DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 80N-0357]

Hair Grower and Hair Loss Prevention Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would establish that over-the-counter (OTC) hair grower and hair loss prevention drug products for external use are not generally recognized as safe and effective and are misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by May 15, 1985. New data by January 15, 1986. Comments on the new data by March 17, 1986. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by May 15, 1985.

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Managment Branch (HFA-305), Food and Drug Administration, Rm., 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTRY INFORMATION: In the **Federal Register** of November 7, 1980 (45 FR 73955) FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking that would classify OTC hair grower and hair loss prevention drug products for external use as not generally recognized as safe and effective and as being misbranded and would declare these products to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)). The notice was based on the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products, 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 February 5, 1981. Reply comments in response to comments filed in the initial comment period could be submitted by March 9, 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 (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. In response to the advance notice of proposed rulemaking, 1 research laboratory, 6 drug marketing firms, 2 drug manufacturers, 3 physicians, 12 consumers, 2 United States Senators, and the U.S. Postal Service submitted comments. These comments are on public display in the Dockets Management Branch.

In this proposed rule to amend Part 310 by adding to Subpart E new § 310.527 (21 CFR 310.527), FDA states for the first time its position on OTC hair grower and hair loss prevention drug products for external use. Final agency action on this matter will occur with the publication at a future date of a final rule relating to OTC hair grower and hair loss prevention drug products for external use.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC hair grower and hair loss prevention drug products for external use, based on the comments received and the agency's independent evaluation of the Panel's report. As discussed in the final rule revising the procedural regulations for reviewing and classifying OTC drugs, FDA will no longer use 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 rule stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). (See the **Federal Register** of September 29, 1981; 46 FR 47730.) This document retains the concepts of Categories I, II, and III at the proposed rule stage.

In the advance notice of proposed rulemaking, the agency stated that if it proposed to adopt the Panel's recommendation it would propose that hair grower and hair loss prevention drug products for external use be eliminated from the OCT market effective 6 months after the date of publication of a final rule in the **Federal Register**, regardless of whether further testing was undertaken to justify their future use. Based on all information available to date, the agency is proposing that hair grower and hair loss prevention drug products for external use as a class of drugs be found to be ineffective. If this proposed finding is adopted in the 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 6 months after the date of publication of the final rule in the **Federal Register**. On or after that date, no OTC drug products that are subject to the rule may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application (NDA). Manufacturers are encouraged to comply voluntarily with the proposed rule at the earliest possible date.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Hair Grower and Hair Loss Prevention Drug Products.

1. Two comments agreed with the Panel's conclusion that all OTC hair grower and hair loss prevention drug products are not effective and that they should be classified as Category II. The comments stated that these products are worthless and that their sale bilks the public of large sums of money each year, and one comment added that the proposed regulation should be enacted promptly.

2. Several comments objected to the Panel's recommendation that all OTC hair grower and hair loss prevention drug products be classified as Category II. The comments contended that banning such products from OTC use is an infringement of consumers' freedom of choice by medical experts and the government. Some of the comments expressed concern that the ban will interrupt ongoing hair grower treatment programs which consumers are satisfied with. The comments urged that, because hair grower ingredients are not harmful, consumers should be allowed to decide

whether they want to use these products.

FDA's statutory mandate includes protection and promotion of the public health by ensuring that drugs are not only safe but also effective for their intended use. The Commissioner's Decision on the Status of Laetrile, published in the **Federal Register** of August 5, 1977 (42 FR 39768), expresses the agency's position on freedom of choice with respect to ensuring that drugs are not only safe, but also effective. That statement reads in part as follows:

> In passing the 1962 Amendments to the act—the amendments that require that a drug be proved effective before it may be marketed—Congress indicated its conclusions that the absolute freedom to choose an ineffective drug was properly surrendered in exchange for the freedom from the danger to each person's health and well-being from the sale and use of worthless drugs * * *. To the extent that any freedom has been surrendered by the passage of the legislation which bans from the marketplace drugs that have not been proven to be effective, that surrender was a rational decision which has resulted in the achievement of a greater freedom from the dangers to health and welfare represented by such drugs.

Hair grower treatment programs will not be interrupted pursuant to publication of this proposed rule; however, OTC drug products that are subject to this rulemaking, and that are not the subject of an approved NDA, will have to comply with the final rule. In the absence of data demonstrating that the ingredients present in OTC hair grower and hair loss prevention drug products are generally recognized as safe and effective, these ingredients cannot be included in an OTC drug monograph. After the effective date of the final regulation, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this regulation will be subject to regulatory action.

3. While supporting the prosecution of those parties who mislead the public with allegedly outrageous claims such as those made by some mail order houses, one comment opposed the Panel's recommendation for Category II classification of OTC hair grower and hair loss prevention drug products, stating that such a classification would impose an economic hardship on legitimate businesses and suppliers. The comment further stated that the company submitting the comment does not have the resources to conduct a double-blind study on the effectiveness of its drug products, which have "properties" similar to the ingredients reviewed by the Panel, and that even if double-blind studies were to prove that its products were no more effective than a placebo, it can point to hundreds of heads of healthier, fuller hair and a large number of satisfied customers. The comment stated that it believed that the burden of proof for safety and effectiveness should be borne by FDA, rather than businesses, and requested FDA to examine closely the need for and the equity of a proposed rule.

