

I offer the following comments regarding the Food and Drug Administration's (FDA's) "Draft Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Labeling for Male Condoms Made of Natural Rubber Latex" (URL: <http://www.fda.gov/cdrh/comp/guidance/1548.pdf>). These comments cross-reference FDA's accompanying review of the scientific literature on condom effectiveness provided in the document "Obstetrical and Gynecological Devices; Designation of Special Control for Condom and Condom With Spermicidal Lubricant" (URL: <http://www.fda.gov/OHRMS/DOCKETS/98fr/05-22611.htm>).

To a large extent, the proposed label successfully distills a large and complex body of scientific literature regarding condom effectiveness and presents this information in an accessible and concise manner befitting a user-oriented package insert. Likewise, the accompanying literature review draws reasonable conclusions through a synthesis of laboratory and epidemiologic data, combined with an understanding of the various transmission modes for sexually transmitted infections (STIs) and the attributes of STI organisms. There are several areas, however, where these documents should be improved.

1. Evidence supports a stronger statement regarding condoms' efficacy for STI prevention, particularly those STIs transmitted by contact with genital fluids.
2. Every effort should be made to distinguish the attributes of the device (the male latex condom) from the behavior of condom users in parsing effectiveness. The package insert should emphasize the attributes of the device and the protective benefits users can anticipate if they use it properly.
3. The literature review should give greater attention to the limitations of epidemiologic studies in assessing condom effectiveness, which often lead to underestimates of effectiveness.
4. The report from the 2000 NIH workshop on condom effectiveness is outdated and derived from a scientifically flawed process. It should not be used as the primary reference in the Draft Guidance.

My rationale for these recommendations is offered below.

1. Evidence supports a stronger statement regarding condoms' efficacy for STI prevention, particularly those STIs transmitted by contact with genital fluids. The

literature review and draft guidance use the terminology “risk reduction” in describing the protective effect of condoms against STIs. Variations in this terminology include statements that condoms can “reduce the risk” or “greatly reduce, but do not eliminate, the risk” of STI transmission. For example, FDA recommends that “Labeling should indicate that latex condoms can **reduce the risk** (emphasis added) of STDs transmitted to or from the penis by contact with the vagina or genital fluids, such as chlamydia and gonorrhea.” This is an incomplete statement. If the condom contains penile secretions or prevents contact of the male urethra with vaginal secretions, as the FDA states is possible with correct use, STI transmission cannot occur. Thus, it is both plausible and possible for condoms to prevent, not merely “reduce the risk” of, transmission some STIs with correct use. The labeling should acknowledge this possibility. The draft label is correct in noting that less protection is afforded by incorrect use. Additionally, terminology such as “greatly reduce, but not eliminate” is needlessly redundant and unnecessarily raises the reading and health literacy levels required by readers and condom users. This could negatively impinge on condom use—surely exactly the opposite of intended effect.

2. Every effort should be made to distinguish the attributes of the device (the male latex condom) from the behavior of condom users in assessing effectiveness. The package insert should emphasize the attributes of the device and the protective benefits users can anticipate if used properly. One of the greatest challenges in measuring the protective effect of condoms is distinguishing the attributes of the device from the behavior of condom users. Both the public and scientific debates regarding condom effectiveness have not sufficiently made this distinction, but it is critical in developing a label that accurately informs prospective condom users. The label should allow the individual condom user to correctly answer the following questions:

- What do I need to know in order to use this device properly?
- If I use this device properly, what degree of protection from STIs or unintended pregnancy can I expect?
- If I use this device incorrectly, what loss of protection can I expect?

