DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 351

[Docket No. 82N–0291]

RIN 0905–AA06

Vaginal Drug Products for Over-the-Counter Human Use; Withdrawal of Advance Notice of Proposed Rulemaking

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of withdrawal of advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice to withdraw the advance notice of proposed rulemaking of October 13, 1983 (48 FR 46694) that would have established conditions under which over-the-counter (OTC) vaginal drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of withdrawal after considering the report and recommendations of the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products (the Vaginal Panel) and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This action is being taken in part because the agency has determined that some of the recommended labeling indications relate to cosmetic claims and not drug claims. In addition, recommended labeling indications and ingredients used for minor irritation, itching, or soreness are not unique to the vaginal area and are already being considered in other OTC drug rulemakings (e.g., antifungal, antimicrobial, and external analgesic). Therefore, those ingredients and indications will be considered in those other rulemakings, as appropriate.

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 October 13, 1983 (48 FR 46694), 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 drug products, together with the recommendations of the Vaginal Panel, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by January 11, 1984. Reply comments in response to comments filed in the initial comment period could be submitted by March 19, 1984.

In accordance with § 330.10(a)(10), the data and information considered by the Vaginal Panel were put on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857, after deletion of a small amount of trade secret information.

In this notice, FDA states for the first time its position on the establishment of a monograph for OTC vaginal drug products based on the Vaginal Panel's conclusions and recommendations on OTC vaginal drug products, the comments received, and the agency's independent evaluation of the Vaginal Panel's report. In the preamble to the advance notice of proposed rulemaking for OTC vaginal drug products (48 FR 46694 at 46695), the agency expressed its concerns about: (1) The ability of a woman to recognize the nature or cause of the symptom(s) of vaginal itching, irritation, or soreness in order to determine which kind of drug product to select to treat the condition, and (2) whether 1 to 2 weeks of self-medicating with an OTC drug product may pose an unacceptable delay in seeking professional attention if the symptom(s) of itching, irritation, or soreness are due to *N. gonorrhoea*, *Trichomonas*, *Candida*, or other organisms that will not be eradicated by topical therapy with nonantimicrobial OTC drug products. At that time, no final agency decisions were made regarding the Vaginal Panel's recommendations or the above stated concerns. The agency invited specific comments on these issues.

In response to the advance notice of proposed rulemaking, four drug manufacturers, two trade associations, nine consumers, four medical associations, two pharmaceutical associations, three surgeons general, one poison control center, three consumer groups, two community health associations, and three practicing medical groups submitted comments. Copies of the comments received are on public display in the Dockets Management Branch (address above).

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 under docket number 82N–0291.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments

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 to 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, 696–698 (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. One comment disagreed with the Vaginal Panel's statement that "If an active ingredient is present in a therapeutic concentration, the product is a drug, even if that product does not claim to produce the effect which will result from the action of the therapeutically effective ingredient * * *," (48 FR 46694 at 46701). The comment argued that drug status of a product is determined only by its intended use, not by the inclusion of certain ingredients, and the presence of a certain ingredient in a product offered solely as a cosmetic does not make the product a drug. The comment stated that FDA's policy concerning drug versus cosmetic status has been stated in many documents, including the procedural regulations governing the OTC drug review (37 FR 9464 to 9475), and that the Vaginal Panel did not properly apply this policy. The comment added that there is no justification to apply a different principle to this rulemaking for vaginal drug products. The comment requested that the term "drug product" be used throughout the regulation wherever products are specifically identified to emphasize the difference between

cosmetic and drug products, e.g., vaginal douche drug products.

The Federal Food, Drug, and Cosmetic Act (the act) provides the statutory definitions that differentiate a drug from a cosmetic. A "drug" is defined in part as an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "intended to affect the structure or any function of the body * * *." (See 21 U.S.C. 321(g)(1)(B) and (C).) A "cosmetic," on the other hand, is defined as an article intended to be "* * * applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, * * *." (See 21 U.S.C. 321(i)(1).) Therefore, the agency agrees with the comment that the intended use of a product is the primary determining factor as to whether a product is a drug, a cosmetic, or both. This intended use may be inferred from the product's labeling, promotional material, advertising, and any other relevant factor. See, e.g., *National Nutritional Foods Ass'n* v. *Mathews*, 557 F.2d 325, 334 (2d Cir. 1977).

The type and amount of ingredient(s) present in a product, even if that product does not make explicit drug claims, must be considered in determining its regulatory status. For example, the mere presence of a pharmacologically active ingredient could make a product a drug even in the absence of explicit drug claims. In these cases, the intended use would be implied because of the known or recognized drug effects of the ingredient (e.g., fluoride in a dentifrice).

The agency does not believe that it is necessary to use the term "drug product" throughout OTC drug monographs to distinguish between drug and cosmetic products because the labeling in final monographs applies only to products that fall within the statutory definition of a drug, and does not apply to cosmetic products. However, if a product is intended for both drug and cosmetic uses, e.g., cleansing and treating a disease condition, it must conform to the requirements of the applicable final monograph(s) for OTC drug products, as well as bear appropriate labeling for cosmetic use in conformity with section 602 of the act (21 U.S.C. 362) and the provisions of parts 701 and 740 (21 CFR parts 701 and 740).

