

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 80N-0280]

RIN 0905-AA06

Vaginal Contraceptive Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would require manufacturers of over-the-counter (OTC) vaginal contraceptive drug products to obtain approved applications for marketing of their products. The agency is taking this action because the effectiveness of these products is dependent upon the final formulation. Therefore, each product must be tested in appropriate clinical trials under actual conditions of use. This action will ensure the maximum effectiveness of OTC vaginal contraceptive drug products for consumers. This proposed rulemaking does not affect the current marketing status of OTC vaginal contraceptives. Thus, persons who are using or wish to use these drug products may do so. However, on the effective date of a final regulation, an OTC vaginal contraceptive drug product that is not the subject of an approved application would be regarded as a new drug and subject to regulatory action. Manufacturers will have adequate time to conduct studies and submit applications before the effective date of the final rule. Under existing procedures, there is a minimum of 26 months from today before a final rule could become effective. Despite this timeframe, manufacturers are urged to contact the agency regarding submission of their application as soon as possible. OTC contraceptives that are marketed for use with or as part of a device, e.g., diaphragm, condom, or contraceptive cervical cap will not be addressed in this document but will be addressed in a separate publication. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products, public comments on an advance notice of proposed rulemaking that was based on those recommendations, and evolving new information about these

products. This proposal is part of the ongoing review of OTC drug products conducted by FDA. While this document does not address the use of vaginal contraceptive drug products for prophylaxis against human immunodeficiency virus (HIV) and other sexually transmitted diseases (STD's), FDA is aware of literature reports and other data relative to such use. FDA strongly encourages manufacturers to evaluate these products for use in the prevention of infectious diseases.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by June 5, 1995. New data by February 5, 1996. Comments on the new data by April 3, 1996. Written comments on the agency's economic impact determination by June 5, 1995.

ADDRESSES: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 12, 1980 (45 FR 82014), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC vaginal contraceptive drug products, together with the recommendations of the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in OTC vaginal contraceptive drug products. Interested persons were invited to submit comments by March 12, 1981. Reply comments in response to comments filed in the initial comment period could be submitted by April 13, 1981.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (address above), after deletion of a small amount of trade secret information.

In response to the advance notice of proposed rulemaking, six drug manufacturers, two governmental agencies, two reproductive health groups, one trade association, one chemical company, and one consumer submitted comments. Copies of the

comments received are on public display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on December 12, 1980, was designated as a "proposed rule" in order to conform to terminology used in the OTC drug review regulations § 330.10. Similarly, the present document is designated in the OTC drug review regulations as a tentative final rule. Its legal status, however, is that of a proposed rule. To establish new § 310.535 by this notice of proposed rulemaking, FDA responds to public comment and states, for the first time, its position on OTC vaginal contraceptive drug products. Final agency action on this matter will occur with the publication, at a future date, of a final rule relating to OTC vaginal contraceptive drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC vaginal contraceptive drug products as modified on the basis of the comments received, the agency's independent evaluation of the Panel's report, and evolving new information on these products. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC drug procedural regulations (§ 330.10) provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage. In place of Category I, the term "monograph conditions" is used; in place of Category II or III, the term "nonmonograph conditions" is used.

Based on all information available to date, the agency has tentatively concluded that any OTC vaginal contraceptive drug product should be regarded as a new drug and be subject to regulatory action unless it is the

subject of an approved application or abbreviated application (hereinafter called application).

The agency has concluded that although nonoxynol 9 and octoxynol 9 kill sperm in vitro and in vivo, the spermicidal activity and resulting effectiveness of these contraceptive active ingredients cannot be considered separately from a product's vehicle. Studies show that these active ingredients lose some of their effectiveness in humans when the spermicide in final formulation is diluted by varied amounts of genital secretions during coitus. Thus, clinical studies are necessary to establish the effectiveness of the spermicide's final formulation when used in humans. (See discussion in section I.A., comment 3 of this document.) Such clinical studies would determine the influence of the potential interactions among the genital secretions, microorganisms, and contraceptive product vehicle.

The agency recognizes a need for consumers to continue to have access to OTC vaginal contraceptive drug products and to avoid disruption in the marketplace. The majority of OTC vaginal contraceptive drug products currently marketed contain nonoxynol 9. At the present time, two approved applications exist for OTC vaginal contraceptives: Delfen Contraceptive Foam (new drug application (NDA) 14-349) and Today® Sponge (NDA 18-683). The NDA for Delfen Contraceptive Foam was approved a number of years ago, and the product as currently marketed uses a different formulation from the one approved in the NDA. The manufacturer of this product will be required to provide additional information. The manufacturer of the Today® Sponge recently announced that it plans to discontinue production of this product. However, the firm has not indicated to FDA that it plans to withdraw its application.

