost estimates were adjusted to account for inflation

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[3] Eastern Research Group, Inc., Cost Impacts of the Over-the-Counter Pharmaceutical Labeling Rule (March 1999). Contract number 223–94–8031, Docket No. 96N–0420, OTC Volume 28 FR, Division of Dockets Management.

[4] The ERG cost estimates were based on estimates made in 1998. The annual PPI for finished consumer goods rose by 9.6 percent between 1998 and 2003 (from 130.7 to 143.3) *http://www.cdc.gov/nchstp/dstd/Stats_trends/trends2000.pdf*, extracted July 7, 2004. Wage estimates are from the Bureau of Labor Statistics, May 2003 National Industry-Specific Occupational Employment and Wage Estimates, NAICS 339100—Medical Equipment and Supplies Manufacturing, (*http://stats.bls.gov/oes/2003/may/naics4_339100.htm*), extracted July 7, 2004. (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**.)

using the producer price index (PPI) for finished consumer goods, and current wage rates specific to the medical device industry were substituted for the wages used by ERG in the original OTC drug labeling impact study.[4] We request specific comment on the values and methodology used to estimate the costs in the following paragraphs.

We estimate that the regulatory component of each labeling redesign would require between 8 to 16 hours per SKU. Using a wage rate of $43.69,[5] the incremental cost of the one-time regulatory component cost to redesign would be $350 to $700 per labeling redesign (8 (to 16) hours x $43.69/hour). The one-time cost of the graphic component was estimated to be $550 per labeling redesign.[6] The one-time cost of the manufacturing component, which included the incorporation of the new labeling into the manufacturing system and discarding the remaining inventory of the old labeling, was estimated to require between 3 and 5 hours per label. Using the wage rate of $19.25 for a production employee,[7] this cost would range from about $58 to $96 per label (3 (to 5) hours x 19.25/hour). The value of the old labeling inventory would vary greatly depending on the type and complexity of the labeling, the average sales per SKU, and the length of the implementation period granted. Based

[5] Mean hourly wage for a compliance officer, SOC 13–1041, in NAICS 339100 is $31.21, which was increased by 40 percent to account for employee benefits and equals $43.69 (*http://stats.bls.gov/oes/2003/may/naics4_339100.htm*). (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**.)

[6] ERG estimated the cost at $500 per redesign. Adjusting for inflation, the cost would be $548 ($500 x 1.096) and was rounded to $550. (See footnotes 3 and 4.)

[7] Mean hourly wage for the average production worker is $13.75, SOC 51–0000, in NAICS 339100, which was increased by 40 percent to account for employee benefits and equals $19.25, (*http://stats.bls.gov/oes/2003/may/naics4_339100.htm*). (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**.)

[8] ERG estimated that when there was no implementation period granted, the average inventory loss for OTC drug container labels ranged from $1,500 to $6,000 for small to medium sized OTC drug firms. With a 12-month implementation period that loss decreased by 3/4. The value of carton inventory was estimated to be about 3 times greater than container labels. Allowing for inflation (see footnote 4) the 0-month estimates are approximately $1,650 and $6,575, respectively (e.g., $1,500 x 1.096).

on the ERG study, with a 12-month implementation period we estimate that the one-time inventory loss would range from $410 to $1,650 per foil or package insert and from $1,250 to $4,950 per carton.[8]

FDA believes that by providing a 12-month implementation period, manufacturers would have enough time to sell their existing product inventory and have enough newly labeled inventory on hand to meet demand without a disruption in supply. The total estimated incremental one-time costs to the industry for each component of a labeling redesign was calculated by multiplying the cost per label by the number of labels affected and are presented in table 3 of this document. Because of the uncertainty of the estimates, only the lowest and highest estimated costs are presented rather than reporting the intermediate values that would be obtained using other pairings of high with low values in the ranges estimated. The total one-time incremental cost to the industry was estimated to be between $1.5 and $7.9 million.

The cost to individual firms to comply with this proposed rule would vary greatly depending on the number of products they produced, how the products were packaged, and the sales volume. As stated earlier in this document, frequent labeling changes are a cost of doing business in the consumer healthcare products market and firms would have the skills necessary to comply with this proposed rule. Because the steps followed for a firm-initiated change are the same as for regulatory change, the labeling recommendations could be incorporated at the time a firm is implementing a firm-initiated labeling change for little additional cost, and thus, if this rule became final, the economic impact of this proposed rule would be mitigated by the number of firm-initiated labeling changes made during the implementation period. In addition, because most labeling equipment can handle different labeling sizes

and types and because there are a large number of companies available that can provide contract labeling services, we do not believe that any manufacturer would incur major costs such as the need to purchase new labeling or packaging equipment as a result of this rule.

There are about 12 domestic entities that manufacture or repackage condoms. The Small Business Administration (SBA) has established criteria to identify small entities in given industries using the North American Industry Classification System Code (NAICS). The NAICS for manufacturing latex condoms is 326299 (All Other Rubber Product Manufacturing). Firms in this industry are considered small if they have fewer than 500 employees. Ten of the 12 domestic entities affected by this proposed rule are small as defined by SBA.