3. In response to the agency's specific request for comment on the appropriateness of OTC drug products for treating the symptoms of itching, irritation, and soreness in or around the vagina (48 FR 46694 at 46695), several comments stated that treating these symptoms with OTC drug products is appropriate and rational therapy because women can readily recognize these symptoms and the benefits to be derived from the use of these drugs far outweigh any risks associated with their OTC availability. A number of comments stated that there is no valid medical basis to conclude, as was suggested by FDA in the preamble of the advance notice of proposed rulemaking for OTC topical antifungal drug products (47 FR 12480, March 23, 1982), that a serious health hazard could result from self-treating the symptom of external feminine itching. The comments contended that the likelihood of masking more serious gynecological disorders such as gonorrhea or trichomoniasis, or masking a more serious condition such as diabetes, was highly unlikely provided the labeling of the products advises consumers to consult a physician if symptoms worsen or persist for longer than 1 week. To further support its contention that serious complications or delays in proper medical diagnosis are not likely to occur if the symptoms of external vaginal itching are treated with OTC drug products, one comment cited the safe marketing experience of OTC hydrocortisone products labeled with an indication that included "external genital (feminine) itching." The comment stated that none of the possible problems projected, i.e., the masking of serious disease, the inability to self-diagnose, and the presumed side effects of the drug, had materialized since the marketing of OTC hydrocortisone began in 1979. Several comments also argued that external vaginal itching and irritation are not necessarily caused by infection, but can often be caused by irritating clothing, sensitivities to cosmetics, inappropriate hygiene, or other external factors.

In contrast, several comments stated that women should never self-treat the symptoms of vaginal itching, irritation, or soreness because they are not capable of self-diagnosis (i.e., specifically determining an appropriate drug product to use based on various vaginal symptoms) and should always be evaluated by a physician. The comments added that self-treatment could unreasonably delay a proper diagnosis and could even complicate it.

The agency notes that all of the products submitted to the Vaginal Panel were intended for intravaginal use and with the exception of vaginal contraceptives, the use of these OTC vaginal products, e.g., douches, suppositories, had been for the most part limited to cosmetic purposes, e.g., cleansing, deodorizing, mechanical flushing. Thus, the agency concludes that with the exception of indications relating to minor itching, irritation, and soreness, all other recommended vaginal monograph indications listed in the Vaginal Panel's report (48 FR 46694 at 46729) are cosmetic in nature or outside the scope of the OTC drug review, e.g., "Astringent," "Removes vaginal discharge," "Removes vaginal secretions," "Mild detergent action." Such indications for vaginal products refer to a product's transitory cleansing effects rather than to claimed therapeutic effects. (See drug/cosmetic discussion in comment 2.) Therefore, except for some "astringent" claims (see comment 13), the agency considers these indications outside the scope of the OTC drug review. The agency has no objection to the continued availability of vaginal products bearing labeling claims related to cleansing for cosmetic purposes, but does not believe that these cosmetic products should be labeled or used for therapeutic purposes except under the advice and supervision of a physician. As a result of this withdrawal notice, manufacturers may need to relabel or reformulate some products now or in the future. However, if reformulation and/or relabeling are necessary, the cost will be minimal because reformulation and relabeling will be required, in any event, under other appropriate rulemakings.

The agency believes that consumers should have access to OTC drug products to provide temporary relief of vaginal itching and irritation. The agency recognizes that the safe marketing experience of hydrocortisone, which has been available OTC since 1979 with an indication that includes use on itchy anal and genital areas, provides support that serious complications or delays in proper medical diagnosis are not likely to occur if the symptom of vaginal itching is treated with OTC drug products. Therefore, based on the available data and information, the agency believes that the relief of vaginal symptoms such as itching and irritation is an acceptable labeling claim for certain OTC drug products.

As stated above, all of the products submitted to the Vaginal Panel were intended for intravaginal use and concerns arose about self-diagnosis, selection of an appropriate drug product, and self-treatment of intravaginal disorders. The Fertility and Maternal Health Drugs Advisory Committee (the Committee), in a meeting held June 14 and 15, 1990, discussed the proposal that vaginal fungicides be sold OTC for the treatment of yeast (*Candida*) infections. Although

a mechanism for initial self-diagnosis was not considered, the Committee believed that consumers could safely and adequately recognize and treat subsequent intravaginal yeast infections after an initial diagnosis had been made by a physician and recommended that vaginal antifungal drug products whose safety was well-established be made available OTC with appropriate labeling (Ref. 1). Based on the Committee's recommendations and other available data, the agency has determined that certain OTC drug products for intravaginal use to treat yeast infections or for the relief of minor irritation, itching, and soreness can be safely used OTC. However, as recommended above, the agency believes that antifungal or other drug product ingredients for OTC intravaginal use are appropriate only for those women who have previously been diagnosed by a physician as having had the condition for which these drug products are intended and are therefore able to subsequently recognize the symptoms of the condition. The agency intends to discuss proposed labeling and specific ingredients for OTC intravaginal use in an amendment to the final monograph for OTC antifungal drug products in a future issue of the **Federal Register.**

While a number of ingredients in OTC drug products could be used in and around the vagina to relieve symptoms such as itching, irritation, or soreness, the use of these ingredients is not specific or unique to the vaginal area; i.e., they could be used topically to relieve these same symptoms elsewhere on the body. For example, antifungals, antipruritics, skin protectants, and astringents all have potential for relieving symptoms occurring externally around the vagina as well as on other parts of the body. It should be noted, however, that certain drug product classes, e.g., antifungals, may be capable of relieving itching and irritation by means of killing the cause of the itch (e.g., yeast/fungus). These products would not be expected to be routinely effective in treating "itch" due to other causes, e.g., poison ivy, eczema, insect bites, etc.

Also, in other OTC drug rulemakings, the agency has included, where appropriate, the various conditions for which an ingredient is considered generally recognized as safe and effective for OTC use in one monograph. (See, for example, the discussion on hydrocortisone for use in psoriasis (51 FR 27346 at 27360) and the discussion menstrual claims for internal gesics (53 FR 46204 at 46209).) fore, for those ingredients that are fe and effective for use in relieving conditions in and around the vagina, the agency believes it is more appropriate to include a vaginal claim in the applicable OTC drug monograph rather than to have a separate monograph for ingredients and claims related to vaginal use only. (See, for example, "external feminine itching" claims for hydrocortisone products included in the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5868).)