Under the statutory scheme established by Congress, an OTC drug may not legally be marketed unless it is generally recognized as safe and effective by qualified experts and has been marketed to a material extent and for a material time (21 U.S.C. 321(p)), or is the subject of an approved new drug application (21 U.S.C. 355), and is not adulterated or misbranded (21 U.S.C. 351, 352). Those persons marketing OTC drugs have an obligation to comply with the law.

In order to ensure that only safe and effective OTC drugs are marketed, FDA began this ongoing review of OTC drug ingredients in 1972. Under the regulations establishing the procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, the agency has requested interested persons to submit data and information pertinent to the designated categories of OTC drugs (21 CFR 330.10a(a)(2)). Calls for data on hair grower products were published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179). Interested persons had an opportunity to submit data and information after publication of the advance notice of proposed rulemaking and again have such an opportunity after publication of this proposed rule (21 CFR 330.10(a) (6) and (7)). The agency makes its determinations with respect to ingredients in each OTC drug rulemaking proceeding on the basis of the data and information in the administrative record for that rulemaking (21 CFR 330.10(a)(10)). Standards for effectiveness are detailed in § 330.10(a)(4)(ii), and include a requirement for controlled clinical investigations. Isolated case reports, random experience, and reports lacking the details that permit scientific evaluation are not considered adequate to establish effectiveness. General recognition of effectiveness is ordinarily based upon published studies which may be corroborated by unpublished studies and other data. If there are no controlled studies, an explanation as to why such studies are not considered necessary must be provided. Anecdotal evidence is not sufficient to demonstrate general recognition among experts of a drug's safety and effectiveness, See, e.g., *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609, 629 (1973).

The comment has failed to provide any data in accordance with the procedures described above, and its anecdotal evidence of "hundreds of heads of healthier, fuller hair and a large number of satisfied customers" is insufficient to meet the burden of proof established by law to demonstrate that the products at issue are generally recognized as safe and effective hair grower of hair loss prevention drug products for OTC use.

FDA has closely examined the need for and equity of the proposed rule. The need for the OTC drug review proceedings was described in detail in the **Federal Register** notices establishing the applicable procedures. (See the **Federal Register** of January 5, 1972 (37 FR 85) and of May 11, 1972 (37 FR 9464).) Although the comment argued that similar ingredients were reviewed by the Panel and that its firm does not have the resources to conduct a double-blind study for effectiveness, the agency cannot accept the comment's argument as a valid reason to waive standard procedures. FDA has a statutory mandate to assure that all OTC drug products are safe and effective for their intended use. Special economic concerns of individual firms cannot override the agency's charge to carry out the public health requirements of the statute.

4. One comment, which cited several references, urged that FDA postpone indefinitely any action on the recommended Category II classification of hair grower and hair loss prevention drug products until current products and techniques have been thoroughly researched and investigated (Refs. 1 through 9). Urging that FDA abandon its current data base on hair grower drug products on the basis that it is "outdated and insufficient," the comment recommended that FDA reclassify only those active ingredients that have been researched, and allow the free enterprise system to promote further research and development of hair grower products. The comment discussed what it considered to be the seven most important causes of hair depletion and the six principal methods of treating male pattern baldness: massage, vitamins, hormones, high frequency electrical units, cosmetics, and galvanic stimulation. The comment stated that a system that combines current techniques with biotin therapy will have the best success rate in treating hair loss and stimulating hair

regrowth. Another comment contained a consumer's testimonial on the use of hot water packs applied to the scalp to stop the balding process.

The references cited by one comment included general descriptions of the hair growth process, possible causes of hair loss, the use of electricity to stimulate the scalp and also bone growth, and the processes of hair transplanting, implanting, and weaving (Refs. 1 through 8). The references also contained general descriptions of the use of germicides to arrest male pattern baldness, topical and oral estrogen therapy for hair loss in women, and the use of oral ferrous gluconate in iron-deficient persons with hair loss (Refs. 1 and 7). Another article dealt with the possible role of alcohol ingestion in promoting hair growth (Ref. 9).

This rulemaking proceeding addresses OTC drug products for external use as hair growers or for hair loss prevention. Thus, the following products or methods discussed by the comments are not included in this rulemaking: oral estrogen therapy, oral ferrous gluconate, alcohol ingestion, cosmetics, hot water packs, massage, high-frequency electrical units, galvanic stimulation, hair transplanting, hair weaving, and hair implanting.

None of the references provided data to show that germicides or topical estrogens are effective as hair growers or for hair loss prevention. The use of biotin as an OTC hair grower is discussed in comment 12 below, and topical estrogen use is further discussed in comment 10 below.

The agency will not delay its OTC drug rulemaking proceedings to allow additional time for further research. In accordance with agency regulations, additional information or data on OTC hair grower or hair loss prevention drug ingredients may be submitted following the publication of this proposed rule (21 CFR 330.10(a)(7)) or in accordance with the NDA procedures (21 CFR Part. 314).

