

carcinogenesis statement on the outer package labeling but does have the statement in a package insert included inside the package.

FDA issued a Compliance Policy Guide on October 1, 1980 (Ref. 3), revised on May 22, 1987 (Ref. 3), that addressed urinary tract preparations containing phenazopyridine HCl. FDA advised that it was not taking regulatory action against products containing this ingredient and lacking a prescription legend or full-disclosure labeling [based on their deferral to the OTC drug review].

FDA has a number of questions and issues that it plans to consider when it evaluates phenazopyridine HCl for urinary tract analgesic/antiseptic use as part of this review.

1. Is this condition appropriate for self medication?

2. If the answer to the first question is yes, should the product labeling mention the possible need for treatment with an antibacterial drug also?

3. Is there a valid basis for having single-ingredient prescription products with a 200 mg dosage and OTC products with a 190 to 195 mg dosage? What data support these dosages?

4. Have any epidemiological studies been done since 1978 that address the neoplasia findings in the National Cancer Institute technical report (Ref. 1)?

5. Are the neoplasia findings of sufficient concern to restrict this drug to prescription status?

6. Do consumers adequately understand the required carcinogenesis labeling statement? If the answer is no, how should this statement be revised?

7. Should the carcinogenesis labeling statement be required to appear on the outer package labeling, or is it adequate that it appear only in a package insert?

8. Provide updated safety data both from the literature and from adverse event reports for the last 20 years, especially those adverse events reported to companies that market these products.

FDA invites parties interested in the OTC status of this ingredient to submit their answers to these questions and any supporting data to the Division of Dockets Management as comments to this notice so that this information will be publicly available when FDA reviews this ingredient. Adverse event reports should not include names or telephone numbers.

#### C. Urinary Acidifiers and Alkalinizers

FDA is also aware of OTC drug products that have been marketed as urinary acidifiers and urinary alkalinizers. Ammonium chloride and

ascorbic acid have been used as OTC urinary acidifiers, and sodium bicarbonate has been used as an OTC urinary alkalinizer. These products have not been included in any previous call-for-data notices as part of the OTC drug review. Therefore, at this time FDA invites interested persons to submit data or information on these and any other ingredients for use as OTC urinary acidifiers and alkalinizers.

#### D. Aloe Vera and Urea

Aloe vera has been present in a variety of OTC drug products. It has been listed as both an active and inactive ingredient. It has been marketed as a skin remedy for minor cuts, burns, abrasions, and for relief of minor irritations of the vagina. The Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products (Vaginal Drug Products Panel) placed stabilized aloe vera in Category III (for effectiveness) for the relief of minor irritations of the vagina (advance notice of proposed rulemaking (ANPRM), 48 FR 46694 at 46711 to 46712, October 13, 1983). The panel mentioned that treatment of minor burns, insect bites, and other conditions in which a wet dressing of aloe vera is used has been widely reported and handed down from generation to generation. FDA withdrew this ANPRM in the **Federal Register** of February 3, 1994 (59 FR 5226), because 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, FDA planned to consider the ingredients and indications from the vaginal drug products ANPRM in those other rulemakings, as appropriate. However, no submissions for aloe vera were made to the other rulemakings. Because there may not have been an adequate opportunity for interested parties to submit data and information on aloe vera to those rulemakings, FDA invites interested parties to submit any available data and information at this time before it finalizes the monographs for OTC topical antimicrobial and external analgesic drug products. The monograph for OTC topical antifungal drug products is finalized (21 CFR part 333, subpart C), so any interested parties should submit any data and information on aloe vera for this use as a petition to amend the final monograph.

Urea has been marketed as an antipruritic and keratolytic in a number of topical products, with claims that range from "drug" (relieves itching) to

"cosmetic" (for total body dry skin care, soften dry rough skin). Several submissions on products containing urea were made to the Advisory Review Panel on OTC Miscellaneous External Drug Products, but that panel did not complete its review of those submissions before it was disbanded. The submissions need to be updated for FDA to consider them at this time. No data or information on urea have been submitted to the rulemaking for OTC external analgesic drug products. At this time, FDA invites any interested parties to submit data or information on the use of urea as an external analgesic drug product or for any other OTC drug use.

#### E. Wrinkle Remover Products

Whether a wrinkle remover product should be regulated as a drug or a cosmetic depends on the claims the manufacturer makes for the product. The regulation of cosmetics is covered in 21 CFR part 700. Manufacturers of these products should examine their labeling for these products and to determine if the products should be submitted to the OTC drug review for evaluation. Manufacturers should determine if the ingredients in those products affect the structure of the skin in some physiological way and, thus, should be submitted for review as drug ingredients section (see section 201(g)(1)(C) of the act (21 U.S.C. 321(g)(1)(C))). For example, some products marketed since 1971 contain alpha hydroxy acids and beta hydroxy acids. These ingredients are included in this request for data and information.

#### F. Lubricants and Vaginal Moisturizers

The Vaginal Drug Products Panel reviewed OTC drug products for a number of vaginal uses (48 FR 46694). However, those uses did not include vaginal lubricant or moisturizer. A number of products are marketed as a lubricant, personal lubricant, or lubricating jelly. These products have uses that include: "For personal lubrication when vaginal dryness causes discomfort," "acts as a moisturizer for vaginal dryness," "enhances the comfort and ease of intimate activity," and "enhances sexual pleasure by adding to the body's natural lubrication." Other products are marketed as lubricating spermicides [lubricant plus nonoxynol-9] or as a lubricant with nonoxynol-9. These products have claims that state "spermicide, nonoxynol-9, plus safe water-soluble personal lubrication, feels natural and helps enhance sexual pleasure, lubricating protection against unplanned pregnancy," and "enhances sexual pleasure by adding to the body's natural lubrication, not a contraceptive;