Therefore, based on the discussion above, the agency is withdrawing the advance notice of proposed rulemaking for OTC vaginal drug products, which indicated the intention to create new subpart B of proposed part 351. This withdrawal reflects the agency's intention regarding the language previously published for potential codification in part 351, but does not negate or reject the advisory panel's report. Specific vaginal claims for the various pharmacologic classes of ingredients will be considered in other appropriate monographs. Because the issues raised by the comments may significantly affect these other OTC drug rulemakings, the agency believes it is useful to respond to these issues in this document. These issues and the agency's response to them will also be discussed in other appropriate OTC drug rulemakings. Interested persons may, at that time, submit comments to the applicable rulemakings.

Reference

(1) Summary Minutes of the Fertility and Maternal Health Drugs Advisory Committee, dated June 14–15, 1990, in OTC Vol. 11BTFM.

4. Several comments supported the recommendations of the Advisory Review Panel on OTC Antimicrobial II Drug Products (the Antimicrobial II Panel) that proposed a prescription to OTC switch of certain topical antifungal drugs for treating external feminine itching associated with a yeast infection (47 FR 12480). These comments stressed that candidal (yeast) infections of the vagina are extremely common and recurrent and that women can recognize with reasonable certainty when they have a yeast infection, especially if they have had one before.

The agency is aware that all three OTC advisory review panels charged with reviewing products that could be used in or around the vagina concluded that vaginal infections could not be self-diagnosed or self-treated. The panels' conclusions are consistent with FDA policy that infections in general should not be self-diagnosed by consumers or self-treated with OTC drug products. The only exception to this general policy is the OTC use of topical antifungals for treating athlete's foot, jock itch, and ringworm. The Antimicrobial II Panel that reviewed topical antifungal drug products and FDA have determined that these infections are so common and recurrent that they are amenable to self-diagnosis and treatment. In addition, the Antimicrobial II Panel recommended that haloprogin, miconazole, and nystatin be switched from prescription to OTC status for external feminine itching associated with a yeast infection. The Antimicrobial II Panel did not recommend these ingredients for treatment of the infection itself, but believed that OTC availability of these ingredients would be beneficial in providing rapid symptomatic relief of itching. The issue of consumer diagnosis of recurrent infections after appropriate physician diagnosis of the initial infection was not discussed during any of the panels' consideration of this issue.

The Antimicrobial II Panel also recommended that haloprogin, miconazole, and nystatin be available OTC for the treatment of superficial skin infections caused by yeast (*Candida*) (47 FR 12480 at 12565) However, the agency concluded in the tentative final monograph for OTC antifungal drug products (54 FR 51136 at 51140) that no antifungal ingredient should be labeled for OTC use for the treatment of cutaneous candidiasis. However, the agency stated that cutaneous candidiasis claims for effective antifungal ingredients could appropriately be included in professional labeling. As stated in comment 3, in light of the recommendations of the Committee, the agency has reevaluated its position on the availability of antifungal drug products for OTC treatment of vaginal yeast (*Candida*) infections. The antifungal ingredients clotrimazole and miconazole nitrate, at specific concentrations, have been approved for OTC intravaginal use, for specific indications, under new drug applications (Refs. 1 and 2).

References

(1) Labeling from NDA 18–052 for Gyne-Lotrimin Vaginal Cream, in OTC Vol. 11BTFM, Docket No. 82N–0291, Dockets Management Branch.

(2) Labeling from NDA 17–450 for Monistat 7 Vaginal Cream, in OTC Vol. 11BTFM, Docket No. 82N–0291, Dockets Management Branch.

5. One comment disagreed with the Vaginal Panel's recommendation that ingredients classified as Category II for use in OTC vaginal drug products be removed automatically from vaginal

cosmetic products (48 FR 46694 at 46710). The comment stated that this action is unwarranted because the safety of cosmetic ingredients is assured by the manufacturers, who consider not only the scientific analyses done by the OTC advisory panels and FDA, but also additional published and unpublished data that may not have been reviewed by the panels. The comment also contended that the specific use of an ingredient in a cosmetic may differ from its use in a drug product.

The agency notes that the Vaginal Panel made this recommendation in discussing Category II combination vaginal drug products. The Vaginal Panel recommended to the agency that any Category II ingredient that causes a combination product to be placed in Category II for safety reasons be removed from products regardless of whether they are intended for use as a drug or a cosmetic because of concerns about protecting consumers from unsafe ingredients. While sharing the Vaginal Panel's concern, the agency agrees with the comment that automatic removal of Category II drug ingredients from cosmetic products is not warranted because other factors need to be considered. For example, while an ingredient may not be safe in one concentration for use as a drug, it may be acceptable for use at a lower concentration in a cosmetic product. However, the agency will look carefully at any ingredients that are present in cosmetic products when those ingredients have been found unsafe for use in OTC drug products. FDA is prepared to take appropriate regulatory action in preventing the use of ingredients in cosmetic products when a potential health hazard is known to exist with their continued use. (See 21 CFR part 700—subpart B.)

6. One comment stated that the Vaginal Panel "may have inappropriately suggested the need for effectiveness testing for vaginal drug product final formulations" (48 FR 46694 at 46724 and 46725). The comment stressed that the OTC drug review is intended to be an active ingredient review and that testing is not necessary for final formulations of these products.

In discussing testing guidelines for vaginal douche products, the Vaginal Panel simply stated that it did not require effectiveness testing for douches that make only cosmetic claims, e.g., "cleansing." However, the Vaginal Panel recommended that effectiveness testing should be required for those ingredients in vaginal douches that make drug claims, e.g., "relieving irritation."