Only a few vaginal contraceptive drug products contain octoxynol 9, and none have approved applications. Because the final rule for this class of OTC drug products will be effective 12 months after the date of its publication in the **Federal Register**, FDA strongly recommends that manufacturers of products not having an approved application consult with the agency as soon as possible concerning the content of these applications. Elsewhere in this issue of the **Federal Register**, the agency is announcing the availability of a guidance document that is intended to help manufacturers of vaginal contraceptive drug products develop data in support of new drug applications.

OTC vaginal contraceptive products that are marketed for use with or as part of a condom, diaphragm, or a contraceptive cervical cap will not be subject to the final rule. When labeled for use only with a device such as a condom (see 21 CFR 884.5310), diaphragm (see 21 CFR 884.5350), or cervical cap (a premarket approval application has been approved for a cervical cap for use as a barrier method of contraception, when used with a spermicidal cream or jelly), a spermicide is considered an accessory to a device. The regulation of spermicides for use only with a device will be addressed at a future date by the agency. In the interim, manufacturers of such products should direct inquiries to the Obstetrics/Gynecology Branch (HFZ-471), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 1390 Piccard Dr., Rockville, MD 20850, 301-594-1180.

The agency has determined that nonoxynol 9 and octoxynol 9 would be appropriate ingredients for an approved application. This determination is based on: (1) The findings of the Panel (nonoxynol 9 and octoxynol 9 were recommended as Category I active ingredients), and (2) the history of use of drug products with approved NDA's containing nonoxynol 9.

Applications for products containing these ingredients will not need to include preclinical data, but, instead, may refer to the Panel's report as a general basis for the safety of these ingredients. The applications will need to include the results of clinical studies that establish the effectiveness of the contraceptive ingredient in the product's final formulation. These studies to establish the effectiveness of the product's final formulation need to comply with the requirements of 21 CFR part 314. The clinical studies should contain evidence of the effectiveness of the spermicide in final formulation in normal volunteers or patients that is consistent with correct use of the product. In addition, the agency is aware that the use of either of the contraceptive ingredients addressed in this proposed rulemaking may be associated with varying degrees of vaginal irritation under certain conditions of use and it is unclear whether this may play a role in the transmission of STD's (Refs. 1 through 5). Therefore, as part of the application for approval of these products for contraceptive use, information regarding the rate of occurrence and degree of vaginal irritation should be presented. FDA encourages manufacturers to consult with the agency as soon as

possible concerning the content of these applications. Inquiries should be directed to the Division of Metabolism and Endocrine Drug Products (HFD-510), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3490.

The Department of Health and Human Services has published the "13th Edition of Approved Drug Products with Therapeutic Equivalence Evaluations," commonly called "the Orange Book," which identifies currently marketed products approved by FDA on the basis of safety and effectiveness data. The main criterion for the inclusion of any product in the Orange Book is that the product is the subject of an approved application that has not been withdrawn for safety or effectiveness reasons. For vaginal contraceptive drug products for which there is a previously approved listed drug product in the Orange Book, an abbreviated application may be submitted. The abbreviated application must contain information to show bioequivalence to the listed drug product. Further, the abbreviated application may contain labeling only for the claims approved for the product, i.e. a contraceptive. None of the products containing nonoxynol 9 that are listed in the Orange Book has a claim for the prevention of infectious disease. Manufacturers should consult with the Office of Generic Drugs (HFD-600), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-0340, to determine the procedures for obtaining approval of abbreviated applications. For vaginal contraceptive drug products for which there is no previously approved listed drug product in the Orange Book, an abbreviated application may not be submitted. For these products, an application that includes adequate and well-controlled clinical studies of the effectiveness of the specific formulation of the vaginal contraceptive must be submitted. Manufacturers of such products should direct inquiries to the Division of Metabolism and Endocrine Drug Products, as noted above.

Both types of applications, i.e., full or abbreviated, would also have to include information on the drug product's formulation, manufacture, and quality control procedures to ensure that the applicant has the ability to manufacture a safe and effective OTC vaginal contraceptive drug product. (Also, see section I.C., comment 15 of this document.)

