DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 28 1997

1797 '97 SEP -3 P12:30

Associated Pharmacologists & Toxicologists
Attention: Armand Lione, Ph.D., President
Suite 402
40007 Connecticut Avenue
Washington, D.C. 20008

Empire State Consumer Association, Inc.
Attention: Judith Braiman
50 Landsdowne Lane
Rochester, New York 14618

Re: Docket No. 83P-0187/CP1 & CP2

Dear Dr. Lione and Ms. Braiman:

This letter is in response to your citizen petitions regarding VLI Corporation's (now Whitehall-Robins') Today Contraceptive Sponge.[1] The petitions request that FDA withdraw approval of the Today Sponge based on the possible links between the Today Sponge and such manifestations of toxicity in humans as cancer, toxic shock syndrome, and vaginal irritation.

FDA has concluded that any slight theoretical risks posed by carcinogens in the Today Sponge and any small increase in the incidence of toxic shock syndrome or vaginal infections do not warrant the withdrawal of the product's approval, and the agency is accordingly denying your request.

BACKGROUND

The active spermicide in the Today Contraceptive Sponge is nonoxynol-9 (N-9), a commonly used spermicide that has been available over-the-counter (OTC) for over 30 years (45 FR 82014 at 82029). Despite N-9's long history of safe and effective OTC use, FDA regarded a sponge as a new delivery system for N-9 and permitted a study of the Today Sponge only under an investigational new drug application (IND) and required that the product be the subject of an approved new drug application (NDA) before marketing. In April 1983, FDA approved VLI Corporation's NDA 18-683 for the Today Sponge.

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[1] As you probably are aware, Whitehall-Robins has voluntarily suspended manufacture of the Today Sponge. The approved status of the new drug application for the Today Sponge (NDA 18-683) is unaffected by this voluntary action, and the holder of the approved application may, at its discretion, resume manufacture of the product as long as full compliance with the Federal Food, Drug, and Cosmetic Act is maintained.

83P-0187

PDN1

The laboratories that conducted the laboratory tests of the Today Sponge designed the tests according to FDA guidelines (45 FR at 82020-82024).

The clinical studies were designed and conducted by the International Fertility Research Program (IFRP). The studies were funded through the IFRP by the U.S. State Department, Office of Population, Agency for International Development, and the National Institutes of Health. The studies were designed and conducted in accordance with FDA guidelines for clinical investigations of drug products.

ISSUES RAISED

FDA's responses to the specific claims made in the petitions follow.

1. That a link may exist between the Today Sponge and cancer.

Evaluation of the possible carcinogenicity of the Today Sponge involves calculating the potential risk from several low level contaminants. Even using FDA's conservative (i.e., high) assumptions about the amount of contaminants that might be absorbed from the Today Sponge, and assuming lifetime daily exposure, the risk of developing cancer from the Today Sponge is extremely low, on the order of two cancers per million women.

One of the petitioners cites three items in support of the view that there is a link between the Today Sponge and cancer.

First, a study by Volfson[2] reports a high frequency of precancerous and cancerous lesions in mice that received daily insertions of polyurethane sponge tampons.

The Today Sponge cannot be appropriately compared to the sponge tampons used in Volfson's studies. The Today Sponge is made from components significantly more pure than the sponges used in the Volfson research in the late-1960's and early- to mid-1970's. Specifically, the content of the polyurethane contaminant 2,4-toluenediamine (TDA) in the Today Sponge polyurethane is less than 1 part per million (ppm) by the sponsor's assay, and 0.057 ppm by Schering's more sensitive assay (0.4 microgram per 7-gram sponge).

Moreover, the incidence of lesions in the polyurethane group of animals was similar, in Volfson's studies, to that in the control group. This suggests that the cause of the lesions was chronic irritation, not a substance in the polyurethane.

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[2] N. I. Volfson, "Evaluation of the Carcinogenic Risk of Chemicals to Humans," IARC Monographs, World Health Organization, February 1979.

Second, a study by Slade and Peterson[3] reports that implanted polyurethanes have disintegrated and been absorbed in tissue.