As discussed in comment 3, the agency is withdrawing the advance notice of proposed rulemaking for OTC vaginal drug products and is referring consideration of specific claims and ingredients for use in and around the vagina to other appropriate OTC drug rulemakings. Any necessary final formulation testing will also be discussed in those rulemakings, e.g., ingredients used in vaginal antiseptic drug products.

B. Comments on Active Ingredients

7. Two comments objected to the Vaginal Panel's conclusion that data are insufficient to prove the safety of quaternary ammonium compounds (i.e., benzalkonium chloride, benzethonium chloride, and methylbenzethonium chloride) for vaginal use (48 FR 46694 at 46717). The comments stated that although the Vaginal Panel's concern was based on published literature reports where the use of these compounds was associated with infections caused by *Pseudomonas*, it was not scientifically sound to use these reports to conclude that a safety problem exists. The comments mentioned that the Vaginal 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 drug products presents a health hazard to normal individuals.

The comments cited several references (Refs. 1 through 7) to show that the Vaginal Panel's concerns with respect to vaginal contamination by *Pseudomonas* in the presence of quaternary ammonium compounds are not supported by the weight of scientific data. The comments added that extensive toxicological studies on these compounds have been published (Ref. 8). The comments requested the agency to affirm the safety of quaternary ammonium compounds and classify them as Category I for use in relieving minor irritations of the vagina.

Another comment stated that quaternary ammonium compounds historically have been included in vaginal products as preservatives and that these ingredients should be allowed to continue to be used for this purpose.

The agency agrees with the comments' reasoning that the reports cited by the Vaginal Panel about *Pseudomonas* infections are not adequate to conclude that the use of quaternary ammonium compounds in OTC vaginal drug products may present a health hazard to normal individuals. The agency has no objection to the continued use of quaternary ammonium compounds as preservatives in OTC drug and cosmetic products provided the products are manufactured in accordance with established procedures that assure the adequacy of preservative systems and microbial limits of products.

With respect to the use of quaternary ammonium compounds as active ingredients in OTC vaginal drug products for relieving symptoms of itching, irritation, or soreness, the Vaginal Panel stated that it was unaware of any data that demonstrated effectiveness for these uses (48 FR 46694 at 46718). The comments did not include any new data, and the agency is unaware of any such data.

As explained in comment 3, the agency has decided to consider specific vaginal claims for the various ingredients in other appropriate rulemakings. Quaternary ammonium compounds are included as Category I ingredients in the tentative final monograph for OTC first aid antiseptic drug products, published in the **Federal Register** of July 22, 1991 (56 FR 33644). Any comments or new data received regarding specific vaginal use of quaternary ammonium compounds will be considered by the agency in the rulemaking for OTC topical antimicrobial drug products.

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, pp. 71–73, 1960.

(2) Gardner, H. L., and R. H. Kaufman, "Nonvenereal Bacterial Vulvovaginitides," in "Benign Diseases of the Vulva and Vagina," C. V. Mosby Co., St. Louis, p. 212, 1969.

(3) Charles, D., "Major Problems in Obstetrics and Gynecology," W. D. Saunders Co., pp. 4–5, 1980.

(4) Pidieu, C. M., "The Vulva, Major Problems in Dermatology," vol. 5, edited by A. Rook, W. B. Saunders Co., Philadelphia, p. 99, 1979.

(5) Monif, G. R. F., "Infectious Disease in Obstetrics and Gynecology," 2d edition, Harper and Row, Hagerstown, MD, pp. 524–525, 1982.

(6) Mead, P. B., and D. W. Gump, "Antibiotic Therapy In Obstetrics and

Gynecology," in "Clinical Obstetrics and Gynecology," edited by H. J. Osofsky and G. Schaefer, Harper and Row, Hagerstown, MD, pp. 109–129, 1976.

(7) Gardner, A. et. al., "Long Term Multicenter Trial with Ta-Ro-Cap, A New Spermicidal Product," *Contraception*, 20:489–495, 1979.

(8) Finnegan, J. K., and J. B. Dienna, "Toxicity of Quaternaries," *Soap and Sanitary Chemicals*, February 1954.

8. One comment supported the Vaginal Panel's Category I classification of potassium sorbate (48 FR 46694 at 46704) and disagreed with the agency's conclusion that potassium sorbate is a new drug because it has not been marketed as a drug to a material extent and for a material time in the United States (48 FR 46694 at 46695). The comment stated that a product containing potassium sorbate had been marketed for over 2 years and that this ingredient is generally recognized as safe and effective for the treatment of minor vaginal itching and irritation and should be included as a monograph ingredient. The comment contended that potassium sorbate is safe because it was so recognized by the Vaginal Panel, and because of the lack of "any report of major side effects, adverse reaction or complaint" while 14 million units of a product containing this ingredient were sold for over 2 years before marketing was discontinued. The comment argued that potassium sorbate is effective because it was so recognized by the Vaginal Panel based on two adequate and well-controlled clinical studies (48 FR 46694 at 46704). The comment added that this ingredient has been historically used by physicians for treatment of vaginal itching and irritation, and that this professional use constitutes use "for a material time and to a material extent." The comment also argued that potassium sorbate is safer than povidone-iodine, which the Vaginal Panel recommended as a Category I ingredient for these uses. The comment concluded that potassium sorbate is not a new drug because of its historical use and because of its marketing history, and should be placed in Category I as a monograph ingredient.

In the preamble to the Vaginal Panel's report (48 FR 46694 at 46695), the agency stated its opinion as follows:

> The agency is not aware of the marketing of any drug product containing potassium sorbate as an active ingredient prior to adoption of the Panel's report, although at least one product has entered the marketplace since that time. Because potassium sorbate has not been marketed as a drug to a material extent and for a material time in the United States, the agency considers this ingredient to be a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)). It may not be marketed until FDA has approved a new drug application (NDA) for such use.