The agency is aware of literature reports and other data concerning the

use of certain contraceptive active ingredients to prevent sexual transmission of infectious diseases (Refs. 1 through 17). However, none of these products currently has an approved indication for this use. Although this document is not intended to address the use of vaginal contraceptive drug products in preventing the transmission of STD's, the identification of safe and effective products to prevent the transmission of HIV and other STD's is a high priority public health concern. Therefore, FDA strongly encourages evaluation of OTC contraceptive products for this use. Manufacturers who wish to submit applications for such use should be aware that the study designs for effectiveness as a contraceptive and for prevention of infectious disease may be different. Therefore, manufacturers should consult with the agency concerning the content of contraceptive applications that also include an indication for prevention of infectious disease. Inquiries regarding use for prevention of infectious disease for antiviral prophylaxis should be directed to the Supervisory Consumer Safety Officer, Division of Antiviral Drug Products (HFD-530), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-9550, and inquiries regarding bacterial and other nonviral pathogens should be directed to the Division of Anti-Infective Drug Products (HFD-520), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4310.

If this proposal is adopted as a final rule, the agency advises that the conditions under which the drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions) will be effective 12 months after the date of publication of the final rule in the **Federal Register**. On or after that date, no OTC drug product that is subject to the rule may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to the final rule that is repackaged or relabeled after the effective date of the final rule must be in compliance with the final rule regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with

the proposed rule at the earliest possible date.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of May 16, 1973 (38 FR 12840) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch (address above).

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I. The Agency's Tentative Conclusions on the Comments

A. General Comments on OTC Vaginal Contraceptive Drug Products

1. One comment contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464 at 9471 through 9472), and in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. (See, e.g., *National Nutritional Foods Association v. Weinberger*, 512 F.2d 688, 696 to 698 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers v. FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

2. Referring to the Panel's recommendation on the advertising of OTC vaginal contraceptive drug products (45 FR 82014 at 82025), one comment agreed that labeling should be truthful and nondeceptive but disagreed that only those words adopted by the Panel be allowed in OTC drug advertising. The comment pointed out that on February 11, 1981, the Federal Trade Commission (FTC) declined to propose a rule which would require that

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 Cholinol 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.

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 it 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).

The comments concluded that the agency should affirm the safety of quaternary ammonium compounds and reclassify these ingredients in Category I for use as preservatives in OTC vaginal drug products.

Although the comments requested that the agency affirm the safety of quaternary ammonium compounds for use as preservatives and reclassify them as Category I, the agency points out that the OTC drug review is primarily a review of active ingredients, not inactive ingredients. However, because the purpose of the OTC drug review process is to determine the safety and effectiveness of OTC drugs, the OTC advisory review panels occasionally made recommendations with respect to inactive ingredients. These recommendations were made to call attention to those inactive ingredients that could potentially interfere with the safety and effectiveness of the product.

In the case of the quaternary ammonium compounds, the agency agrees with the comments' reasoning that the reports cited by the Panel cannot be used to conclude that the use of these compounds as preservatives in OTC vaginal contraceptive drug products may present a health hazard to normal individuals.

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. Information regarding the appropriateness of ingredients used in the product as preservatives should be included in the application.

References

1. Forkner, Jr., C. E., "Pseudomonas Aeruginosa Infections," in "Modern Medical Monographs," vol. 22, edited by I. S. Wright and R. H. Orr, Gruen and Stratton, New York, p. 71, 1960.
2. Gardner, H. L. and R. H. Kaufman, "Nonvenereal Bacterial Vulvovaginitides," in "Benign Diseases of the Vulva and Vagina," 2d ed., G. K. Hall Medical Publishers, Boston, p. 306, 1981.
3. Ridley, C. M., "The Vulva," in "Major Problems in Dermatology," vol. 5, edited by A. Rook, W. B. Saunders Co., Philadelphia, p. 99, 1975.
4. Mead, P. B. and D. W. Gump, "Antibiotic Therapy in Obstetrics and Gynecology," in "Clinical Obstetrics and Gynecology," vol. 19, No. 1, edited by H. J. Osofsky and G. Schaefer, Harper and Row, Hagerstown, MD, p. 114, 1976.

6. Several comments disagreed with the Panel's recommendations that inactive ingredients and the quantity of the ingredient be listed in the labeling of OTC vaginal contraceptive drug products. The comments argued that a

list of inactive ingredients would be meaningless to all but a few consumers and that such a list might overemphasize the importance of the inactive ingredients; obscure more meaningful information such as warnings, directions for use, and the name and quantity of the active ingredients; and be more confusing than helpful. The comments also stated that if the quantity of the inactive ingredients had to be listed there would be an additional problem and expense of changing the labels whenever the quantity of an inactive ingredient is changed.

The act does not require the identification of all inactive ingredients in the labeling of OTC drug products. Section 502(e) of the act (21 U.S.C. 352(e)) does require disclosure of active ingredients and of certain ingredients, whether included as active or inactive components in a product. Although the act does not require the disclosure of all inactive ingredients in the labeling of OTC drug products, the agency agrees with the Panel that listing of inactive ingredients in OTC drug product labeling would be useful information for some consumers. Consumers with known allergies or intolerances to certain ingredients would then be able to identify substances that they may wish to avoid.

