COMMENTS: **April 9, 2003.**

TO: **THE FOOD AND DRUG ADMINISTRATION**
21 CFR Part 201

RE: **DOCKET NUMBER (80N-0280)**
Over-the-Counter Vaginal Contraceptive Drug Products Containing Nonoxynol 9: Required Labeling.

FROM: **HOWARD MIRSKY, PHARM. B**
EDITOR, STD SPOTLIGHT
CITIZENS ALLIANCE FOR VD AWARENESS (CAVDA)
800 W. CENTRAL ROAD, SUITE 128,
MOUNT PROSPECT, IL 60056.
Phone: 847-398-3378 --- FAX: 847-398-7309
e-mail: cavdarx@ earthlink.net

I. Prefatory Statement

Communicable disease control is more than prevention, treatment and cure. It also involves a fragile relationship and interface among private industry, public perception, and the baggage that the health consumer, the health professional and the public health service bring with them. When one or more of these factors are out of focus, they must be refocused or corrected or we risk losing the focal point of the process, namely the safety of the patient.

An article in the March 21, 2003, issue of Science directly addresses this problem:

> "There is still plenty of room to improve international efforts to track and treat emerging and existing infectious diseases, says a sobering new report from the Institute of Medicine (IOM). Its conclusions, released this week, echo those reached 11 years ago in a similar study.
>
> "To improve public health, the 18-member IOM panel, co-chaired by Joshua Lederberg of Rockefeller University in New York City, calls for an array of changes, including accelerated vaccine and antimicrobial drug development....**and greater cooperation among governments, academia, and corporations...."**

In the case before us, we are talking about life, death, and health issues. In this rule proposal, the bottom line is that the consumer must be made aware of the dangers inherent in using these products more than once a day, and how to further protect themselves and their partner by communicating sensitive sexuality information. Our task is to determine how that goal is best achieved and if the Food and Drug Administration's rule proposal helps or hinders that case.

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II. Opening Statement

A. Considering the controversial nature of the subject, the Food and Drug Administration should be commended for taking the lead in presenting this issue to the drug manufacturers, health professionals and the public-at-large for their comments.

B. While this proposed rule was lengthy in seeking to communicate complex, scientific information to audiences consisting of highly trained health professionals and lay persons, the FDA should be applauded for researching, compiling and arranging all the necessary documentation in a logical sequence.

In addition, the language used, while necessarily complex, did communicate in understandable terms and well-defined jargon, the essential and definitive parameters of the scientific documentation, by liberally using definitions, which of course added to the reader's understanding.

C. However, the conclusions reached by the FDA in expecting caution labels to prevent a potentially deadly and/or a health problem for the female consumer, due to the documented problems caused by nonoxynol 9 (N-9) in vaginal creams, aerosol sprays, sponges, and films, while appearing to be logical, lacked some of the understanding both of what exactly transpires, a) in the market place where all of these products are displayed and sold over-the-counter (OTC), and b) in what can and does happen where the sexual act actually occurs from the bedroom to the back seat of a car.

D. It is obvious that the FDA believes that the consumer needs to be informed about these products with nonoxynol 9. But how can they be, if the products continue to be available OTC without professional consultation from a physician or a pharmacist? The FDA is assuming that the new package caution labels will accomplish that task. I absolutely disagree with that premise in the strongest terms.

E. I was reminded recently about the physicians Hippocratic Oath whose main theme is "Do No Harm." How does relabeling these potentially deadly or debilitating OTC products accomplish that? It's a lot like re-doing a basement wall that has mold. If the wall is painted over with enough coats of paint, the wall may appear to be clean---but the underlying mold problem remains. So it is with a newly relabeled OTC vaginal contraceptive with nonoxynol 9. With label warnings which may not either be seen, read, or understood and without consultation provided by a competent health professional, little will have changed---thus leaving the products in an OTC status and exacerbating the current problems.