This study does not suggest that toxic material is formed after slow polyurethane disintegration. The researchers found no evidence of carcinogenic changes when they studied the histological responses of the host. Hoopes et al.[4] cite Arons' studies on the effects of imbedded polymers on growth characteristics of transplantable tumors in rodents. Arons concludes that the placement of such tumor transplants next to various foreign materials did not influence the latency period, take, or local growth of the tumors. There is no evidence that intermittent use of a sponge, diaphragm, tampon, or other such device that is not permanently kept in place effects a carcinogenic outcome.

Third, it is suggested that the fact that Procter and Gamble Corporation stopped using polyurethane in the Rely tampon after the issue of carcinogenic effect was raised constitutes evidence of the potential carcinogenicity of the Today Sponge.

It is true that Procter and Gamble replaced polyurethane with another filler in the Rely Tampon it was test marketing. This action was apparently taken in response to the adverse publicity resulting from unsubstantiated allegations in a student newspaper that 2,4-TDA has a carcinogenic effect. Procter and Gamble did not consider the product unsafe, and the polyurethane was examined and found not to be a health hazard by health authorities in the Rochester, New York, area and by FDA's then Bureau of Medical Devices.

Also, the polyurethane in the Today Sponge is made by a different process than the old Rely tampon, with specific efforts to limit the 2,4-TDA content. 2,4-TDA is not detectable in the Today Sponge at the 1 ppm level.

2. That the spermicide, N-9, used in the Today Sponge contains a demonstrated carcinogen, dioxane.

N-9 was granted Category I status (i.e., it was considered generally recognized as safe and effective) in 1979, pursuant to a finding of the Advisory Panel on Over-the-Counter Contraceptives and Other Vaginal Products. FDA regards the Today Sponge as a new delivery system for an already marketed product with a long history of safe use.

While evaluating the NDA for the Today Sponge, FDA learned that N-9 might contain low levels of the carcinogen 1,4-dioxane. Many years ago, the National Academy of Sciences

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[3] C. L. Slade and H. D. Peterson, "Disappearance of the Polyurethane Cover of the Ashley Natural-Y Prosthesis," *Plastic and Reconstructive Surgery*, 70(3):379-83, 1982.

[4] J. E. Hoopes, M. T. Edgerton, Jr., and W. Shelley, "Organic Synthetics for Augmentation Mammaplast: Their Relation to Breast Cancer," *Plastic and Reconstructive Surgery*, 39(3):263-270, 1967.

(NAS) established a specification of 10 ppm for 1,4-dioxane in polysorbate, a food additive. NAS believed that the 10 ppm limit was the lowest level of 1,4-dioxane that could be achieved in manufacturing polysorbates. FDA considered the same level, 10 ppm, to be an acceptable limit for 1,4-dioxane in N-9.

The sponge-forming process is thought to drive off some of the 1,4-dioxane, so if the 10 ppm acceptable level of 1,4-dioxane were present in the N-9, this same level would probably not appear in the sponge. Nonetheless, FDA calculated the carcinogenic risk that the 10 ppm level of 1,4-dioxane might pose to a contraceptive sponge user.

1,4-dioxane causes squamous-cell carcinoma of the nasal turbinates in rats and hepatocellular tumors in female rats and in mice of both sexes, according to studies performed under the auspices of the National Cancer Institute. The female rat groups were chosen for the risk assessment because they were the most sensitive to the carcinogenic effect of 1,4-dioxane.

Using the linear proportional model, FDA calculated that the upper bound limit of lifetime risk from 1,4-dioxane from daily exposure to the Today Sponge would be less than 5 in 10 million. The agency estimated this risk using procedures for determining the safety of food and color additives with carcinogenic constituents. These procedures are outlined in the *Federal Register* of April 2, 1982 (47 FR 14464).

The assessment is based on very conservative presumptions: Daily lifetime exposure to a sponge containing 1 gram of N-9, with 10 ppm of 1,4-dioxane, and complete absorption of all of the dioxane in the sponge each day. (These assumptions greatly exaggerate exposure. After normal use, about 80 percent of the N-9 remains entrapped in the sponge, presumably with its associated dioxane. Moreover, a woman's reproductive life is only about one-third of her life span, and few women in trials used the sponge more than one-third of all days.) The calculated risk of 5 in 10 million thus should, realistically, be reduced about forty fold to fifty fold to about 1 in 100 million.

Because 1,4-dioxane requires metabolic activation for activity in salmonella testing, topical carcinogenicity is unlikely. Chronic testing of the contaminant was not considered necessary. Also, available techniques for such testing are poorly developed.

