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To: Colin M Pollard & John Farnham
From: Gary L Rose, MD, President and CEO
Cc: Andrew C von Eschenbach, MD, Acting Commissioner
Date: February 9, 2006

Re: Food and Drug Administration
Docket No. (2004N-0556) RIN 0910-AF21
&
Food and Drug Administration
Docket No. 2004D-0555

The Medical Institute for Sexual Health (MI) is a nonprofit medical, educational, and policy-shaping organization headquartered in Austin, Texas. Since 1992 MI has promoted sexual health by identifying, evaluating, and communicating credible scientific data in a variety of formats. This letter contains our comments on Food and Drug Administration, Obstetrical and gynecological devices: Designation of special control for condom and condom with spermicidal lubricant, 70 Fed Reg 69102 (2005) (proposed rule amending 21 CFR § 884) and on Food and Drug Administration *Class II special controls guidance document: Labeling for male condoms made of natural rubber latex. Draft guidance for industry and FDA staff*. Rockville, MD: Food and Drug Administration, Center for Devices and Radiological Health, November 14, 2005. Available at: <http://www.fda.gov/cdrh/comp/guidance/1548.html>.

Enclosed please find 1) a marked up version of the proposed rules, 2) a marked up version of the draft guidance, 3) a report titled *Condom label comprehension study*, 4) a white paper on *Nonoxynol-9 & STDs, Including HIV*, and 5) a CD with the marked up proposed FDA rules and guidance.

The proposed rules include 1) terminology and citations that were outdated prior to publication, 2) slight misstatements, and 3) significant overstatements and 4) omissions and 5) use of easily misunderstood qualitative risk reduction statements when quantitative statements would better convey known risks. The labeling recommendations for the principal display panel, the package insert, and the primary condom package in the *Draft Guidance for Industry and FDA Staff -- Class II Special Controls Guidance Document: Labeling for Male Condoms Made of Natural Rubber Latex* are 1) written in language that is far too complex for the average user and 2) convey some messages that are medically inaccurate. In some instances, the recommended language overstates benefits; in others, it minimizes or omits significant risks.

Some of the terminology and citations in the proposed rules was outdated prior to publication and the phrase "correct and consistent use" appears throughout the document. A sexually transmitted infection (STI) is the invasion and multiplication of a disease-causing

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microorganism that is usually transmitted by sexual activity. In contrast, a sexually transmitted disease (STD) is pathology (damage) that results from an STI. Thus, STI is a far more inclusive term and applies equally to STDs and asymptomatic infections. Because most condom use studies evaluate infection rather than disease as an outcome, FDA statements pertaining to condom use should generally use STI rather than STD. Reference 12 is an abstract that was presented at a conference – a paper by the same author has now been published on this body of work.¹ Peer-reviewed references are preferable. Although “correct and consistent use” appears 15 times, almost all condom use studies with an STI outcome actually only measured **consistent** condom use. The word “correct” should be struck from the document when it occurs in this context.

The benefits of condom use are often overstated in the proposed rules and significant risks are not mentioned. Conclusions based on *in vitro* studies are generalized to *in vivo* situations with no caveats. Some particularly egregious examples of overstatement appear in the following two sentences from section III. Review of the Medical Accuracy of Condom Labeling, C. Plausibility for STD Risk Reduction Attributable to Condoms.

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** [emphasis added] mucosa...It also **protects** [emphasis added] a man’s urethra from STD pathogens contained in his partner’s secretions. STDs that meet these conditions include HIV, gonorrhea, chlamydia, trichomoniasis, [h]epatitis B...

First, there are **no data** suggesting statistically significant risk reduction associated with condom use for anal intercourse for HIV. Second, the use of the word “protect” is inappropriate. According to Webster’s New Universal Unabridged Dictionary, the primary meaning of the word protect is “to cover or shield from danger or injury; to defend; to guard; to preserve in safety.” It is conceivable that some members of the general public might construe the 85% risk reduction for HIV that is afforded by consistent use as falling within the commonly understood meaning of the word “protect.” Few, however, would feel “protected” if they knew that consistent condom use decreased their risk by for gonorrhea or chlamydia by only ~ 50% and for trichomoniasis by an unknown amount.