F. A frightening fact overrides this discussion: The Centers for Disease Control and Prevention (CDC) recently announced that there are approximately 900,000 people in the United States carrying the AIDS virus. They also announced that approximately 280,000 of these people are unaware that they are HIV positive. This is a frightening reality when dealing with this nonoxynol 9 issue, because it increases the possibility of spreading HIV and other STDs to an ever increasing number of potential female contacts who may still be unaware of the dangers that nonoxynol 9 or the deadly consequences their HIV positive partner presents.

G. If the numerous devastating health dangers which could occur as a result of using these products with nonoxynol-9 in the manner described in the monograph, were caused by a similar or dissimilar over-the-counter drug, I would assume that drug would be **WITHDRAWN FROM THE MARKETPLACE** until a safe replacement product could be developed and approved eg: Tylenol, 1982.

III. The Significance of Adverse Effects

For those of the review panel who demand, require or just want quantified specific adverse events enumerated before you decide how to act in this rule proposal, please consider the following:

The Federal Register detailed the results of more than 20 studies/trials in which the results were observed, recorded and reported about the use of these OTC N-9 vaginal contraceptive products. Of the studies, many showed specific adverse events ranging from genital lesions, abrasions, and epithelial disruption to inflammation. You may ask., "How many specific adverse events caused injury and how many people died?" At the end of the various study periods, a large number of specific adverse events were reported from a majority of the studies.

As to the second question, "How many people died?", the AIDS virus doesn't work on a timetable that can be reduced to a simple formula and replicated. The AIDS virus (HIV) has as many time tables as people it infects, although the sequellae may differ. The Federal Register did not report any deaths during the various study periods. But, that doesn't necessarily mean that no one died. To me, if one person expired, that is ONE PERSON TOO MANY.

One additional point, when you read a study, which states that one percent of the subjects died, that figure may not be statistically significant to you or to the research world. But to the person who died, their family, friends and colleagues, that one percent figure is highly significant. In fact, to them that figure is really 100 percent, because it means someone who they knew died from that condition or disease.

IV. The Stealth Factor

This dangerous game of semantic gymnastics is a sure loser; even if one female doesn't see, read and understand the warning statements, fails to discuss them with her partner to reach a logical decision about their relationship---and contracts AIDS and dies---or contracts an STD with symptoms---this semantic exercise will have failed. With OTC products, old buying habits are hard to break. And what if dozens or hundreds of females miss the clues in this dangerous game and die or are injured in the process? As a review panel member, how would you feel knowing that you signed off on this proposed rule?

I believe that there are going to be many new cases of HIV and STD infection across the country, because these vaginal contraceptives with N-9 will <u>still be available</u> on an OTC basis without consultation with a health professional.

The female consumer will still be able to buy that contraceptive product with N-9 she has been accustomed to buying with no checks and balances. Months later, who will be able to connect their OTC purchase of these products, with a certain partner, and a resultant viral or bacterial infection? Nobody. HIV may not produce signs/symptoms for six months or up to 10 years. And some STDs have clear symptoms in women, while others do not. Relabeling won't prevent that either.

Even if the woman's partner wears a condom, and she uses the OTC vaginal contraceptive with N-9, and continues to have "frequent" sex, she makes herself vulnerable to damaging the epithelium of her vagina or cervix, with the lesions and other sequellae that N-9 products reportedly produce.

A well meaning but ill-begotten act of adding warning statements to a dangerous OTC product can easily convert what initially seemed like a good idea, into a stealth consumer disaster. This action brings new meaning to the phrase, caveat emptor, let the buyer beware---for that is what the consumer must be---aware that these products can do irreparable harm. And unless and until the FDA sees this problem for what it is, namely, a stealth hazard, it will remain a hazard.

V. The Proposed Rule

In my opinion, ----considering the devastating health consequences which could occur to females who may purchase and who may or may not see, read, understand and follow the advice contained on the warning labels and then use these products in their bodies, and to a lesser degree to males who may or may not see, read, understand and follow the advice contained on the display carton or on the vaginal contraceptive container itself,---this scenario describes a long list of serious questions and potential problems which, unless resolved before sexual intercourse takes place, could devastate both partners, but in particular, the female consumer of the products.