The Nonprescription Drug Manufacturers Association (formerly known as The Proprietary Association), the trade association that represents approximately 85 OTC drug manufacturers who reportedly market between 90 and 95 percent of the volume of all OTC drug products sold in the United States, has established guidelines (Ref. 1) for its member companies to list voluntarily inactive ingredients in the labeling of OTC drug products. Under another voluntary program begun in 1974, the member companies of the Association have been including the quantities of active ingredients on OTC drug labels. The agency is not at this time proposing to require the listing of inactive ingredients in OTC drug product labeling. However, the agency commends these voluntary efforts and urges all other OTC drug manufacturers to similarly label their products.

Reference

1. "Guidelines for Disclosure of Inactive Ingredients in OTC Medicines," The Proprietary Association, Washington, July 12, 1984, in OTC Vol. 11ATFM.
7. One comment urged that the label of OTC vaginal contraceptive drug products contain a list of all active ingredients, arguing that consumers

have a right to an informed choice when buying such products.

As discussed in section I.A., comment 6 of this document, listing of active ingredients is required for all drug products under section 502(e)(1) of the act (21 U.S.C. 352(e)(1)).

B. Comments on OTC Vaginal Contraceptive Active Ingredients

8. Three comments supported the Panel's Category I classification of menfegol and disagreed with the agency's conclusion that menfegol is a new drug because it is a new molecular entity, never before marketed as a drug in the United States. The comments stated that a lack of United States' marketing experience does not preclude a drug from being considered generally recognized as safe and effective nor require a drug to be considered a new drug. One comment argued that data on the marketing of vaginal contraceptive drug products in foreign countries can be equated to marketing in this country because the mode of action of these products is based on the spermicidal activity of an ingredient in the vagina and not on the medical problems, diets, customs, and environments of other countries. The comment urged FDA to reconsider its decision to refuse to recognize data on the marketing of a product outside the United States regardless of the ingredient, type of product, or its mode of action. Another comment added that the act defines a new drug as any drug not generally recognized as safe and effective among experts, whereas menfegol was so recognized by a panel of experts.

The Panel's Category I classification of menfegol was based on its review of safety and effectiveness data. The Panel's recommendation did not address the issue whether menfegol meets the statutory requirement concerning use of a drug. Menfegol was determined to be a new drug within the meaning of section 201(p)(2) of the act (21 U.S.C. 321(p)(2)), which defines a new drug as: * * * "any drug * * * that * * * has become so recognized, but which has not * * * been used to a material extent or for a material time under such conditions." The agency's longstanding interpretation of section 201(p)(2) of the act has been that marketing outside the United States cannot fulfill this independent statutory requirement of use to a "material extent" and for a "material time." Currently, based on several petitions to another OTC drug review rulemaking (Refs. 1, 2, and 3), the agency is reevaluating this interpretation of the act. (See section II.C., comment 34 of this document, in the tentative final

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

method of administration, of the potential hazard of mercury to offspring when the drug is systemically absorbed by the mother. Therefore, because of the possibility that mercury-containing compounds which can be metabolized to inorganic mercury may pose a risk to fetuses and nursing infants, the agency concurs with the Panel that such compounds are unsafe for use in vaginal contraceptive drug products.

References

1. Al-Jobori, I. M., "Mercury Levels in Females Exposed to Phenylmercuric Acetate," Master Thesis, University of Baghdad, pp. 10-110, 1975, in OTC Vol. 110058.
2. Fukuchi, H. et al., "The Absorption of Organomercurial Compounds from the Vaginal Route of the Rabbits. I. Comparative Study on the Effect of Suppository Vehicles on the Absorption of Omega-Ethylmercurithio-*n*-undecanoic Acid, Phenylmercuric Acetate and Ethylmercuric Chloride after Single Dose Administration," *Chemical and Pharmaceutical Bulletin*, 12:540-548, 1964.
3. Fukuchi, H. et al., "The Absorption of Organomercurial Compounds from the Vaginal Route of the Rabbits. II. Distribution and Excretion of Omega-Ethylmercurithio-*n*-undecanoic Acid and Phenylmercuric Acetate," *Chemical and Pharmaceutical Bulletin*, 12:548-557, 1964.
4. Murkami, U., Y. Kameyama, and T. Kato, "Effects of a Vaginally Applied Contraceptive with Phenylmercuric Acetate Upon Developing Embryos and Their Mother Animals," *Annual Report of the Research Institute of Environmental Medicine, Nagoya University*, pp. 88-99, 1955.