The agency has not at this time changed its position on potassium sorbate for the treatment of minor vaginal itching and irritation. However, issues about the agency's interpretations regarding marketing to a "material extent" and for a "material time" as threshold criteria for inclusion of an ingredient in the OTC drug review have been raised in a number of rulemakings. Citizen petitions (Refs. 1 and 2) have been filed requesting the agency to change its longstanding position on these threshold criteria, especially with regard to permitting foreign marketing to satisfy the material time and extent criteria. The agency intends to address the material time and extent issues in a consolidated response in a future issue of the **Federal Register**.

References

(1) Comments No. CP2, CP3, and CP4 Docket No. 78N–0038, Dockets Management Branch.

(2) Comment No. CP1, Docket No. 92P–0309, Dockets Management Branch.

9. One comment requested that Category I approval of povidone-iodine as an active ingredient for the relief of minor irritations of the vagina be extended to include a vaginal suppository as well as a douche dosage form. The comment stated that the absorption potential with a suppository dosage form should be no greater than with a vaginal douche, and that there is no basis for making a distinction between a suppository and a douche dosage form with respect to effectiveness.

In response to a comment comparing the relative safety of potassium sorbate to povidone-iodine (see comment 8), one comment contended that the safety and effectiveness questions raised by the other comment with respect to povidone-iodine were superficial and erroneous and were in disregard of the facts. The comment stated that over 1,000 published studies and over 30 years of experience demonstrate the safety and effectiveness of povidone-iodine and confirm its Category I status for vaginal use as a douche.

Povidone-iodine in various formulations for vaginal use, i.e., douche and gel, was originally reviewed under the FDA Drug Efficacy Study Implementation (DESI). The DESI panel concluded that povidone-iodine was effective as a douche, i.e., for cleansing purposes, and that povidone-iodine could offer some partial or temporary relief of itching and odor when infection was present. Only the douche formulation was deferred for consideration to the OTC drug review. In the **Federal Register** of October 13, 1983 (48 FR 46694 at 46705), the Vaginal Panel reviewed the povidone-iodine douche product (0.15 to 3 percent) and placed it in Category I for the relief of minor irritations of the vagina. The Vaginal Panel did not review povidone-iodine in a suppository dosage form because no data on this dosage form were submitted. However, the Vaginal Panel did consider the suppository dosage form for claims relating to relief of minor irritation, and reduction of number of pathogenic microorganisms, and stated that such claims must be substantiated by testing (48 FR 46694 at 46702). The safety and effectiveness of povidone-iodine for the relief of itching and minor irritation in and around the vagina will be discussed by the agency in the rulemaking for OTC topical antimicrobial drug products in a future issue of the **Federal Register**. (See also discussion in comment 17 regarding professional labeling claims.)

C. Comments on Labeling

10. One comment objected to the Vaginal Panel's recommendation that OTC drugs be labeled with the components of perfumes that are included in the products. The comment explained that fragrances and flavors are often made up of dozens of ingredients and that to list each of these individually would be a practical impossibility; furthermore, the composition of a perfume is a significant trade secret. The comment pointed out that this issue had been considered and rejected by Congress and FDA on several occasions over the past decade, and concluded that there was no reason whatsoever to change these previous decisions.

Because section 502(e) of the act (21 U.S.C. 352(e)) specifies the requirements for the labeling of active and inactive ingredients in drug products, there is no need to include such requirements in an OTC drug monograph. However, the agency notes that although section 502(e) of the act does not require the complete identification of all inactive ingredients in the labeling of OTC drugs, it does require the disclosure of certain ingredients, whether included as active or inactive components in a drug product. Although FDA does not require the inclusion of all the inactive ingredients in OTC drug product labeling, the agency urges manufacturers to list all inactive ingredients voluntarily as recommended by the Vaginal Panel. This information will enable the consumer with known

allergies or intolerance to certain ingredients to select products with increased confidence of safe use.

After the Vaginal Panel made its recommendations to FDA, the Nonprescription Drug Manufacturers Association (NDMA) (formerly the Proprietary Association), the trade association that represents OTC drug manufacturers who reportedly market 90 to 95 percent of all OTC drug products sold in the United States, implemented a program under which its member companies voluntarily list inactive ingredients in the labeling of OTC drug products under guidelines established by NDMA (Ref. 1). Although these guidelines do not specify the listing of each ingredient contained in the fragrance or perfume in the product, they do provide for such inactive ingredients as flavors and fragrances to be listed as "flavors" and "fragrances." Hence, the consumer with known allergies or intolerances to such inactive ingredients as flavors, fragrances, or perfumes would be generally aware of their inclusion in certain OTC drug products. The agency commends these voluntary efforts and urges all OTC drug manufacturers to label their products voluntarily in accordance with NDMA's guidelines.

Reference

(1) "Proprietary Association Adopts Voluntary Disclosure of Inactive Ingredients," news release, The Proprietary Association, Washington, May 14, 1984, copy included in OTC Vol. 11BTFM, Docket No. 82N–0291, Dockets Management Branch.

11. Several comments argued that FDA cannot legally and should not, as a matter of policy, prescribe exclusive lists of terms from which statements of identity and indications for use of OTC drug products must be drawn and prohibit alternative OTC labeling terminology which is truthful, not misleading, and intelligible to the consumer to describe such indications. Two comments argued that such a restriction is an unconstitutional restriction of commercial speech and exceeds FDA's authority. One comment stated that this "exclusivity policy" is not warranted as a matter of sound public policy, and recommended that FDA follow a guideline labeling policy instead of an exclusive one. One comment objected that the advance notice of proposed rulemaking was more restrictive in limiting the "statements of identity" than is the regulation in § 201.61 (21 CFR 201.61). The comment urged the agency to allow manufacturers the alternative ways of describing the statements of identity that are allowed in § 201.61.