VI. Consumer OTC Study.

As the proposed rule regarding nonoxynol 9 depends on the consumer seeing, reading and understanding the new caution statements, a literature search of appropriate research has produced many blind alleys, but at last, one study and one professional letter to the FDA will be of particular interest to the review committee. The National Council on Patient Information and Education (NCPIE) commissioned a comprehensive study to survey the opinions influencing the self-medicating behaviors of the American public.

Conducted by Harris Interactive, the survey consisted of two complementary polls: one of 1,011 adult Americans aged 18 and over and conducted between October and November, 2001, and the other involving 451 pharmacists, nurses and general practice physicians who were surveyed in November and December, 2001. The results, pertinent to this rule change are as follows:

1. "Of special concern to health professionals is a lack of understanding about active ingredients in OTC medicines, especially since different OTC products may contain the same active ingredient. Of the 79 percent

of physicians, nurses and pharmacists in the poll who say that the potential for inappropriate use of OTC remedies is a concern, seven in ten (69 percent) cite not understanding active ingredients as the biggest problem.

2. "Although the vast majority of Americans (95 percent) read some portion of the OTC drug label, the survey finds that many do so selectively when buying or using a nonprescription medicine.

3. "When asked what information they look for when buying an OTC drug for the first time, two in five (4l percent) cite usage information (e.g. directions for use, information on dosage level and symptoms), one in three (34 percent) mention the active ingredient, and **one in five (2l percent) say warnings information.**"

Considering that the major thrust of this FDA proposed rule is aimed at relabeling OTC vaginal contraceptives with nonoxynol 9 for the expressed purpose of adding warnings about their use, it appears that such a move to inform this consumer base is doomed to failure, based on the results of this survey.

Even if one in five read warnings information, would the review panel members feel comfortable knowing that four out of five who didn't read the warnings were susceptible to possible infection by the AIDS virus (HIV) or sexually transmitted diseases (STDs) because they did not read warnings information? It certainly would make me anxious, and I would presume the review panel members feel the same way.

VII. OTC Drug Labeling

In 1997, John Gans, Pharm.D, American Pharmacists Association (APhA), executive vice-president, sent a letter to the FDA, Dockets Management Branch, about an FDA rule published in The Federal Register, on February 27, 1997, pertaining to labeling requirements for over-the-counter (OTC) human drugs.

He said, "A study of industry labeling practices by S. Sansgiry and colleagues, at the College of Pharmacy at Idaho State University, examined 100 nationally available analgesic and cough-cold OTC preparations for the congruence of their labeling.

"Sansgiry et al. found that as OTC package size increased, the font size used for the product increased. However, the font size for warnings remained constant. This finding is relevant to a recommendation of the American Association of Retired Persons (AARP) that FDA require larger font size and/or more information, on the label of larger size OTC packaging.

"Sansgiry et al. also found that 22% of the product packages examined used smaller than 6-point type for warnings.

"**Bold Print**. In sharp contrast to the Nonprescription Drug Manufacturers Association's (NDMA) guidelines, 63% of the OTC labels studied by Sansgiry et al. used no bold print in the warnings section of the labeling.

"**Hyphenated text**. Although NDMA guidelines recommend against the use of hyphens, 63% of the labels examined by Sansgiry et al. used hyphens in the text.

"**Uppercase print**. Thirty percent of the OTC labels studied used uppercase lettering for about half of the text of their labeled warnings. NDMA has recommended against the use of all capitol lettering. "

"It is extremely important that consumers have access to consistent, and comprehensible information on OTC drug products. However, it is neither optimal nor feasible for the OTC drug product label alone to supply all the information of value. Space limitations mean only the most important information regarding the product and other sources of information can appear on an OTC container, not only to preserve legibility, but to encourage the consumer to read the label.