The size of a firm alone, however, would not be a determinant factor on the economic impact of this proposed rule. The relative impact per SKU would be less for products with a high volume of sales because the one-time costs are spread over a larger number of units. The cost of actual replacement labeling should also be lower for products with high volume sales. Our experience with the device industry in general, as well as with the latex condom industry in particular, indicates that a small-sized company is just as likely as a large-sized one to have products with high sales volume and to have the same or a greater number of SKUs.

The agency considered three alternatives before choosing to issue this proposed rule. They included the options of issuing a guidance that would not be designated as a special control, issuing a labeling regulation mandating exact wording, and the option chosen, issuing a proposed rule that designates a special controls guidance document with labeling recommendations. We

rejected the issuance of a guidance document alone because it would not provide enough assurance that consumers would receive the information regarding the issues of latex condoms with or without N–9 and thus would not provide sufficient assurance of safety and effectiveness. We rejected the option of a labeling rule with specified wording because it would not provide manufacturers with any flexibility in addressing these issues today and would not, in the future, permit flexibility in addressing new scientific information relevant to these issues.

We chose to issue a proposed rule that designates a special controls guidance document because it requires that the device either meet the recommendations or in some other way provide equivalent measures of safety and effectiveness. This approach protects the public health by ensuring that manufacturers address the issues related to latex condoms with or without N–9, while, at the same time, it affords manufacturers some flexibility in implementing the mitigation measures outlined in the special controls labeling guidance document.

We also considered different implementation periods before proposing a 12-month implementation period. The agency believes that consumers should have the most up-to-date information and that this labeling will lead to better understanding of the health risks and benefits of the product. We believe that allowing for a longer implementation period unnecessarily postpones consumer's access to the information. However, an implementation period shorter than 12 months would increase the costs imposed by the rule, and it would be difficult for those manufacturers producing many SKUs to accomplish the task within a shorter time frame because of the large number of label designs that would need to be changed. We have learned through

industry and trade association comments submitted in response to proposed OTC drug rules that the OTC drug industry can accommodate a 12-month implementation period without undue economic hardship and believe that the condom industry can accommodate a similar implementation period without undue economic effects on the industry or harmful effects on the costs or supply of condoms.

As discussed earlier in this document, while we believe the cost to revise latex condom labeling is small, we lack sufficient specific information on the costs and characterization of the industry to certify that this rule would not have a significant economic impact on a substantial number of small entities. Thus, while FDA does not believe that this proposal will have a significant effect on a substantial number of small entities, we recognize the uncertainty of our estimates. We request specific comments regarding the assumptions and methodology used in this analysis. FDA intends to consider all comments and data received and will reassess the economic impact of this proposed rule in the preamble to the final rule.

TABLE 2.—ESTIMATED NUMBER OF LABEL DESIGNS THAT MAY NEED TO BE MODIFIED

Component	Low-End Estimate	High-End Estimate
Cartons	475	950
Foils	183	367
Inserts	144	288
Total	802	1,605

TABLE 3.—ESTIMATED RANGE OF COMPLIANCE COSTS BY FUNCTION

Component	Range	Hours	Wage/hour	Cost/label	Number of labels	Total	
						Low	High
Regulatory	low	8	$43.69		802	$280,315	
	high	16			1,605		$1,121,952
Graphic	low			$550	802	441,100	
	high				1,605		882,750
Manufacturing	low	3	$19.25		802	46,317	
	high	5			1,605		154,480
Inventory	foil and insert						

TABLE 3.—ESTIMATED RANGE OF COMPLIANCE COSTS BY FUNCTION—Continued

Component	Range	Hours	Wage/hour	Cost/label	Number of labels	Total	
						Low	High
	low				$410	327	134,070
	high			$1,650	655		1,080,750
	carton						
	low			$1,250	475	593,750	
	high			$4,950	950		4,702,500
Total Cost						$1,495,552	$7,942,432

VII. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520) is not required.

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~~FDA also tentatively concludes that the special controls guidance~~ document identified by this rule contains no new information collection provisions that are subject to review and clearance by OMB under the PRA. The labeling recommendations in the draft guidance, as well as the latex allergy caution required by § 801.437 and referenced in the guidance, do not constitute "collections of information" under the PRA. Rather, they are "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)). The expiration dating requirements established by § 801.435 and referenced in the ~~guidance have been approved by OMB under OMB control number 0910–0485~~.

VIII. Specific Request for Comments

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

OMB

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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

INSERT #1 for p. 53

FDA also tentatively concludes that the special controls guidance document identified by this rule contains new information collection provisions that are subject to review and clearance by OMB under the PRA. Elsewhere in this issue of the Federal Register, FDA is publishing a notice announcing the availability of the draft guidance document entitled "Class II Special Controls Guidance Document: Labeling for Male Condoms Made of Natural Rubber Latex"; the notice contains an analysis of the paperwork burden for the draft guidance.

INSERT F, page 53:

As discussed in more detail in section IV of this proposed rule, 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.

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.

In addition, 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 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**.)

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Insert G

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

INSERT G, page 58, additional references:

31. Kjaer SK, Svare EI, Worm AM, Walboomers JM, Meijer CJ, van den Brule AJ. 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.

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34. 11th Report on Carcinogens, National Toxicology Program (Jan. 31, 2005) (FactSheet).

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: _____

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[FR Doc. 05–????? Filed ??–??–05; 8:45 am]

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