The word prevention is used 60 times in the proposed rules; the word protection, 45 times; and prevent, 15 times. Such statements about risk reduction are easily misunderstood; quantitative statements would more accurately convey known risks.

The risks associated with inconsistent condom are not specifically mentioned. For instance, in some studies, inconsistent use is associated with increased STI risk.² And, with the exception of

¹ Warner L, Stone KM, Macaluso Met al. Condom use and risk of gonorrhea and Chlamydia: a systematic review of design and measurement factors assessed in epidemiologic studies. *Sex Transm Dis.* 2006 January;33(1):36-51.

² Ahmed S, Lutalo T, Wawer M et al. HIV incidence and sexually transmitted disease prevalence associated with condom use: a population study in Rakai, Uganda. *AIDS.* 2001 November 9;15(16):2171-2179.

herpes³ and HIV,⁴ inconsistent condom use provides no risk reduction for STIs. No mention is made of the fact that there are no data to suggest consistent condom use significantly decreases HIV risk for anal intercourse.

The labeling recommendations for the principal display panel, the package insert, and the primary condom package in the *Draft Guidance for Industry and FDA Staff – Class II Special Controls Guidance Document: Labeling for Male Condoms Made of Natural Rubber Latex* are 1) written in language that alternates complexity with imprecision and 2) convey some messages that are medically inaccurate. In some instances, the recommended language exaggerates benefits; in others, it minimizes or omits significant risks. The guidance for industry and FDA staff is inadequately referenced.

To assess how the general public perceives condom label information, we interviewed 247, 18- to 30-year-old males and females in public venues in the Austin area in January 2006 to assess their comprehension of the proposed condom labels (see enclosed report). Nearly 80% of our respondents had attended college (median education 15 years). 45% had **never** read any of the information on the outside of a condom box; 50% had **never** read any of the information in the package insert; and 55% checked the expiration date **never, rarely, or sometimes**. One-fourth of the respondents were unable to name even one “genital fluid.” Of those who responded to the open-ended “List all the genital fluids that you know,” about 60% mentioned synonyms/colloquial terms for semen and 20% mentioned synonyms/colloquial terms for vaginal fluids. Other fluids mentioned included blood, urine, lubrication, secretions, pus, saliva, and sweat.

After reading some of the proposed FDA labeling recommendations, respondents were asked to answer questions pertaining to these statements. They were asked how much risk reduction they would expect for a variety of STIs (and pregnancy) if they used perfect condom use. The median amount of risk reduction perceived by respondents was 90% for HIV and 85% for pregnancy. Respondents grossly overestimated the amount of risk reduction provided by consistent condom use for chlamydia (85%) and herpes (70%). Spontaneous comments offered by respondents to data collection staff included statements that the proposed label language is “retarded” and “hilarious.” Respondents indicated that the use of comparative terms such as “greatly reduce,” “reduce,” and “less protection” was not particularly helpful. In general, survey respondents preferred statements that are easy to understand and provide detailed and specific information.

Overall, the condom label language recommended for the principal display panel, the package insert, and the primary condom package is far too complex for the average user. A majority of US adults read at the 8th – 9th grade level.⁵ And many experts recommend that, for optimal

³ Wald A, Langenberg AG, Krantz E et al. The relationship between condom use and herpes simplex virus acquisition. *Ann Intern Med*. 2005 November 15;143(10):707-713.

⁴ Davis KR, Weller SC. The effectiveness of condoms in reducing heterosexual transmission of HIV. *Fam Plann Perspect*. 1999 November;31(6):272-279.

⁵ Kirsch I, Jungeblut A, Jenkins L, et al. *Adult literacy in America: a first look at the findings of the national adult literacy survey*. Washington, D.C.: National Center for Education Statistics, U.S. Department of Education; 1993.

comprehension and compliance, materials be written at or below a 6th grade level.⁶ The reading level of written materials can be easily assessed by using a feature of MS Word – the Flesch – Kincaid grade level index.