"APhA agrees that OTC product labeling should advise the consumer to speak with a physician or pharmacist before purchasing or using a nonprescription drug. APhA suggests two principles or guidelines for FDA in making the decision as to which health professionals the label might most usefully direct the consumer to consult.

1. Labeling should direct the consumer to health professionals who have the requisite information and training. And,
2. Labeling should direct the consumer to the health professional who is most likely to be accessible when and where a decision regarding OTC purchase or use is going to be made.

Taking into consideration these two principles, APhA believes that the in-depth education of the pharmacist in pharmacotherapy---as well as the tremendous advantage of having the pharmacist located precisely where and when most OTC drug purchasing decisions are made---argues in favor of including the pharmacist on the label as a primary and explicitly identified source of OTC drug information."

VIII. Alternatives To Relabeling

In proposing alternatives to relabeling in order to continue to provide open access of these products to consumers, the advocates of open access or OTC, continue to say that these products be made available OTC, still closing their eyes to the facts, clearly established in the NCPIE study above, that,
CONSUMERS DO NOT CONSISTENTLY READ CAUTION LABELS.

The fact that too many consumers are now buying these potentially dangerous products with N-9, completely unaware of the dangers of N-9, doesn't seem to resonate with them. Thus, they continue to cling to the carefree OTC days of the past. I imagine that for many of them, "Ignorance is Bliss" could be their credo. Nevertheless, the mission of the FDA is clear--- namely, to provide SAFE AND EFFECTIVE MEDICATIONS TO THE PUBLIC.

The question remains, how do you communicate the fact that N-9 is dangerous, and protect the consumer unless the product is used within the strict parameters set forth on the warning labels, if the consumers continue to have free access to the OTC vaginal contraceptive products with N-9?

It seems logical and obvious to me that the sooner the OTC status of these vaginal contraceptives is changed either to provide restricted access or having the products removed from the marketplace, the better off these female consumers will be. In short, I am suggesting that,

I. The manufacturers could voluntarily recall and remove these products from the marketplace.

II. FDA could convert the current OTC status to Rx only. Restricted access would limit consumers to visiting a physician for an examination and a new prescription with multi-refills noted (to avoid extra office visits).

III. FDA could order the removal of OTC vaginal contraceptives with N-9, which could stimulate contraceptive manufacturers to find and add other safe and effective spermicides or microbicides to their products. I know this would require research, which is expensive, but the dollar costs would certainly be less than the human cost borne by the heirs of the female victims, should the products remain in the marketplace, as OTC items.

IV. FDA could mandate the removal of the existing OTCs, and the manufacturers might decide, based on market data, to not respond.

IX. Lurking in the Shadows

It should come as no surprise to any member of the review panel that communicating about human sexuality issues from parent to child, and from school teachers to students, are not among our strong points in the United States. As a result, the U.S. leads the "developed world" in sexually related abuses of various types from sexual assault, rape, child abuse, to pornography.

Therefore, when a topic such as vaginal contraceptive products is on the table, and we discuss "frequent sex" there are too many who assume that we are talking, by-and-large, about prostitutes and the many separate and unique issues surrounding that topic. In fact, many males and females from "middle America" actually enjoy having sex with their partner more than once a day. The point here is that these too, are the females who may use these N-9 products in question more than once a day, and represent a large number of citizens in the U.S., who are putting themselves in jeopardy,

This is the target audience who use the N-9 products "frequently" and to whom this relabeling provision would largely be directed. When the FDA recounts the devastating results of the studies resulting from using N-9, as listed in the Federal Register, and relabeling is suggested as the solution, we should be asking some very serious questions about relabeling in view of the NCPIE study quoted in this paper, as well as the anecdotal evidence that most pharmacists can provide about this subject, specifically, that consumers rarely read product labels, leave alone warning labels.

In short, while relabeling may offer a solution for other OTC products which do not produce life threatening or life altering results, in the case of N-9 products, in my opinion, relabeling is neither an ideal nor a partially acceptable alternative.