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 § 330.1(c)(2) (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., §§ 201.63 or 330.1(g).

12. One comment stated that FDA's exclusivity policy is a drug labeling policy that has no application to cosmetic claims appearing in the labeling of products that are both cosmetics and drugs.

The agency agrees with the comment that the labeling restrictions in OTC drug monographs apply only to products that fall within the statutory definition of "drugs" and not to cosmetic products. This distinction between drugs and cosmetics is discussed in comment 3.

Final OTC drug monographs cover only the drug use of the active ingredients listed therein. The concentration range, limitations, statements of identity, indications, warnings, and directions established for these ingredients in a monograph do not apply to the use of the same ingredients in products intended solely as cosmetics. However, if a product is intended for both drug and cosmetic use, it must conform to the requirements of the applicable final monograph(s). In addition to any indications allowed for OTC drug products bearing claims for vaginal use, such products may also bear appropriate labeling for cosmetic use(s), in conformity with section 602 of the act and the provisions of parts 701 and 740. In accordance with the final rule on the agency's exclusivity policy (51 FR 16258, May 1, 1986), cosmetic claims may not appear within the boxed area designated "APPROVED USES." As discussed at 51 FR 16258 at 16264 (paragraph 14), cosmetic claims may appear elsewhere in the labeling but not in the box should manufacturers choose the labeling alternative provided in § 330.1(c)(2)(i) or (c)(2)(iii) for labeling cosmetic drug products.

13. One comment agreed with the Vaginal Panel's conclusions that the terms "cleansing," "producing soothing and refreshing effects," and "deodorizing" (as used in the definitions of vaginal douche and vaginal suppository) are cosmetic claims (48 FR 46694 at 46701). The comment urged the agency to accept the Vaginal Panel's recommendation. In addition to the claims above, another comment also considered the claim "producing an astringent effect" to be a cosmetic claim. The comment argued that these claims do not make a vaginal product into a drug, that it is legally inappropriate to include them in the definitions of these products in proposed § 351.103 of the monograph, and that they should be removed from the definitions section and anywhere else they appear in the document.

The agency agrees that cosmetic claims should not be included in OTC drug rulemakings. Therefore, the cosmetic claims "cleansing," "soothing," "refreshing," and "deodorizing" will not be included in OTC drug monographs. The agency believes, however, that astringency can be either a drug claim or a cosmetic claim, depending on the intended use and labeling of the product. For example, astringent products intended and labeled for the relief of minor vaginal irritation or reduction in local edema would be considered as drugs, while astringent products intended and labeled for a refreshing effect would be considered as cosmetics. A product making both claims would be both a drug and a cosmetic. Thus, the agency will consider the intended use in determining whether it is a cosmetic, a drug, or both (see also comment 3).

14. One comment stated that the Vaginal Panel's categorization of cosmetic claims as Category II drug claims is inappropriate because cosmetic claims are not within the jurisdiction of the OTC drug review. The comment contended that the following claims were inappropriately classified as Category II drug claims by the Vaginal Panel (48 FR 46694 at 46710) because these claims are really cosmetic claims:

Effectively cleanses

Effectively deodorizes
Cleans thoroughly
Destroys odor
Continued vaginal cleanliness
Cleanses more thoroughly than other douches
Removes contraceptive jellies and creams
Changes water into a cleansing solution
Complete feminine hygiene
Personal hygiene
Hypoallergenic
Feminine hygiene
Intimate cleanliness
Prevents disagreeable odors
Effective germ killer
Routine feminine hygiene
Completely refreshed

The comment also contended that the Vaginal Panel placed the following "other product quality claims" in Category II and that these claims do not belong in the rulemaking because they are not drug claims:

Fortified triple strength
Scientifically balanced formula
Intimately understood
Changes water into a cleansing solution
Naturally safe ingredients
Formula like the natural environment in your body
Ph of 3.5
Effective liquid
Nonacid
Intended for all women who want to enjoy extra confidence in meeting people
As with all vaginal douches, its function is not to cover up odor
Unlike spray deodorants which offer less protection
Complete feminine daintiness
Clinically tested
Dainty and feminine
Gentle
Safe for delicate membranes
Contains only the mildest ingredients
Completely compatible with normal vaginal environment
Buffered to control a normal vaginal pH

Stating that the Vaginal Panel did not provide a reason for its recommendation, the comment requested that reference to these claims be deleted at the next stage of the rulemaking.

Although there will not be another stage in this rulemaking, the comment's concerns regarding these label terms are relevant to vaginal claims for OTC drug products subject to other OTC drug monographs. Therefore, the agency believes it is pertinent to address the comment's concerns.

The OTC drug review establishes conditions under which some OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients and allowable labeling. FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: 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. The agency agrees with the comment that some of the claims listed above are either solely cosmetic claims or do not relate in a significant way to the safe and effective use of OTC vaginal drug products and, therefore, are outside the scope of the OTC drug review. Although these terms are considered outside the scope of the review, if used in the labeling of OTC drug products they will be evaluated by the agency on a product-by-product basis, under the provision of section 502 of the act relating to labeling that is false or misleading. Moreover, any term that is outside the scope of the review, even though it is truthful and not misleading, may not appear in any portion of the labeling required by a monograph and may not detract from such required information. However, terms outside the scope of a monograph may be included elsewhere in the labeling, provided they are not false or misleading. In addition, as explained in comment 2, the labeling restrictions in final monographs apply only to products that fall within the statutory definition of a drug, and not to cosmetic products. However, if a product is intended for both drug and cosmetic use, it must conform not only to the requirements of the applicable final monographs, but also to section 602 of the act and the regulations in parts 701 and 740.