3. **That the polyurethane used in the Today Sponge has not been subjected to intravaginal animal studies to evaluate its biodegradation, toxicity to the vaginal wall, or carcinogenicity.**

Please see response to issue 1, above.

4. **That the dose of the spermicide N-9 used in the Today Sponge has not been reviewed or approved by the FDA Section on Contraceptive Drugs.**

Although the Today Sponge contains a larger dose of N-9 than previous products, most N-9 stays in the sponge, releasing approximately 125 to 150 milligrams (mg) of N-9 over a 48-hour period (the 48-hour wear-period -- a significantly longer time period than the 30 hour maximum now recommended for Today Sponge use -- was studied because the manufacturer originally intended recommending use for 48 hours). By comparison, representative contraceptive foams and creams provide from 133 mg to 250 mg of N-9, with dosage repeated for each coital episode. FDA's Fertility and Maternal Health Advisory Committee was informed about the dose of N-9 and recommended approval of the Today Sponge.

5. **That the vaginal toxicity of polyurethanes and N-9 for animals has been reported, but the vaginal toxicity of the Today Sponge has not been studied in animals.**

An attempt was made to perform vaginal studies of a sponge in rats and monkeys. Steel sutures were used to close the vaginal opening in the rats; however, the rats gnawed the sutures and the test material was expelled. The sponge was not kept in place for more than 1 month in the monkey. VLI therefore performed toxicity studies on the skin of rabbits and humans (see page 4 of the enclosed "Review and Evaluation of Pharmacology and Toxicology Data" dated November 4, 1981). It should again be noted that N-9 had had widespread human use for about two decades at the time of approval of the Today Sponge.

6. **That the absorption and accumulation of N-9 has been demonstrated in animal experiments using radioactive tracers, but similar animal experiments have not been done to evaluate how the regular use of a contraceptive sponge may cause the accumulation of N-9 in human tissues.**

As explained previously, N-9 is not a new product and there is no reason to suspect that absorption of N-9 from the Today Sponge is greater than absorption from cream and foam spermicides. In fact, there is considerable doubt concerning the finding of intravaginal absorption of N-9 in the studies by Chvapil et al., to which you referred. These results have not been confirmed by others.

In another study, rats were treated intravaginally with ^{131}Iodine (I)-labeled N-9. Continuous monitoring for 5 hours, during which the rats remained anesthetized, showed the drug to be localized in the vagina; no uptake of ^{131}I was recorded in any other organ (unpublished data). These results cannot be extrapolated to the human with confidence. Using a newly developed method of detecting N-9 concentration in serum, however, healthy premenopausal women showed no detectable presence of N-9 in serum after 6 hours following a standard 125 mg intravaginal dose of commercially available contraceptive cream (unpublished information).

Thus, vaginal absorption of N-9 in the animal model or the human, with accumulation in body tissues, has not been clearly demonstrated.

7. That tests have not been completed and evaluated to determine the breakdown products of N-9 in the Today Sponge when it remains at body temperature for two days.

No detectable degradation of the Today Sponge or N-9 occurred after storage for 3 months at human body temperatures, or after 5 years at ambient temperatures. Women should not leave the Today Sponge in place for more than 30 hours, according to the approved labeling.

8. That a plan for the postmarketing surveillance of the harmful side effects of the Today Sponge has not been devised.

The Center for Drug Evaluation and Research's Office of Epidemiology and Biostatistics maintains constant surveillance of reports of harmful side effects associated with use of the Today Sponge as reported to the agency, to the Centers for Disease Control (CDC) via State health departments, to the CDC's own reporting/reviewing system for toxic shock syndrome (TSS), and to the medical literature. When VLI Corporation manufactured the Today Sponge, the company had in place a toll-free "hotline" that consumers could use to report problems or ask questions about the Today Sponge.

9. That the Today Sponge may increase the incidence of TSS.

Because estimates of TSS incidence are not precise, it is not possible to generate a completely reliable comparison of the magnitude of the relative risk of sponge-associated TSS with background nonmenstrual TSS. TSS is a rare disease, with overall incidence of 0.53/100,000 women, and the risk attributable to sponge use is low, despite a high relative risk.