C. Comments on Labeling of OTC Vaginal Contraceptive Drug Products

Although the proposed rule included in this document does not include monograph conditions, the responses to the following comments should be considered as FDA's tentative position on the labeling of OTC vaginal contraceptive drug products. FDA has considered the Panel's labeling recommendations and the following comments in developing the agency's position on labeling for OTC vaginal contraceptive drug products. This document will serve as the basis for the development of guidelines for the content and format of the labeling of OTC vaginal contraceptive drug products similar to those currently available for oral contraceptive drug products. (See 54 FR 22585 and 22624, May 25, 1989.) The agency intends to complete these guidelines for OTC vaginal contraceptive drug products after the comments to this proposal are evaluated.

11. One comment noted its continuing position that FDA lacks statutory authority to prescribe exclusive lists of

terms from which indications for use for OTC drug products must be drawn and to prohibit labeling terminology which is truthful, accurate, not misleading, and intelligible to the consumer. A second comment stated that it would be inappropriate to restrict manufacturers to the specific wording recommended by the Panel for package insert statements.

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either: (1) The specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g). There will be no monograph for OTC vaginal contraceptive drug products, and all labeling for these products will be approved via applications. Therefore, the comments are moot with respect to this current rulemaking.

12. Several comments agreed with the Panel that quantitative claims of effectiveness should not be required in the labeling of OTC vaginal contraceptive drug products because of the difficulty in conducting the studies that would be necessary to substantiate such claims. The size of the sample that would be needed, the variations in subject motivation, varying methods of product use, and the lack of an adequate representative population of American women were specifically cited in the comments as factors that would make such studies difficult to conduct. The comments also pointed out that the consensus of the participants in the symposium on vaginal contraception,

held by the Panel on April 28 and 29, 1978, was that quantitative effectiveness claims should not be required.

A number of comments indicated that quantitative effectiveness claims should not be required, but that manufacturers should be permitted to use these claims at their own discretion. Several of these comments also objected to the Panel's recommendation that such claims be permitted in labeling only after prior approval by FDA through the new drug procedures.

Two comments questioned whether the quantitative effectiveness claims could be written in a manner that would be understood by consumers. Providing consumers with actual numbers relevant to method effectiveness, use effectiveness, and extended-use effectiveness was specifically cited as a potential source of confusion.

One comment pointed out that the patient labeling of oral contraceptives is required to contain a discussion comparing the effectiveness of different contraceptive methods and, therefore, it would be inconsistent for FDA to conclude that there are insufficient data available to support the validity of comparative effectiveness claims in the labeling of OTC vaginal contraceptive drug products.

The agency believes that consumers should be provided with the most informative labeling available when choosing a contraceptive drug product. After reviewing the complete administrative record for this rulemaking, including the record of the Panel's symposium on vaginal contraception and the comments submitted to the Panel's report on this issue, the agency concludes that the most informative labeling for users of vaginal contraceptive drug products is information on the relative effectiveness of the various methods of contraception. The agency is currently working to create a consistent and understandable presentation of this important information to include in the labeling of all marketed contraceptive products, drugs, and devices.

13. Two comments objected to the Panel's labeling recommendations for the outer and primary containers of OTC vaginal contraceptive drug products (45 FR 82014 at 82031). The comments questioned the propriety of the Panel in specifying the order of appearance and location of the various required statements. The comments also objected to the number of required labeling statements. One comment stated that listing of all the recommended labeling statements would require the use of small illegible typeface. The second comment noted that if space were

limited, listing of all items in the recommended order would preempt those labeling statements required by law. The second comment also requested that the general warning statements, "Keep this and all drugs out of the reach of children" and "In case of accidental ingestion call a Poison Control Center, emergency medical facility, or a doctor," not be included in the Panel's priority system of labeling. The comment pointed out that warnings similar to these are already required by 21 CFR 330.1(g), which only requires that these warnings appear somewhere in the labeling. The comment stated that there is no basis for special treatment of these warnings for OTC vaginal contraceptive drug products.

Existing regulations (21 CFR 201.15 and 21 CFR part 201, subpart C—Labeling Requirements for Over-the-Counter Drugs) adequately address the placement and prominence of labeling statements. While there may be certain selected situations where it is necessary to alter these general requirements, the agency is unaware of any data demonstrating that it is necessary in the case of OTC vaginal contraceptive drug products. In addition, the labeling statements required by § 330.1(g) are similar to those recommended by the Panel and the agency considers the labeling requirements in § 330.1(g) to be appropriate for OTC vaginal contraceptive drug products.