In contrast, managers of programs aimed at preventing STIs or unintended pregnancy require information on the patterns of behavior associated with condom use, including the type and frequency of user mistakes and non-use (e.g., incorrect use and inconsistent use, respectively). This information is needed to anticipate the population-

level public health benefit of condom promotion programs and to guide efforts to promote correct and consistent condom use. The condom label, as a document geared to informing individual condom users, should focus on the interests and concerns of those users--not on the interests and concerns of program managers or policy makers. While the proposed label and the accompanying background document strive to maintain such a focus, the inclusion of information on effectiveness under “typical use” situations, which includes in unknown mix of correct, incorrect and non-use, risks losing this focus. Fundamentally, the “typical use” information incorrectly conflates use error, which evidence shows is common but reducible with information and education, and true product failure, which laboratory studies indicate is rare and probably not reducible into a single “condom failure rate.” Thus, “typical use” measures of “condom failure” are misleading and could result in an inaccurate and risky degradation in confidence in condom effectiveness and a corresponding reduction in safe condom use—surely exactly the opposite of the federal government’s intention.

3. The literature review should give greater attention to the limitations of epidemiologic studies in assessing condom effectiveness, which often lead to underestimates of effectiveness. While the FDA has provided an updated literature review, the literature review does not give sufficient attention to published reports that assess the impact of common biases in epidemiologic studies of condom effectiveness. In general, the most critical of these limitations tend to bias studies in ways that yield underestimates of protection. This point is crucial to the quality of the literature review. If epidemiologic studies are taken at face value without sufficient consideration of their strengths and limitations, policy will be misinformed and population health may suffer as a consequence. Examples of the ways that such studies can be biased include the following:

- The measurement of condom use relies primarily on information reported by research participants. Because condom use is promoted as an STI prevention strategy, participants in research studies may be tempted to over-estimate their use of condoms, reporting that they used condoms correctly and consistently when they did not. The tendency to over-report what may be perceived as a desirable behavior is a well-recognized limitation of behavioral research. If only a few people report that they used condoms when they did not and contracted an

STI as a result, such epidemiologic “misclassification” (e.g., misinformation) leads to an underestimation of condom effectiveness.

- Dr. Lee Warner of CDC is a leading expert in the methodology of condom research. Dr. Warner has observed that few studies of condom effectiveness report whether participants used condoms correctly (see: Warner L, et al. Condom use and risk of gonorrhea and chlamydia: a systematic review of design and measurement factors assessed in epidemiologic studies. *Sexually Transmitted Diseases*, 2006;33(1):36–51). The person who reports using a condom but in reality used the condom incorrectly (e.g., did not put on the condom until after initiating sexual contact or used the condom with a petroleum-based lubricant that could weaken the latex) may contract or transmit an STI as the result of this incorrect use yet still be classified as a condom user. In a study of condom effectiveness, this would be counted as an instance of “failure” of the condom to protect against an STI, when in fact it represents a failure of the user to use the condom properly.
- Dr. Warner has also observed that failure to account for differences in STI-associated risks between condom users and non-users, such as differences in their exposure to infected sex partners, may also lead to underestimations of condom effectiveness (see: Warner L, et al. Application of the case-crossover design to reduce unmeasured confounding in studies of condom effectiveness. *American Journal of Epidemiology*, 2005;161(8):765-73; and see: Warner L, et al. Condom effectiveness for reducing transmission of gonorrhea and chlamydia: the importance of assessing partner infection status. *American Journal of Epidemiology*, 2004;159(3):242-51).

In summary, the methodologic limitations of epidemiologic studies of condom use and STI and pregnancy prevention will generally result in under-estimating condom effectiveness (the epidemiologic terminology for this effect is “bias towards the null”). The literature review does not adequately discuss these limitations, and the draft guidelines and proposed label do not adequately reflect the consequences of these limitations. The net result, again, could have detrimental effects on condom use—undoubtedly not the federal government’s desired outcome.