As of September 10, 1992, FDA's Spontaneous Reporting System had received reports of 22 patients hospitalized with confirmed TSS. Many had predisposing and extenuating circumstances; for instance, some women left the Today Sponge in place longer than the recommended 30 hours. These cases, and cases in which the women are postpartum or menstruating, should not be included in risk calculations without qualification.

In some cases, women who subsequently got TSS had difficulty removing the Today Sponge. There was no evidence in the clinical trials of physical disintegration of the Today Sponge, besides the fragmentation resulting from forceful attempts at removal. However, because improper use or fragmentation during removal may contribute to the risk of TSS in Today Sponge users, the approved labeling emphasized instructions regarding removal of the sponge and advised women having difficulty removing the Today Sponge to call the company's information line or to consult their physicians or clinics immediately.

In light of the temporal association between the Today Sponge use and the onset of TSS in the reported cases, the very low estimated background rate of nonmenstrual TSS, and the well-proven association of menstrual TSS with tampon use, there may be a slightly increased risk of nonmenstrual TSS associated with use of the Today Sponge.

Therefore, despite the nominal risk, FDA requested that the labeling be revised to include information about TSS, based on FDA's and CDC's conclusions that there is an increased risk of TSS in nonmenstruating Today Sponge users. FDA recommended that women carefully read the package insert and follow the directions.

The original approved labeling for the Today Sponge warned that its use was not recommended during the menstrual period and noted that clinical studies were not large enough to assess the risk of developing TSS. As a result of new data, warnings in the package insert have been strengthened to alert users to symptoms of TSS. Also, a caution has been added to the outside of the package concerning the warning signs of TSS and the importance of removing the Today Sponge within the specified time limit.

The Today Sponge contains several antimicrobial agents besides the spermicide N-9. Baehler's study, which concluded that N-9 had no inhibitory activity on staphylococci or group B streptococci, did not consider the effects of the numerous other microbial inhibitory agents in the sponge.[5] Other laboratory tests have demonstrated that the sponge inhibits the growth of *S. aureus* and also suppresses the production of the pyrogenic exotoxin associated with TSS (unpublished reports submitted by VLI Corporation). The agency, however, agrees that there is no clear demonstration that the Today Sponge suppressed the cited microorganisms and asked that the company stop implying this in its promotion of the Today Sponge.

In the supplement of February 27, 1992, you cite an article[6] reporting that the use of the Today Sponge was associated with an increased incidence of TSS. Although use of the Today Sponge may slightly increase the risk of contracting TSS, this slight risk does not justify withdrawal of approval, because TSS is a rare disease; the risk attributable to the Today Sponge is very low; and the approved labeling includes adequate information about TSS.

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[5] E. A. Baehler, et al., "The Effects of Prolonged Retention of Diaphragms on Colonization by *Staphylococcus aureus* of the Lower Genital Tract," *Fertility and Sterility*, 39:162-166, 1983.

[6] G. Faich, et al., "Toxic Shock Syndrome and the Vaginal Contraceptive Sponge," *Journal of the American Medical Association*, 255:216-218, 1986.

10. That data, including data in the Drug Experience Network as of January 16, 1992, indicate that the Today Sponge is frequently associated with vaginal irritation.

The Today Sponge's approved labeling includes the risks of itching, irritation, rash, and allergic reactions. This labeling is appropriate, in light of the fact that, as of September 10, 1992, with approximately 176 million sponges distributed, there had been 347 accounts of vaginitis and 16 accounts of cervicitis worldwide reported to the Spontaneous Reporting System since marketing began. Any topical device or drug has the potential of causing irritation. Women who experience irritation are, of course, free to discontinue use of the product.

The Bernstein study you cite was specifically designed to determine the ability of a woman to tolerate the Today Sponge for extended time periods representing extreme conditions. (Studies of this type are frequently performed in the early stages of drug development to determine the maximum tolerated dose.) The investigator concluded from the first phase of the study, in which each of 10 women was to wear 1 sponge continuously for 7 days, that a single sponge could not be left in place for 7 days without undesirable side effects.

The sponges were better tolerated in the second phase, in which each of 15 women used 4 separate sponges over the 7-day wear period. The investigator reported, however, that 7 continuous days of wear remained a strong challenge, even when the sponges were changed every 48 hours.

