Addendum For
NDA Petition dated
4/25/83

Associated
Pharmacologists &
Toxicologists

May 23, 1983

Dr. Soloman Sobel,
Product Development & New Drug Approval
Metabolic & Endocrine Drugs
HSN - 130
Food and Drug Administration
Rockville, MD 20857

Dear Dr. Sobel:

There are several questions I have regarding the safety review of the Polyurethane Foam Contraceptive Sponge (PFCS). The enclosed reprints and literature cited will provide you with some of the detailed data on which my questions are based.

First of all, the publication by Slade and Peterson (1) is probably too recent for previous review by your staff. The article describes the total disappearance of the polyurethane cover from an implanted breast prosthesis. Slade & Peterson also review the research literature on the biodegradation of polyurethanes and discuss the breakdown of implanted polyurethanes as described in several previous reports. With regard to the safety review of the PFCS, were any animal studies performed to evaluate the intravaginal degradation of the polymer used in this product?

The WHC publication (2) summarizes the work done by Volfson (1969, 1976) which suggests that the twice weekly insertion of polyurethane sponge tampons as well as rubber sponge tampons caused precancerous and malignant lesions in the vaginas and ovaries of mice.

(contd)

I understand that Dr. Elizabeth Connell is now a scientific advisor for the company developing the PFCS (VLI Corporation, Costa Mesa, CA). As the former Chairman of the FDA OTC Panel on Contraceptives and Other Vaginal Drug Products, Dr. Connell published a summary of the Panel's recommendations in 1979 (3). In Dr. Connell's article, the animal carcinogenicity studies recommended by the Panel for new products include the vaginal application of new contraceptives in rabbits (see table 22-5, ref. (3)). Dr. Vorhauer, the President of the VLI Corp., has reported elsewhere (4) a summary of the safety studies done during the development of the PFCS. The vaginal application of the product in test animals was not described in that article. I have also reviewed the transcript of the recent VLI presentation to the FDA regarding the PFCS (5) and have not uncovered any references to such studies. Unfortunately, the Summary for the Basis of Approval for the PFCS is not currently available, and no other data on animal tests performed with the PFCS have been made available to me. Therefore, I would like to know if the intravaginal application of the PFCS has been used in animal tests to evaluate its carcingenicity. If so, how does this data compare with the previous reports by Volfson (2)?

One of the articles enclosed with this submission (6) discusses the carcinogenicity of several polyurethanes. I believe that the specific polyurethane used in the PFCS is a methyl diisocyanate polymer. I would be interested in learning if the polymer termed "Y-302" in the report by Autian et al. ("Carcinogenesis from Polyurethans" (6)) is the same polymer used in the PFCS. If so, was this carcinogenicity data considered in the safety review of the polyurethane contraceptive sponge?

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As you may know, a polyurethane foam was incorporated into the Rely tampon when it was first formulated and test-marketed in Rochester, N.Y. in 1975. A review of the carcinogenicity data available at that time, led the Proctor & Gamble Corp. to reformulate Rely and remove the polyurethane before it was marketed nationally. This incident demonstrated one of the many practical advantages that can follow from the introduction of a new vaginal product in a few limited markets before it is distributed nationally. Among the chief advantages of this approach is the possibility of monitoring users for adverse effects that can not be uncovered in clinical research. Recently, Stolley et al. (7) described an epidemiological system for the post-marketing surveillance of adverse effects of vaginal contraceptives. What plans have been made to have a surveillance system in place when the contraceptive sponge is brought to market? I did not see any reference to a surveillance plan, if it exists, in the transcript of the FDA meeting held Oct. 28, 1982 to review the PFCS.

In light of the recent biodegradation and carcinogenicity data I have briefly reviewed above, as well as the apparent absence of some fundamental animal tests on the safety of the PFCS and a suitable post-marketing surveillance plan to monitor for adverse effects, it would seem that this new product may not satisfy the safety requirements established by the FDA for non-prescription drugs and medical devices. I would appreciate your review of the enclosed data and a prompt response to the safety questions discussed in this submission.

Sincerely yours,

Armand Lione, Ph.D.
President
APT

Enc.

## Literature Cited

*1. Slade, C.L. & Peterson, H.D., "Disappearance of the polyurethane cover of the Ashley Natural Y Prosthesis," Plast. Reconstruc. Surg. 70 (3) 379-83, 1982.

*2. International Agency for Research on Cancer, "Evaluation of the carcinogenic risk of chemicals to humans: some monomers, plastics and synthetic elastomers, and acrolein," Vol. 19, p. 326-331, World Health Organization, Feb. 1979.

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4. Vorhauer, B.M., "Human reproduction: bioengineering aspects of contraception applied to the development of a new female contraceptive," p. 93- in: Biofluid Mechanics - 2, ed. by D.J. Schneck, Plenum, N.Y. & London 1980, 519 p.

5. Transcript of Fertility and Maternal Health Drugs Advisory Committee Meeting. October 28, 1982, Afternoon session, p. 145-232. FDA, Hearing Clerk, Rockville, MD.

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7. Stolley, P.D., Davies, J.L., Shapiro, S., Slone, D., "Components of an Epidemiologic system for the surveillance of adverse effects due to vaginal contraceptives," p. 271-276 in: Vaginal Contraception: new developments, ed. by G.I. Zatuchni, A.J. Sobrero, J.J. Speidel, J.J. Sciarra, Harper & Row, Hagerstown (1979) 389 p.

* - reprint enclosed with this submission