monograph for OTC sunscreen drug products published in the **Federal Register** of May 12, 1993, 58 FR 28194 at 28210). The agency will discuss its decision on this matter in a future issue of the **Federal Register**. Thus, the agency is reconsidering its policy on foreign marketing data, as the comment requested. However, in view of the agency's tentative conclusion that all vaginal contraceptive drug products will need an approved application for marketing, this issue, as it relates to menfegol, is moot.

References

1. Citizen Petition, submitted by BASF AG, March 16, 1990, coded CP2, Docket No. 78N–0038, Dockets Management Branch.

2. Citizen Petition, submitted by Haarmann and Reimer Corp., July 27, 1990, coded CP3, Docket No. 78N–0038, Dockets Management Branch.

3. Citizen Petition, submitted by Givaudan Corp., October 31, 1990, coded CP4, Docket No. 78N–0038, Dockets Management Branch.

9. Two comments submitted data and information on the safety of nonoxynol 9 (Ref. 1). These data were submitted after publication of the Panel's report in response to concerns regarding the potential teratogenicity or carcinogenicity of this ingredient (Refs. 2, 3, and 4).

Although nonoxynol 9 was classified by the Panel as a Category I ingredient for use as an OTC vaginal contraceptive, concern over the possible carcinogenicity of nonoxynol 9 surfaced in relation to the agency's approval of an application for a vaginal contraceptive sponge product containing this ingredient. In reviewing the data in support of the application, the agency learned that nonoxynol 9 may contain low levels of the suspected carcinogens 1,4-dioxane and ethylene oxide as residuals from the manufacturing process. The concern that the agency had approved an application for a product containing suspected carcinogens was one of the bases of a congressional hearing held by the Subcommittee on Intergovernmental Relations and Human Resources on July 13, 1983. At that hearing, FDA presented testimony and evidence that the levels of 1,4-dioxane and ethylene oxide contained in the sponge product are within the residue limits that are considered acceptable by the agency.

However, because the presence of 1,4-dioxane and ethylene oxide is not unique to the sponge product and it is possible that other products could contain different levels of these contaminants, the agency believes that manufacturers should submit as part of the application required for these products (see section I.A., comment 3 of this document) data and information specifying the levels of 1,4-dioxane and ethylene oxide that are contained in the finished product.

The concern over possible teratogenicity of OTC vaginal contraceptives was also raised at the congressional hearing. The agency explained at the hearing that animal teratogenicity data and recent epidemiological data indicate that nonoxynol 9 is not teratogenic. However, FDA stated that it was considering a special warning concerning the use of any spermicide by women who suspect that they may be pregnant. Data and information on the possible teratogenicity of vaginal spermicides were subsequently presented to the agency's Fertility and Maternal Health Drugs Advisory Committee to determine if any of the studies contains sufficient evidence to warrant a special warning in the labeling concerning the use of vaginal spermicides during pregnancy. At its December 15, 1983 meeting (Ref. 5), the committee decided that such a warning was not warranted. The agency concurs with the advisory committee's conclusion.

References

1. ''Nonoxynol 9 Safety Information,'' Advanced Care Products, Division of Ortho Pharmaceutical Corp., coded RPT and RPT002, Docket No. 80N–0280, Dockets Management Branch.

2. Jick, H. et al., ''Vaginal Spermicides and Congenital Disorders,'' *Journal of the American Medical Association*, 245:1329–1332, 1981.

3. Rothman, K. J., ''Spermicide Use and Down's Syndrome,'' *American Journal of Public Health*, 72:399–401, 1982.

4. Citizen Petition, submitted by A. Lione, Associated Pharmacologists and Toxicologists, June 20, 1983, coded CP2, Docket No. 83P–0187, Dockets Management Branch.

5. Minutes of the Meeting of the Fertility and Maternal Health Drugs Advisory Committee, National Center for Drugs and Biologics, FDA, pp. 1–3, December 15, 1983, copy included in OTC Vol. 11ATFM.

10. Two comments disagreed with the Panel's intention that data submitted on the safety of phenylmercuric acetate be regarded as equally relevant for all related mercury compounds, such as phenylmercuric nitrate (45 FR 82014 at 82031). One comment stated that the greatest part of the Panel's discussion on phenylmercuric acetate and related compounds is devoted to a discussion of the reported toxicity of orally ingested alkylmercury compounds and that this discussion unjustifiably imputes toxicity to arylmercury compounds when used in topically applied preparations under ordinary conditions. The comments further stated that, although the Panel acknowledged that alkylmercury compounds and inorganic mercury salts have greater toxicity than arylmercury compounds, it should be recognized that differences also occur between mercury compounds within the aryl series. Therefore, the comments argued, conclusions should be limited to the compound specifically considered, phenylmercuric acetate, when used specifically for its spermicidal action and should not condemn phenylmercuric nitrate by association.

The agency acknowledges the comments' concern regarding the varying toxicities of the different mercury compounds, but concurs with the Panel that mercury-containing compounds, when used as active ingredients in vaginal contraceptive drug products, are unsafe. The Panel recommended that all vaginal contraceptives containing mercury compounds as active ingredients be placed in Category II because such compounds are potentially hazardous to the fetus and the breast-fed infant (45 FR 82014 at 82038). Because data in animals and humans indicate that phenylmercuric acetate is absorbed from the vagina into the system and partially metabolized to inorganic mercury in the blood and various tissues where it may accumulate (Refs. 1 through 4), the Panel concluded that mercury-containing compounds related to phenylmercuric acetate, such as phenylmercuric nitrate, may be expected to behave in a similar manner. Other than the comments' contention, no data or information was submitted to demonstrate that phenylmercuric nitrate and related mercury-containing compounds react by a different mechanism or are not absorbed from the vagina. Although no overt symptoms of mercury poisoning from the use of vaginal preparations containing mercury compounds have been detected in infants and children, there are sufficient animal data to suggest that inorganic mercury from mercury-containing compounds can be transferred to the fetus and to breast-fed offspring. (See 45 FR 82014 at 82033 and 82035.) In addition, the Panel cited animal teratology studies that showed a higher percentage of fetal abnormalities when phenylmercuric acetate was administered either vaginally or intravenously (45 FR 82034). The Panel also cited cases of congenital mercury poisoning in humans following ingestion of mercury compounds by the mother (45 FR 82032). These studies are at least suggestive, regardless of the