DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 92N–0311]

Topical Drug Products Containing Benzoyl Peroxide; Required Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing additional labeling (warning and directions) for all topically-applied acne treatment drug products containing benzoyl peroxide. The warning advises consumers to avoid unnecessary sun exposure and to use a sunscreen when using a benzoyl peroxide product to treat acne. The directions provide information about applying benzoyl peroxide and a sunscreen, and about discontinuing use of both products if irritation or sensitivity develops. Prescription drug products will need a patient package insert to convey this information to product users. The agency is requesting public comment on whether a consumer package insert should be required to provide additional information FDA believes users of these benzoyl peroxide products should have. That information would summarize some problems that occurred when benzoyl peroxide was used in tests on mice and would mention that additional studies are currently being conducted. The final status of benzoyl peroxide in over-the-counter (OTC) drug products and the continued need for the additional labeling will be determined when these additional studies are completed and evaluated.

DATES: Written comments on the proposed regulation by May 18, 1995. Written comments on the agency's economic impact determination by May 18, 1995. FDA is proposing that the final rule based on this proposal be effective 6 months after the date of its publication in the **Federal Register**.

ADDRESSES: Written comments 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 August 7, 1991 (56 FR 37622), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an amendment of the tentative final monograph for topical acne drug products for OTC human use in which the agency reclassified benzoyl peroxide from its previously proposed monograph status (Category I) to ''more-data-needed'' (Category III) status. This action (56 FR 37622) was based on new information that raised a safety concern regarding benzoyl peroxide as a tumor promoter in mice (Ref. 1) and a study that reported that benzoyl peroxide has tumor initiation potential (Ref. 2).

Subsequently, a drug manufacturers association submitted data and information in support of the safety of benzoyl peroxide (Refs. 3 through 6). FDA evaluated these data and information and determined that the studies show that benzoyl peroxide is a skin tumor promoter in more than one strain of mice as well as in hamsters. To date, topical studies (which have shown only tumor promotion) have been of short duration (about 52 weeks). Although animal data and human epidemiology data are available, the agency has determined that further studies are necessary to adequately assess the tumorigenic potential of benzoyl peroxide. These studies are currently being conducted (Ref. 7). The agency acknowledges that it may take several years for these studies to be completed and analyzed, and for a final determination to be made on benzoyl peroxide's safety.

Because studies have shown that benzoyl peroxide is a skin tumor promoter in animals, and the relevance of this finding to humans is unknown, the agency was concerned about continued OTC marketing during the several years it will take to resolve the safety issues raised by the studies discussed above. Because of this concern, the agency discussed this matter with its Dermatologic Drugs Advisory Committee (the Committee) on April 10, 1992 (Ref. 8). At that meeting, information was presented by representatives of FDA and industry, consumer, and professional organizations. The Committee was asked to assess the safety and efficacy data available for benzoyl peroxide, to consider the benefit-to-risk ratio, and to recommend whether the product should continue to be available for use while further safety data are developed. The Committee voted unanimously that benzoyl peroxide should remain available as an OTC drug product.

The Committee was also asked whether the OTC labeling of benzoyl peroxide drug products should be changed to include a statement concerning the ingredient's potential to cause skin tumors in animals, what is the relevance of this potential in humans, and how such a statement should be worded for consumers. The Committee recommended by a four to three vote (with one abstention) that information about what is known about benzoyl peroxide should be provided to consumers by some mechanism. Because of the lack of data, however, the Committee recommended that no warning statement concerning cancer should be included in the labeling of benzoyl peroxide products. The Committee recommended unanimously that FDA consider appropriate wording for additional labeling to highlight those areas where there may be risks and that the proposed wording be brought back to the Committee for review.

The Committee was also informed that the agency had previously recommended to industry that a lifetime animal carcinogenicity study to assess benzoyl peroxide's safety include, as part of the protocol, periods of exposure to UV light (Ref. 9). The Committee was asked its opinion on the need for such testing. Industry representatives stated to the Committee that studies already conducted by Iversen (Refs. 10 and 11) showed no evidence that benzoyl peroxide enhanced the carcinogenicity of UV light. After a lengthy discussion, the Committee concluded that the Iversen studies were insufficient to fully resolve this issue because they were not animal lifetime studies and an insufficient number of animals had been used. Further, based on the protocol, it was uncertain that the studies provided assurance that benzoyl peroxide's tumor fostering potential was conclusively assessed. The Committee recommended unanimously that a new photocarcinogenicity study should be conducted (Ref. 12). As noted above, this study is being conducted (Ref. 7).

A comment submitted after the Committee meeting (Ref. 13) from a consumer association urged the agency to move quickly to inform the American public of the possible health and safety risks associated with benzoyl peroxide. The comment did not recommend removal of this drug from the OTC market, but suggested several labeling statements that could be used. Another comment by a national manufacturers association (Ref. 14) suggested that FDA use alternative available methods, rather than labeling, to disseminate information on this subject. The association proposed: (1) Fact Sheets mailed to consumer groups and publishers of medical- and pharmacy-