only FDA-approved words be used in advertisements for OTC drugs, and some of the Commissioners expressed doubt that approved OTC drug labeling would be appropriate for OTC drug advertising.

FTC has the primary responsibility for regulating OTC drug advertising. However, FDA does have the authority to regulate OTC drug advertising that constitutes labeling under the Federal Food, Drug, and Cosmetic Act (the act). Under the act, a manufacturer can be prohibited from advertising a drug to treat a condition for which there are not adequate directions for use on the label. See, e.g., United States v. Article of Drug * * B-Complex Cholinos Capsules, 362 F.2d 923 (3d Cir. 1966); V. E. Irons, Inc. v. United States, 244 F.2d 34 (10th Cir.), cert. denied, 354 U.S. 923 (1957). In addition, if advertising for an OTC vaginal contraceptive drug product offers the product for conditions not included in FDA approved labeling, the drug product could be subject to regulatory action by FDA. (See also section I.C., comment 11 of this document for discussion of FDA's labeling policy.)

3. A number of comments disagreed with the agency's position that clinical testing of all final formulations, conducted under the provisions of a new drug application, may be the only means of assuring effectiveness of OTC vaginal contraceptive drug products. Several of these comments argued that the Panel's recommended in vitro testing procedures are sufficient to demonstrate effectiveness. One comment stated that requiring manufacturers to submit an application contradicts the agency's stated purpose of the monograph process. Another comment was concerned that requiring clinical testing might mean that new clinical trials would be needed each time a manufacturer made changes in a product's inactive ingredients. The comment maintained that this would be costly, would not benefit consumers, and would stifle a manufacturer's incentive to improve products.

Two comments advocated requiring clinical testing of OTC vaginal contraceptives. One comment asserted that such testing would provide needed quantitative effectiveness data and "user information." This comment also questioned how appropriate directions for use could be determined based only on in vitro testing. The other comment claimed that research has shown that certain OTC drug products judged to be effective by standard in vitro testing were in fact largely ineffective when evaluated by standard in vivo testing procedures. The comment also contended that in vitro testing is of

limited usefulness because anatomic and physiologic changes in the vagina during sexual arousal, which can affect the distribution of the contraceptive, are not considered. The comment proposed using a particular in vivo testing procedure prior to full clinical testing.

One comment suggested that the agency require an in vitro test other than that recommended by the Panel, claiming that the Panel's test is "inadequately sensitive in that it only provides pass or fail end-point information, and does not quantitate the spermicidal potency of the contraceptive formulation." Another comment opposed requiring clinical testing, but stated that if such testing is to be required, a recognized postcoital test would be sufficient.

The agency has reviewed the available data and information regarding in vitro testing procedures for vaginal contraceptive drug products and tentatively concludes that in vitro testing is not sufficient to assure effectiveness of the product when used in humans. Although in vitro testing will provide a measure of a product's potential effectiveness, reports in the literature (Refs. 1 through 14) indicate that such in vitro tests will not adequately describe the effectiveness of the final formulation when it is used in humans. In these reports, certain OTC vaginal contraceptives found to be effective when tested in vitro were shown to be ineffective when tested in vivo.

Formulations differ in the speed of distribution in the vagina and the degree of surface coverage and these and other factors have a significant impact on effectiveness (Refs. 3, 15, and 16). Homm et al. (Ref. 3) compared seven marketed vaginal contraceptives (foams, suppository, cream, jelly) in in vitro and in vivo (rabbit) studies and concluded that the dosage form of a vaginal contraceptive product is of considerable importance in its contraceptive potency. Homm et al. found that foam products were more available than suppository products, which were more potent than jelly products. However, the authors stated that these comparative ratings could only be regarded as generalizations because the in vivo contraceptive potencies found in the rabbits were difficult to relate to human contraceptive effectiveness. At present, there is no in vitro test available that can be considered a reliable reflection of in vivo conditions. There is also no reliable in vivo animal model that can simulate the human condition. Bassol (Ref. 15) compared the rupture time of two types of soft jelly capsules containing nonoxynol 9 after vaginal

insertion in 96 women. The authors found that vaginal conditions associated with alkaline pH, multiparity, and vaginal dryness have an important role in the rupture of the capsules. The study points out the importance of the contraceptive vehicle as well as other conditions of the vaginal environment in determining the effectiveness of vaginal contraceptive drug products.

Stone and Cardinale (Ref. 16) conducted a study using a series of in vitro and in vivo tests to evaluate the effectiveness of a suppository product compared to a cream or foam product having the same active ingredient, nonoxynol 9. The authors found some evidence indicating that the solubility of the suppository may vary from subject to subject depending on, for example, the volume of vaginal secretions. In the in vitro study, instant immobilization of all sperm was obtained when foam, cream, or effervescent vaginal suppository foam was mixed with 2 milliliters of semen. In the in vivo study, a good volume of foam covering the external os of the cervix was observed in only 11 of the 20 patients in whom the suppository was inserted. However, very little if any foam was observed in the other nine women, and the suppository was removed almost intact after the 15-minute observation period. The authors commented that in vitro and laboratory evaluations of chemical contraceptives do not correlate well to their effectiveness in clinical trials in different populations. In addition, they noted that formulations containing a highly effective spermicidal agent but that do not diffuse well are less effective.

Postcoital tests in humans have been considered as an alternative to clinical trials. However, the agency does not believe that the currently available postcoital tests can be relied upon. The Sims-Huhner test (SHT) is an in vivo postcoital test that is used to diagnose certain types of infertility and assess the presence, quality, and motility of sperm in the cervical mucus. References in the medical literature indicate that the SHT has poor predictive value because a negative SHT does not confirm the absence of sperm (Refs. 17, 18, and 19). Kably et al. (Ref. 17) stated that they had found the results of the SHT to 'paradoxical'' relative to conception. Therefore, the authors examined whether sperm were present or absent in the peritoneal fluid of five subjects with good SHT's and five subjects with poor or negative SHT's. In three of five subjects with a positive SHT and in four of five subjects with a poor SHT, sperm were found in the aspirate.