Asch (Ref. 18) also reported that pregnancy frequently occurs in women with a negative or poor SHT. Asch reported the recovery of mature, morphologically normal sperm from the peritoneal fluid of six of the eight women who had a negative SHT. In three other women who had a poor SHT, sperm were also recovered in the aspirate. Griffith and Grimes (Ref. 19) reviewed the literature and evaluated the validity of the postcoital test for predicting infertility. The authors concluded that the SHT has poor validity, its reproducibility is unknown, and its suffers from a lack of standardized methodology and a uniform definition of normal. Because the absence of sperm in the SHT frequently has been associated with subsequent pregnancy, the agency concludes that this in vivo postcoital test is not reliable for evaluating the efficacy of a vaginal contraceptive.

Because of the difficulties that arise in trying to simulate the human condition in an in vitro test and determine the influence of the potential interactions among the sperm, cervical mucus, microorganisms, and contraceptive vehicle on the effectiveness of the contraceptive, the results of in vitro testing cannot be relied upon to reach conclusions about effectiveness in humans. For example, due to the varied amounts of cervical mucus and semen that may be present in humans during sexual arousal, the concentration of the contraceptive in the vagina is not always equivalent to the concentration used in in vitro testing. Furthermore, in vitro testing cannot determine the following important information: How long before intercourse the contraceptive should be inserted; if the intravaginal distribution of the contraceptive is sufficient to assure effectiveness; or how long the contraceptive remains effective in the vaginal environment. Therefore, the agency has determined that clinical studies in humans are necessary to establish the effectiveness of final formulations of OTC vaginal contraceptive drug products.

The results of such testing should be submitted in the form of an application that complies with all of the requirements that are necessary to establish the safety and effectiveness of the product's final formulation, as discussed above. Reference to the Panel's report and this document, as appropriate, may be used to satisfy the requirements of portions of the application related to the safety of the active ingredient.

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4. One comment stated that FDA does not have the authority to enforce § 351.30(f) of the Panel's recommended monograph, which would require manufacturers to retain the in vitro effectiveness testing data and permit FDA to inspect these data. The comment requested that § 351.30(f) be deleted.

As discussed in section I.A., comment 3 of this document, the agency is proposing that each OTC vaginal contraceptive drug product should be the subject of an approved application prior to marketing. Therefore, there will be no monograph and the comment's request is moot.

5. Two comments objected to the Panel's statement questioning the safety and effectiveness of quaternary ammonium compounds for use as preservatives in OTC vaginal contraceptive drug products (45 FR 82014 at 82042). The comments stated that the Panel's concern stems solely from a review of eight reports (45 FR 82042) suggesting that the use of quaternary ammonium compounds may be associated with outbreaks of *Pseudomonas* infections because they do not inhibit the growth of *Pseudomonas*. The comments argued that the Panel failed to state that these reports resulted from the contamination of solutions that were employed in laboratory and hospital settings to sterilize medical devices used in urinary and cardiac catheterization or cystoscopic or related invasive procedures. Such procedures are usually conducted on patients whose normal body defenses have been compromised. Because *Pseudomonas* infections occur primarily in debilitated patients and *Pseudomonas* does not cause vulvovaginitis, the comments stated that it is scientifically inappropriate to cite these reports and through extrapolation conclude that the use of quaternary ammonium compounds in vaginal contraceptive drug products presents a health hazard to normal individuals. The comments cited several references to support the argument that the Panel's concern, with respect to vaginal contamination by *Pseudomonas* in the presence of quaternary ammonium compounds, is not supported by the weight of scientific and medical opinion (Refs. 1 through 4).