X. Questions from the Federal Register

1. Do the proposed warnings....adequately convey the safety concerns to consumers?

If one assumes the consumer sees the warnings on the container and the product wrapper; or if the consumer actually goes to the trouble of reading the consumer package insert (CPI), and if one further assumes that the CPI is printed in type larger than the usual and customary small point type in which many CPI's are now printed, and then still further assumes that the consumer can understand the copy, PERHAPS the consumer will receive the message, comprehend the message, and follow through. Still, these are BIG, real and unanswered questions in this process which still leave this and other critical issues unresolved.

What revisions would be useful?
Placing a bug or violator on the product carton and/or on the product itself, might assist in making the warning more visible. It may help if the consumer actually removes the CPI, unfolds the CPI, is not turned off by its length, tries to read it and is able to understand the copy; it will also help if the copy is large enough to read without difficulty.

2. Are there other data to support, expand, or refute the proposed warnings?

The study data appears to be conclusive that females having sex with a vaginal contraceptive product containing nonoxynol 9 more than once a day would be hazardous to their health. Therefore, the proposed warnings appear to be appropriate.

3. The "frequent use" definition of "more than once a day" .....

According to the studies, that definition seems to be appropriate.
However, another question continues to beg for an answer:
If a woman using a nonoxynol 9 vaginal contraceptive has sex with a man using a nonoxynol 9 condom, would this exceed the "once a day" definition of frequent use of nonoxynol-9?

4. Are the symptoms of vaginal irritation adequately defined?
The symptoms seem to be adequately defined.

5. Are there additional data to correlate an increase in vaginal irritation with an increased risk of transmission of HIV and STD's?
I don't know that this data is forthcoming, or if it would be statistically significant.

If so, how should such information be conveyed in labeling?
That would depend on the nature of the data. And if necessary, it might be appropriate to incorporate the alternative suggestions such as those described in item VII. OTC Drug Labeling, above.

6. Is a package insert the best way to provide additional information to consumers or should this information appear on the outer carton?

The package insert **IS NOT** the best way to communicate information; experience with prescription package inserts (PPI) shows that RARELY does the patient ask for such information because the information is offered in type which is usually too tiny to read, leave alone comprehend. It is an established fact that critical information, and that IS what we are discussing here, is best communicated one on one, FACE TO FACE.

The obvious communicators here are the physician and the pharmacist, however, experience indicates that since the 1970's physicians are less willing and able to communicate with patients due to a host of reasons, none the least of which is the shortage of time. It is estimated that a private practice physician spends only eight to nine minutes with each patient. It is hard to imagine this physician having enough time to clearly explain all the problems present in OTC vaginal contraceptives with nonoxynol 9 (N-9) let alone the definitions of these products terms

Pharmacists historically have been the first choice for information for patients; however, since the 1980's, when prescription activity dramatically increased and pharmacists have been in short supply, pharmacists have turned to large type, one-page, one side information sheets and oral communication to communicate critical prescription information.

7. Are the proposed statements for the package insert appropriate?

I would suggest adding the following **bold** words in parenthesis or brackets to the statement in the Federal Register for this labeling;

> "Correct use of a (**dry**) latex condom, (**or a silicone lubricated latex condom, but NOT a condom lubricated with nonoxynol 9**) with every vaginal sexual act will help reduce the risk of transmitting the AIDS virus (HIV) and other STDs."

I also suggest the following statement as a substitute for the final labeling addition;

> **Studies suggest the possibility between increased vaginal irritation from frequent use, and the risk of passing on the AIDS virus (HIV) and other STDs. to your partner. With "frequent use" being defined as using nonoxynol 9 (N-9) products, more than once a day.**

What revisions or additional information, if any, would be useful to make the package insert more informative and consumer friendly?

If you add any more information it will lengthen the insert and add yet another visual and emotional obstacle for the consumer to navigate. Adding color, larger type, and less copy would make the insert more consumer friendly. Of course, this would assume that the consumer seeks further information, or is queued to find the insert and read it.

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