4. The report from the 2000 NIH workshop on condom effectiveness is outdated and represents a scientifically flawed process; thus, it should not be used as the primary

reference in the Draft Guidance. The primary reference cited in the “Draft Guidance” (Reference #1) is the report from the “NIH/CDC/FDA workshop on condom effectiveness (held June 2000, summary available June 2001),” and this document is used as the starting point for the literature review in the accompanying “Obstetrical and Gynecological Devices; Designation of Special Control for Condom and Condom With Spermicidal Lubricant.” Although citing the workshop report is probably unavoidable given the attention it has received, I recommend that it not serve as the scientific foundation for these FDA documents. The NIH workshop report is outdated, and a more recent review is available (Holmes KK, Levine R, Weaver M. Effectiveness of condoms in preventing sexually transmitted infections. *Bulletin of the World Health Organization*. 2004;82(6):454-461, URL: <http://www.who.int/bulletin/volumes/82/6/454.pdf>). The newer article (published in a peer-reviewed journal) is also more credible because the report from the June 2000 government workshop is the result of a scientifically flawed process, beginning with the selection of the members of the expert panel and continuing through to the preparation the final report. I make this statement based on my role as a member of the steering committee that advised NIH in planning the workshop and as a member of the larger panel that reviewed the data presented at the workshop and assisted NIH in drafting the report (during a period when I served as the Associate Director for Science of CDC’s National Center for HIV, STD, and TB Prevention). Specifically, my concerns about the scientific credibility of both the process and the product of the workshop are:

- Criteria for membership on the expert panel were not exclusively determined by the scientific steering committee, and the steering committee did not have the authority to approve or disapprove the full list of proposed panelists. One consequence is that the panel included a mix of highly qualified scientists and some members with limited credentials to evaluate scientific evidence (as measured by their having published few or no articles describing original investigations in peer-reviewed scientific journals). These members’ lack of expertise impinged on the scientific quality of both the deliberations and the final report. As just one example, at a very late stage in the report’s preparation, one panel member recommended inserting wording that demonstrated a strategic and fundamental misunderstanding of the epidemiologic data describing observed associations between the use or non-use of condoms and the occurrence or non-occurrence of STIs (the so-called “2-by-2 table,” which is an elementary and standard format for presenting and describing epidemiologic

- data). If the workshop had been designed as a nonscientific meeting to seek outside opinion on the U.S. government's policy regarding condom promotion, these gaps in scientific expertise would be expected and acceptable. But this purported to be a rigorous scientific examination of the evidence. By that more technical standard, it failed.
- My impression is that some panel members brought to the process an anti-condom bias and sought to position the report accordingly. NIH sought to avoid the problematic possibility of a minority report and worked to find compromise language on issues of sharp disagreement among panelists. Thus, a small group of panel members was successful in leveraging its position as a minority within the panel to influence the report's wording. As a result, the report is peppered with language that shades the interpretation of data to suit the perspective of these panelists. This concern was affirmed when, shortly after NIH released the workshop report, one panel member joined a public call for the resignation of the Director of CDC, because of CDC's inclusion of condom promotion as part of its STI and HIV prevention programs (see: American Family Association Online. *CDC Director Dr. Jeffrey Koplan Should Be Replaced*. July 30, 2001. Available at URL: <http://www.afa.net/activism/aa073001.asp>).
 - The process of participant review and approval of the document was unorthodox. When NIH disseminated the report by e-mail to panelists for their final sign-off before posting the report on the Internet, the e-mail message included a statement that any panelist who did not respond would be counted as approving the draft. The final report provided no accounting of the names or number of panelists who provided a positive approval versus those who did not respond to this message. In contrast, it is standard practice among peer-reviewed scientific journals to require that each co-author provide written approval of the text. When the panel considered submitting the report to a peer-reviewed journal, multiple government scientists on the panel refused to be listed as coauthors. As a result, submission never occurred, and thus the document was not objectively assessed for scientific rigor and accuracy through a peer-reviewed process.
 - Additionally, it is uncertain whether the report actually received formal scientific clearance from all four government agencies involved. CDC, FDA, and USAID co-sponsored the workshop with NIH, but responsibility for the report rested with NIH, as clearly stated on the report's cover page: "This summary report was

prepared by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services.” The title of the report, as posted on the NIH web page, does not attribute it to the agencies (“Workshop Summary: Scientific Evidence on Condom Effectiveness for Sexually Transmitted Disease (STD) Prevention”). It is noteworthy that no agency logos appear on the document. Official documents are imprinted, to demonstrate agency approval.