15. One comment contended that the use of the adjective "vaginal" modifying "douche" in the statement of identity in § 351.152(a) is unnecessary and superfluous because, in common language usage, the word "douche" has become synonymous with vaginal use. The comment added that the agency has codified this class of products as "douche preparations" in 21 CFR 369.20. The comment requested that the statement of identity allow for synonyms for "vaginal douche" such as "feminine douche," "disposable douche," and "douche." The comment argued that the term "vaginal douche" may be too sensitive for certain advertising media and that the requested synonyms plus the accompanying labeling would clearly define the product as intended for vaginal use only.

The agency recognizes the sensitivity to use of the word "vaginal" and will take this into consideration in developing labeling in the appropriate OTC drug monographs. (See, e.g., the labeling developed for hydrocortisone in the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5868).)

16. One comment objected to the Vaginal Panel's recommendation in proposed § 351.152(b) that the two statements "Keep this and all drugs out of the reach of children" and "DOES NOT PREVENT PREGNANCY" appear on the principal display panel of OTC vaginal drug products. The comment argued that including such statements on the principal display panel is contrary to labeling requirements in other OTC drug regulations now in effect in that statements such as these are generally required to be displayed in a warnings section next to the directions for use. The comment further argued that vaginal douche products have not been shown less safe than or different from other OTC drug products to the extent that would necessitate inclusion of separate warning statements. The comment requested that the Vaginal Panel's recommended that proposed § 351.152(b) be deleted and that these statements be included with the recommended label warnings in proposed § 351.154(a).

The agency agrees with the comment that special placement of these warning statements on the principal display panel is unwarranted. The Vaginal Panel recommended that the statement "Keep this and all drugs out of the reach of children" appear on the principal display panel because the attractiveness and colorful appearance of many vaginal drug products may encourage children to open and consume the contents (48 FR 46694 at 46708). The agency is unaware of any evidence that OTC vaginal drug products are any more attractive or more likely to be opened and consumed by children than other OTC drug products. Therefore, the agency has determined that there is no need for special placement of this general warning statement in the labeling of OTC vaginal drug products. Because existing regulations in § 330.1(g) (21 CFR 330.1(g)) already require all OTC drugs to contain the warning "Keep this and all drugs out of the reach of children," there is no need

to include this warning in individual OTC drug monographs.

However, because the Vaginal Panel was concerned that there is a commonly held misconception by some people that douching prevents pregnancy (48 FR 46694 at 46708), the agency encourages manufacturers to voluntarily place the warning "DOES NOT PREVENT PREGNANCY" in the labeling of vaginal douche products. The agency will discuss vaginal drug product labeling regarding prevention of pregnancy and sexually transmitted diseases as part of the rulemaking for OTC antifungal drug products in a future issue of the **Federal Register.**

17. One comment urged deletion of the Vaginal Panel's recommended professional labeling statement in proposed § 351.180(b)(3), which reads: "The use of povidone-iodine as a douche may cause a transient rise of serum protein-bound iodine." The comment argued that in view of the Vaginal Panel's conclusion that a transient rise in serum protein-bound iodine levels (observed in some individuals) does not affect the safety of the drug and has not been shown to have clinical significance with respect to thyroid function (48 FR 46694 at 46705), the statement is unwarranted. The comment added that inclusion of such a statement in professional labeling is misleading because it directs unwarranted emphasis to an essentially meaningless event.

The comment also stated that if the agency decides not to delete this statement, the statement should be amended to read as follows: "While not affecting its safety, the use of povidone-iodine as a douche may cause a transient rise in serum protein-bound iodine in some individuals. Such transient elevation returns to normal within 7 to 30 days and there is no evidence that this has clinical significance with respect to thyroid function." The comment contended that this revised statement would present the full clinical significance of the rise in serum protein-bound iodine according to the Vaginal Panel's stated findings.

As discussed in comment 9, the agency intends to consider povidone-iodine for vaginal use in the rulemaking for OTC topical antimicrobial drug products in a future issue of the **Federal Register.** In the tentative final monographs in which povidone-iodine is a Category I ingredient (antifungal (54 FR 51136, December 12, 1989) and first aid antiseptic (56 FR 33644, July 22, 1991)), a statement regarding the transient rise in protein-bound iodine associated with the use of povidone-iodine has not been included in professional labeling. Any other professional labeling associated with vaginal use of povidone-iodine will be considered as part of the antimicrobial rulemaking and will not be further considered here.

D. Comments on Combinations

18. One comment requested that the Vaginal Panel's recommended list of permitted combinations in proposed § 351.120 be amended to provide for combinations of one Category I ingredient from any two, three, or four of the various pharmacologic classes. The comment stated that there is adequate precedent in the OTC drug review for combining Category I ingredients from one pharmacological class with Category I ingredients from another pharmacological class, without the necessity of elaborate testing of the combination.

As explained in comment 3, the agency is withdrawing the advance notice of proposed rulemaking for OTC vaginal drug products and is referring consideration of specific vaginal claims to other appropriate OTC drug rulemakings. Likewise, combinations of ingredients for vaginal claims will be considered in those respective rulemakings and will not be considered here.

19. The agency recognizes that the Vaginal Panel recommended some professional labeling indications for several of the ingredients it reviewed. (See Proposed § 351.180, 48 FR 46694 at 46729.) For a combination product containing the ingredients dioctyl sodium sulfosuccinate (docusate sodium) and sodium lauryl sulfate, the Vaginal Panel recommended the indication "For the treatment of *Trichomonas vaginalis.*" For a combination product containing the ingredients calcium propionate and sodium propionate, the Vaginal Panel recommended the indication "For the treatment of *Candida albicans.*" For the ingredient povidone-iodine, the Vaginal Panel recommended the indication "Clinically effective in a program of treatment for vaginal moniliasis, T-vaginales vaginitis, and nonspecific vaginitis."