14. One comment suggested that the accidental ingestion warning recommended by the Panel be changed from "In case of accidental ingestion, call a Poison Control Center, emergency medical facility, or a doctor immediately" to "In case of accidental ingestion of large amounts by children, call a Poison Control Center or emergency medical facility, or call a doctor." The comment contended that because of the well-established safety of OTC vaginal contraceptive drug products the Panel's recommended warning is unnecessarily alarming to adult users.

The agency does not believe that the Panel or the comment have presented sufficient data or information to warrant a change from the accidental ingestion warning required by § 330.1(g) or § 369.9 for all OTC drug products.

15. One comment agreed with the Panel that the labeling of an OTC contraceptive drug product should contain an expiration date and information on the product's appropriate storage condition.

To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, existing FDA regulations at 21

CFR 211.137 require an expiration date for the product, except for OTC drug products for human use whose labeling does not bear dosage limitations and which are stable for at least 3 years as supported by appropriate stability data. In addition, the expiration date is also required to relate to any storage conditions stated on the labeling. 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. Information relating to dosage limitations, stability conditions, and storage conditions should be included in the application.

16. Three comments agreed with the Panel that the labeling of OTC vaginal contraceptive drug products should contain precise directions that can be easily understood by the average consumer. One of these comments added that diagrams on proper use of the contraceptive might also be useful. The agency agrees that vaginal contraceptives should contain precise directions that are understandable to consumers, including diagrammed instructions, as appropriate, to show the proper method of application.

17. One comment suggested that the Panel's recommended directions statement in § 351.56(a)(3), which reads, "If this product is used together with another contraceptive method, there will probably be better protection against pregnancy," be modified to include examples of various contraceptive methods, such as a diaphragm, condom, or intrauterine device.

As discussed in section I. C., comment 12 of this document, the agency believes that the labeling of OTC vaginal contraceptive drug products should contain a summary of the effectiveness of the various methods of contraception. In light of this, the agency considers the modification recommended by the comment to be unnecessary.

18. One comment stated that if the indication recommended by the Panel in § 351.56(b)(5), which reads, "Extra protection for women who forget to take one or more contraceptive pills," is adopted, the labeling of the product should also refer the user to the directions for use of the oral contraceptive. The comment reasoned that a woman who has missed more than two consecutive pills should discontinue taking them, whereas the use of the word "extra" implies that the pills should be continued. As an alternative to referring the user to the oral contraceptive's directions for use,

the comment suggested revising the statement to read "Extra protection for women who forget to take one or two contraceptive pills."

The comment added that the indication in recommended § 351.56(b)(8), which reads, "Effective contraceptive alone or in the event the contraceptive pill is forgotten," is more acceptable than the one in § 351.56(b)(5), but it appears to imply that vaginal and oral contraceptives provide equivalent protection. The comment recommended that both statements either be modified or deleted.

The agency believes that information regarding what to do when a contraceptive pill is forgotten is more appropriate for inclusion in the labeling of oral contraceptives. Such information is required to be included in the patient labeling of oral contraceptives. Therefore, the agency does not believe that this type of information is necessary for inclusion in the labeling for OTC vaginal contraceptive drug products.

19. Two comments urged deletion of the statement recommended by the Panel in § 351.56(a)(5), which reads, "If douching is desired, always wait at least 6 hours after intercourse before douching." The comments claimed that there are no data or information in the scientific literature or from common usage demonstrating the need for such labeling. One of these comments specifically argued that the only supporting reference cited by the Panel (Ref. 1) discusses the persistence of sperm in the cervix and vagina following intercourse but does not express any concern about douching following the use of a vaginal spermicide. The comment added that this reference actually indicates that douching was "associated with reductions in proportions of smears containing spermatozoa." Both comments also specifically noted that the Panel admitted that there are no data establishing the optimum time interval between use of a spermicide and douching.

Although the comments are correct that no data are available concerning the optimum time interval between intercourse and douching when using a vaginal spermicide product, it is generally accepted that douching too soon after intercourse could likely interfere with a spermicide by diluting it or removing it from the vagina. Therefore, the agency believes that a statement regarding the time interval between intercourse and douching would provide useful information to the consumer. The Panel stated that it is

generally accepted opinion that when vaginal contraceptives are used as the primary method of birth control, douching should be delayed for at least 6 hours after coitus (45 FR 82014 at 82030). The agency concurs.

Reference

1. Silverman, E. M. and A. G. Silverman, "Persistence of Spermatozoa in the Lower Genital Tracts of Women," *Journal of the American Medical Association*, 240:1875-1877, 1978.