As part of our study on condom label comprehension in 18- to 30-year-olds, we were able to determine the readability of the nine proposed FDA condom label statements included in our survey. This took less than 10 minutes. Six of nine read at a 12th grade level; one, at grade 11.7; one, at grade 9.2; and one, at grade 8.7. Our readability findings are consistent with previous studies. In 1988 Richwald et al found that a majority of condom instructions were written at a 12th grade reading level, and none were written at less than a 10th grade level.⁷ As the federal agency tasked with protecting the public health by assuring the safety, efficacy, and security of medical devices, it is incumbent upon the FDA to ensure that condom labels are written in manner that protects public health. Anything less merely protects the manufacturers.

The labeling recommendations also convey some messages that simply lack utility. One example of this is the following statement.

Important information: There are many types of sexually transmitted diseases (STDs) and different ways of catching or spreading infection. A latex condom can reduce the risk of STD transmission to or from the penis. However, some STDs can also be spread by other types of sexual contact...

This statement would be far more useful if it read

Important information: There are many types of sexually transmitted infections (STIs). STIs can be spread through oral, vaginal, or anal sex, as well as through mutual masturbation. Correct and consistent use of a male latex condom during vaginal sex can partially reduce the risk of spreading many common STIs.

In some instances, the recommended language omits significant issues related to risk. The following statement does both.

When used correctly every time you have sex, latex condoms greatly reduce, but do not eliminate, the risk of catching or spreading HIV, the virus that causes AIDS.

The phrase “every time you have sex,” does not make a distinction between penile-vaginal sex, anal intercourse, and oral sex. While true for penile-vaginal sex, there are no statistically significant data to support this assertion for either anal intercourse or oral sex.

In other instances, the recommended language omits important facts. The directions for use under section G. General labeling requirements do not include any information on how to dispose of a condom. We recommend using the information on condom disposal provided in the FDA Condom Fact Sheet (www.fda.gov/oashi/aids/condom.html).

Wrap the used condom in a tissue and throw it in the trash where others won't handle it. Because condoms may cause problems in sewers, don't flush them down the toilet. Afterwards, wash your hands with soap and water.

⁶ Safeer RS, Keenan J. Health literacy: the gap between physicians and patients. *Am Fam Physician*. 2005 August 1;72(3):463-468.

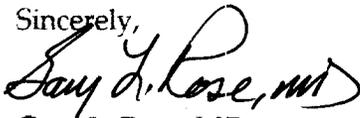
⁷ Richwald GA, Wamsley MA, Coulson AH, Morisky DE. Are condom instructions readable? Results of a readability study. *Public Health Rep*. 1988 July;103(4):355-359.

With frequent use, nonoxynol-9 appears to increase rather than decrease risk for HIV infection. Therefore, condoms with N-9 should not be used at all, for contraceptive or other purposes, by **anyone** who is at **any** risk for HIV infection. This would include everyone outside of a long-term monogamous relationship with an uninfected partner. When asked which of 5 possible N-9 warnings they preferred, our survey respondents chose two of five possible statements: one said "The nonolynol-9 (N-9) lubricant on this condom does not protect against HIV/AIDS or other sexually transmitted diseases," and the other that said "This condom has nonoxynol-9 (N-9). N-9 can increase the risk of HIV transmission. Do not use this condom if either you or your partner could possibly have HIV. Do not ever use for anal sex." The first statement is one of those proposed by the FDA and has a 12th grade reading level. The second was written by MI staff and has a 6th grade reading level. This first statement discusses the absence of benefit, and the second, the presence of risk. We think the duty to warn is more important.

In summary, it is important for the FDA to propose statements and for manufacturers to adopt statements that are easily readable by the general public and that accurately convey the current the current state of medical knowledge - neither overstating nor understating the efficacy of condoms for STI risk reduction. The public needs to be aware that consistent use is required to get risk reduction for most STIs, and that condom use for everything but penile-vaginal sex is "off-label." Proposed statements must be field tested in people from the target population.

Thank you for your attention to this critical public health matter. If you have any questions, please call me at 512-328-6268.

Sincerely,



Gary L. Rose, MD
President/CEO

The Medical Institute for Sexual Health