In the preamble to the Vaginal Panel's report (48 FR 46694 at 46695), the agency disagreed with the Vaginal Panel's recommendations regarding calcium propionate and sodium propionate. Based on previous decisions made by the agency with respect to these ingredients under the DESI program, the agency placed the professional labeling indication recommended by the Vaginal Panel for calcium propionate and sodium propionate in Category II. The agency reaffirms that categorization in this document.

The agency also stated in the preamble to the Vaginal Panel's report that OTC marketing of these ingredients for the relief of minor vaginal irritations could not take place at that time because the studies relied upon by the Panel were the same as those reviewed by the agency and found to be inadequate under DESI. The agency invited comment and data that would support the Panel's recommendations on the safety and effectiveness of calcium propionate and sodium propionate as ingredients in OTC vaginal drug products. No comments or new data were submitted. Therefore, the agency is reaffirming its conclusions that these ingredients, singly or in combination, may not be marketed in OTC drug products with claims for vaginal use.

In recommending a professional labeling claim for docusate sodium and sodium lauryl sulfate, the Panel relied upon one published study (Ref. 1) to support its recommendation. The agency has evaluated this study and finds that it is insufficient to determine the safety and effectiveness of these ingredients for the treatment of *Trichomonas vaginalis.* The study does not satisfy the criteria for an adequate and well-controlled clinical study because it did not include a control group. In addition, it was not designed to determine the effect of these ingredients in treating *Trichomonas* but rather to determine the effect of pH on the removal of secretions from the vagina. Therefore, these ingredients, singly or in combination, may not be marketed in OTC drug products with claims (including professional labeling claims) for vaginal use.

Regarding the active ingredient povidone-iodine, the Panel (48 FR 46694 at 46705) stated that adequate data supported a claim of effectiveness against vaginal yeast (candidiasis or moniliasis), T-vaginales vaginitis and nonspecific vaginitis, but only when used in a treatment regimen consisting of the diluted douche and the full strength (10 percent) povidone-iodine products. Because the Vaginal Panel (48 FR 46694 at 46700) believed that claims of therapeutic benefit for treatment of specific vaginal infections must be restricted to professional labeling, e.g., for the treatment of trichomoniasis or moniliasis, labeling for the full strength (10 percent) product was not included in the monograph. However, the agency has since concluded that recurring vaginal yeast (*Candida*) infections can be safely treated OTC. The agency is currently reviewing the data the Vaginal

Panel considered as well as a subsequent petition filed in support of various vaginal claims and formulations for povidone-iodine (Ref. 4). The agency will discuss the use of povidone-iodine for the treatment of vaginal yeast (*Candida*) infections in a future **Federal Register** publication as part of the rulemaking for OTC antifungal drug products.

Two clinical studies were cited in the data submission to the OTC drug review to support the vaginitis claim (Refs. 2 and 3). The agency has reviewed the two clinical studies and has concluded that they are insufficient to demonstrate that povidone-iodine is effective in the treatment of vaginitis. Neither study satisfies the criteria for adequate and well-controlled studies because a control group was not included. Therefore, they are insufficient to demonstrate the effectiveness of povidone-iodine in the treatment of vaginitis.

References

(1) Fischer, R. R., "Detergent Alkaline Douches," *Pacific Medicine and Surgery*, 73:209–212, 1965.

(2) Shook, D. M., "A Clinical Study of a Povidone-Iodine Regimen for Resistant Vaginitis," *Current Therapeutic Research*, 5:256–263, 1963.

(3) Ratzan, J. J., "Monilial and Trichomonal Vaginitis Topical Treatment With Povidone-Iodine Preparations," *California Medicine*, 110:24–27, 1969.

(4) Comment No. CP, Docket No. 82N–0291, Dockets Management Branch.

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

FDA has considered the comments and other relevant data and information available at this time and determined that specific claims and ingredients for use in and around the vagina will be included in other appropriate OTC drug rulemakings. Accordingly, the advance notice of proposed rulemaking published in the **Federal Register** of October 13, 1983 (48 FR 46694), which would have added a new subpart B (Vaginal Drug Products for Over-the-Counter Human Use) to proposed part 351 (Vaginal Contraceptive and Other Vaginal Drug Products for Over-the-Counter Human Use) (proposed 21 CFR part 351), is hereby withdrawn, effective February 3, 1994. As discussed above, claims that are cosmetic claims only will not be considered in any OTC drug rulemakings. Ingredients and drug claims related to use in and around the vagina will be considered in other appropriate OTC drug rulemakings. The agency has identified the following rulemakings as those appropriate for consideration of ingredients and claims for vaginal drug uses: (1) Antifungal drug products (docket No. 80N–0476), (2) external analgesic drug products (docket No. 78N–0301), (3) skin protectant drug products (docket No. 78N–0021), and (4) topical antimicrobial drug products (Docket No. 75N–0183).

The agency emphasizes that it is withdrawing only the advance notice of proposed rulemaking for these drug products and that this withdrawal does not in any way denigrate the scientific content of the report or negate the excellent work of the Vaginal Panel in its long efforts to produce it. FDA believes that the information in the Vaginal Panel's report will provide valuable guidance to the agency with respect to ingredients and vaginal claims for other OTC drug rulemakings. Further, this withdrawal of the advance notice of proposed rulemaking does not affect the current marketing status of any of the products that were considered in the Vaginal Panel's report. This withdrawal notice is issued under authority of secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

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.

Dated: December 10, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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