20. One comment suggested that the labeling of OTC vaginal contraceptive drug products include a warning specifying possible adverse allergic reactions such as itching and burning in the vaginal area and in the penile area. The comment also recommended that the warning advise consumers to discontinue use if these symptoms occur.

The agency agrees with the comment that consumers should be warned about possible allergic reactions such as burning and itching that may occur when using vaginal contraceptive drug products. The agency also agrees that the warning should advise consumers to discontinue use if these symptoms should occur. Furthermore, if the irritation persists after use has been discontinued, it could indicate a problem other than an allergic reaction to the product, so that a physician should be contacted. The agency believes the following warning is appropriate for inclusion in the labeling of OTC vaginal contraceptive drug products: "If you or your partner develops irritation, such as burning or itching in the genital area, stop using this product. If irritation continues, contact your physician."

21. One comment stated that the Category II labeling claims recommended by the Panel (45 FR 82014 at 82040) are not proper subject matter for the OTC drug review and should not be classified. The comment argued that these claims are not indications for use, but rather are statements of fact which are unrelated to the safety or effectiveness of a vaginal contraceptive drug. The comment added that the claims cannot legally be prohibited if truthful and should not be placed in Category II without a finding that they are inherently false or misleading.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. One aspect of the program is to develop standards for certain parts of the labeling of OTC drug products. Because of time, resources, and other

considerations, FDA has not set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs address only those labeling items that are related in a significant way to the safe and effective use of covered products by lay persons. These labeling items are the product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

Based on the discussion above, the agency tentatively concludes that the Panel's entire list of Category II labeling claims as well as certain descriptive terms included in the Panel's recommended list of other allowable statements (recommended § 351.56(c)), i.e., safe, effective, powerful, highly) would be outside the scope of a monograph, if one were being established. Because all OTC vaginal contraceptive drug products will require an approved application for marketing, such claims can be evaluated, during the approval process, on a product-by-product basis for compliance with section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading.

22. After reviewing the Panel's recommended labeling, the agency has tentatively determined that the following additional changes in the Panel's recommendations are warranted. Although the Panel recommended "spermicide" as an indication, the agency believes that it would be more appropriate as an optional statement of identity. In addition, although the Panel recommended a number of indications statements, the agency believes that the indication "For the prevention of pregnancy" is sufficient to convey to consumers the intended use of the product. The agency has also tentatively determined that the statement "If your physician has told you that you should not become pregnant, ask your physician if you can use this product for contraception," should be a warning instead of a direction statement.

D. Comments on Combinations

23. One comment objected to the Panel's statement at 45 FR 82014 at 82026 that if two or more Category I vaginal contraceptive active ingredients are combined, the specific ingredients as well as the combination product must be subjected to laboratory and clinical testing according to the recommended testing guidelines. The comment argued that no useful purpose is served or information gained by clinical testing of single Category I ingredients and that

such testing is not required under FDA's OTC combination policy.

As discussed in section I. D., comment 25 of this document, testing guidelines for conditions that industry wishes to upgrade to monograph status will not be included. However, criteria for establishing combinations of OTC drugs as generally recognized as safe and effective are provided in 21 CFR 330.10(a)(4)(iv). Guidance on OTC combination drug products has also been provided in the agency's General Guidelines for OTC Drug Combination Products (Ref. 1). Thus, two or more safe and effective OTC vaginal contraceptive active ingredients may be combined provided the final formulation of the product meets the combination policy in all respects. The Panel did not include any contraceptive combinations in its monograph because the data were insufficient for any of the combinations that were reviewed to be generally recognized as safe and effective. The agency concurs with the Panel's decision. Furthermore, as noted in section I. A., comment 3 of this document, the agency is proposing to require that all combination or single-ingredient OTC vaginal contraceptive drug products be subject to approved applications prior to marketing.

Reference

1. Food and Drug Administration, "General Guidelines for OTC Drug Combination Products, September 1978," Docket No. 78D-0322, Dockets Management Branch.

24. One comment stated that the data on which the Panel based its Category II classification of the combinations: (1) Phenylmercuric acetate and boric acid; (2) phenylmercuric acetate, boric acid, and nonoxynol 9; and (3) phenylmercuric acetate, octoxynol 9, and sodium borate show that these combinations were so classified because of "hazards" associated with the use of phenylmercuric acetate rather than with the use of boric acid or sodium borate (Refs. 1 through 6). The comment added that it appears that the use of borates in vaginal contraceptives is for "pH control." The comment also noted that boron compounds were listed as inactive ingredients in the Panel's report (45 FR 82014 at 82042) and were not placed in Category II, as were mercury-containing compounds.