In this second phase, the conversion of cervical/vaginal cytology from Class I (no abnormal cells) to Class II (atypical cells observed, usually caused by inflammation) in four cases demonstrated tissue irritation that could be expected from continuous wearing of the sponge (or any foreign material, such as a tampon) beyond a period of 48 hours. The change from Class I to Class II represents some measure of inflammation and does not suggest carcinoma or dysplasia. Furthermore, these changes reverted to normal upon repeat examination after the study was ended.

Bernstein reported that four of the women in the study developed symptomatic vaginitis, but he noted that there was generally a high prevalence of vaginitis in the clinic population. In sum, the Phase 1 clinical study conducted by Bernstein was an intensified tolerance challenge, and the irritation effects he reported were predictable.

In Phase 3 studies, when sponges were utilized in normal patterns of use, the Phase 1 results were not repeated. You note in your petition that, in a study conducted in the United States, 12 percent of sponge users discontinued use of the sponge after 1 year because of vaginal irritation, compared to 3.7 percent of diaphragm users.[7]

The comparative rates of discontinuation may be biased in favor of the diaphragm. The 12 percent discontinuation from the study you cite includes patients who discontinued sponge use due to unspecific "discomfort," which probably includes a variety of subjective complaints not related to vaginal irritation. Furthermore, 248 of the 717 subjects (34.6 percent) in the diaphragm group of the U.S. study were experienced in this method. These experienced diaphragm users were probably at less risk of discontinuing for reasons of discomfort than were the sponge users, all of whom were new to the sponge method.

Also, your statement, "when discomfort and problems removing the sponge were grouped with all other reasons cited for discontinuing the use of the sponge, the overall rate was about 50 percent," requires clarification. The rates for discontinuation of the sponge, diaphragm, and foaming suppository from worldwide multiclinic studies are 47.9, 43.9, and 33.0 percent, respectively. These discontinuation rates include discontinuations for accidental and planned pregnancy, allergic reactions and other medical problems, discomfort, and product-related reasons. There is not a significant difference between 47.9 and 43.9 percent, the rates for discontinuation of the sponge and the diaphragm, respectively.

In the supplement of June 25, 1984, you noted that the number of women who voluntarily reported vaginal pain, fever, and distress because of the sponge numbered in the hundreds. This figure must be considered in light of the number of sponges used. Data collected by VLI Corporation for the first year of sales indicate that vaginal irritation was reported by 0.004 percent of an estimated user population of 500,000. This is far below the level experienced in controlled clinical trials. The total number of adverse experiences reported to the firm for the first year of sales was 383, which is 0.08 percent of the total estimated number of sponge users, and 0.003 percent of the total number of sponges distributed. These figures do not suggest a safety problem associated with use of the Today Sponge.

In the supplement of February 27, 1992, you emphasize, among other points, the problem of sponge users experiencing either cervicitis or vaginitis. You attribute these difficulties, in large part, to the amount of N-9 in the contraceptive and the amount of time for which the spermicide is left in the body. As detailed in the response to number 4 above, despite the larger dose of N-9 contained in the sponge relative to representative contraceptive foams and creams, the amount of N-9 released from the sponge is substantially less than that provided by these other contraceptive products.

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[7] "New Developments in Vaginal Contraception," *Population Reports*, Series H, #7, Jan.-Feb. 1984, Population Information Program, Johns Hopkins University, Baltimore, MD.

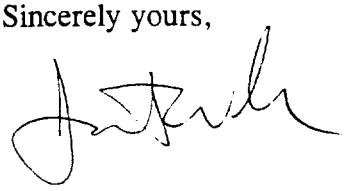
CONCLUSION

FDA reviewers and an outside advisory committee have extensively evaluated the safety of the Today Sponge. Based on their careful analyses of the studies and data available to date, FDA finds that adequate grounds do not exist for withdrawing approval of the Today Sponge at this time.

The Today Sponge is a new delivery system for an already marketed product with a long history of safe use. The Today Sponge has risks associated with it, as do all methods of birth control, but the risks associated with pregnancy far outweigh the risks associated with the use of the Today Sponge.

FDA will continue to monitor information relating to the safety and effectiveness of the contraceptive sponge as warranted. This petition response is necessarily limited to the data that is before the Agency at this time and, therefore, does not constitute either a final determination as to the safety of the Today Sponge, or a determination, pursuant to 21 CFR 314.161, as to the reasons for which the drug product has been voluntarily withdrawn from sale.

Sincerely yours,



Janet Woodcock, M.D.
Director
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Enclosure