The agency agrees that boron compounds should not have been included as active ingredients in the listing of Category II combinations. The submissions of data on OTC vaginal contraceptive drug products containing boron compounds (Refs. 1 through 6) indicate that the boron compounds are included in these products as

pharmaceutical necessities or preservatives and not as active ingredients.

References

1. OTC Vol. 110004.
2. OTC Vol. 110005.
3. OTC Vol. 110006.
4. OTC Vol. 110017.
5. OTC Vol. 110018.
6. OTC Vol. 110021.

E. Comments on Testing Guidelines

25. Numerous comments criticized the safety and effectiveness testing guidelines recommended by the Panel to upgrade a vaginal contraceptive ingredient from Category III to Category I (45 FR 82014 at 82020 and 82043). Generally, the comments stated that the guidelines are unclear, needlessly specific, unnecessary, or based on unsound logic. Some of the comments subsequently proposed using alternative testing methods, while others urged elimination of certain methods.

The agency has not addressed specific testing guidelines in this document. In revising the OTC drug review procedures relating to Category III, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency advised that tentative final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. However, in view of the agency's determination that all OTC vaginal contraceptive drug products should be the subject of approved applications prior to marketing, interested parties can use that forum to meet with the agency to discuss appropriate testing procedures, and the comments do not need to be addressed in this document. Also, elsewhere in this issue of the **Federal Register**, the agency is announcing the availability of a guidance document that is intended to help manufacturers of vaginal contraceptive drug products develop data in support of new drug applications.

II. The Agency's Tentative Conclusions on OTC Vaginal Contraceptive Drug Products

Dodecaethyleneglycol monolaurate, laureth 10S, methoxypolyoxyethyleneglycol 550 laurate, nonoxynol 9, octoxynol 9, phenylmercuric acetate, and phenylmercuric nitrate have been present as ingredients in OTC vaginal contraceptive drug products. Based on the available evidence, the agency has

determined that clinical studies in humans are necessary to establish the effectiveness of final formulations of vaginal contraceptive drug products and, therefore, any drug product that is labeled, represented, or promoted for use as a vaginal contraceptive is regarded as a new drug within the meaning of section 201(p) of the act (21 U.S.C. 321(p)), for which an approved application under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 of the regulations is required for marketing. In the absence of an approved application, such a product also would be misbranded under section 502 of the act (21 U.S.C. 352).

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order, and thus, is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. There are a limited number of OTC vaginal contraceptive products that are not marketed for use with a condom, diaphragm, or contraceptive cervical cap. Accordingly, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC vaginal contraceptive drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC vaginal contraceptive drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on vaginal contraceptive

drug products, a period of 120 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

In the **Federal Register** of December 12, 1980 (45 FR 82014 at 82047), the agency proposed that the monograph for OTC vaginal contraceptive drug products be included in subpart A of new part 351 of Title 21 of the Code of Federal Regulations. In the **Federal Register** of October 13, 1983 (48 FR 46694 at 46727), the agency proposed that a monograph for OTC vaginal drug products be included in subpart B of part 351. The current proposal supersedes subpart A of part 351 and, if finalized as proposed, Part 310—New Drugs would be amended to include OTC vaginal contraceptive drug products.

Interested persons may, on or before June 5, 1995 submit to the Dockets Management Branch written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before June 5, 1995. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before February 5, 1996, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before April 3, 1996. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations

for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final rule for OTC vaginal contraceptive drug products, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on April 3, 1996. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final rule for OTC vaginal contraceptive drug products is published in the **Federal Register**, unless the Commissioner finds that good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner

of Food and Drugs, it is proposed that 21 CFR part 310 be amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Section 310.535 is added to subpart E to read as follows:

§ 310.535 Drug products containing active ingredients offered over-the-counter (OTC) for human use as a vaginal contraceptive.

(a) Dodecaethyleneglycol monolaurate, laureth 10S, methoxypolyoxyethyleneglycol 550 laurate, nonoxynol 9, octoxynol 9, phenylmercuric acetate, and phenylmercuric nitrate have been present as ingredients in OTC vaginal contraceptive drug products. The evidence currently available shows that clinical studies in humans are necessary to establish the effectiveness of nonoxynol 9 and octoxynol 9 in final formulation for use in OTC vaginal contraceptive drug products. There are inadequate data to establish the safety and effectiveness of any other ingredients offered for use as OTC vaginal contraceptive drug products.

(b) Any drug product that is labeled, represented, or promoted for OTC use as a vaginal contraceptive is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use as a vaginal contraceptive is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After (date 12 months after date of publication in the **Federal Register** of the final rule), any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

Dated: January 10, 1995.

William K. Hubbard,

Interim Deputy Commissioner for Policy.

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