References

(1) Zizmor, J., and J. Foreman, "Hang On To Your Hair," *Working Woman*, 3:58–59 and 82–83, 1978.

(2) "Disprove Theory on Cause of Baldness," *Science News Letter*, 76:289, 1959.

(3) Cohn, N., "Hairsapoppin'," *New York*, 11:57–64, 1978.

(4) "Electric Healing," *Time*, 113:139, 1979.

(5) Elliott, J., "Electrical Stimulation of Bone Growth Wins Clinical Acceptance," *Journal of the American Medical Association*, 243:1401–1403, 1980.

(6) "'Muscle Heads' Don't Get Bald," *Science Digest*, 42: (inside cover) 1957.

(7) Benezra, N., "A Hair-Raising Tale," *Family Health*, 9:25–29, 1977.

(8) Crawford, A., and R. Fettiplace, "Reversal of Hair Cell Responses by Current," *Journal of Physiology*, 295:66P, 1979.

(9) DeLeon, G., "The Baldness Experiment," *Psychology Today*, 11:62–66, 1977.

5. One comment reserved the right to contest the legality of any rulemaking as applicable to its biotin-containing hair preparations, which are available only to consumers enrolled in a professional treatment program for the control and prevention of hair loss. The comment contended that these preprations are not subject to classification under the OTC drug review program.

This rulemaking applies to all drug products offered OTC, i.e., without prescription, for external use as hair growers or for hair loss prevention. Criteria for limitation to prescription use are set forth in 21 U.S.C. 353. By law, prescription drug product labels must bear the statement, "Caution: Federal law prohibits dispensing without prescription" (21 U.S.C. 353(b)(4)) prior to dispensing.

The comment submitted no evidence to show that the firm's product is available by prescription only. Nor is there evidence that this product appropriately would be limited to prescription use. The comment submitted a product brochure containing guidelines for the proper utilization of its preparations: a cream, a lotion, and a shampoo. The brochure states that the preparations are primarily directed toward the control of excessive hair loss and the stimulation of regrowth of hair where the follicles are still viable. The brochure also states that all dispensers of the preparations have been trained in the parent clinic, and that no person may avail himself of the treatment without first being examined by a trained doctor or technician thoroughly indoctrinated in the fundamental concepts of using the preparations. However, the comment did not submit any labels for the preparations. At this time the agency is unable to determine whether the proposed regulation is or is not applicable to the preparations referred to by the comment. Further discussion of biotin as an OTC hair grower drug ingredient appears in comment 12 below.

6. One comment contended that the advance notice of proposed rulemaking on OTC hair grower and hair loss prevention drug products went beyond its intended scope in recommending Category II status for *all* OTC drug products offered for use as hair growers or for hair loss prevention, including ingredients of products that were not submitted to the OTC drug review. For this reason, the comment argued that the procedural requirements of section 553 of the Administrative Procedure Act (APA) were violated.

The APA, in 5 U.S.C. 553, requires that a published notice of proposed rulemaking include the terms or substance of the proposed rule or a description of the subjects and issues involved. Interested persons must then be given an opportunity to comment on the proposal. The rulemaking on OTC hair grower and hair loss prevention drug products not only meets the APA requirements, but affords interested persons more notice and a greater opportunity to participate in the rulemaking process than the APA requires.

There has been clear public notice that the OTC hair grower and hair loss prevention drug products rulemaking will apply to each product within the drug category, whether or not a submission has been made for each product. The original notice requesting data and information for all miscellaneous external OTC drugs (specifically including hair growers) pointed out that the submission of data was entirely voluntary. However, the notice also stated that "the monographs resulting from the OTC drug review will, pursuant to [§ 330.10], be regarded by the Food and Drug Administration as fully applicable to every OTC drug regardless whether any such submission has been made for a particular product. See *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645 (1973); *Warner-Lambert Company* v. *Federal Trade Commission*, 361 F. Supp. 948 (D.D.C. 1973); and *United States* v. *Coli-Trol 80 Medicated*, CCH F.D. Cosm. L. Rep., Para. 40,837 (N.D. Ga. 1973)." (See the **Federal Register** of November 16, 1973; 38 FR 31697.) A subsequent call for data, giving interested persons another opportunity to submit information on miscellaneous external OTC drug products, including hair growers, was published in the **Federal Register** of August 27, 1975 (40 FR 38179). That notice repeated the statement describing the scope of the monographs and provided another opportunity to submit data to the panel "because any OTC drug product containing an active ingredient not listed in the appropriate monograph will be considered misbranded or a new drug requiring a new drug application."

As the comment observed, the advance notice of proposed rulemaking published in the **Federal Register** of November 7, 1980 (45 FR 73960) stated that the rule under consideration would apply to any OTC drug product labeled, represented, or promoted for external use as a hair grower or hair loss

prevention agent. Under § 330.10(a)(6) any interested person was given 90 days to comment on the advance notice. This tentative final order is a proposed rule, which again makes it clear that the final rule would cover all OTC hair grower or hair loss prevention drug products for external use (see proposed § 310.527 below). Under § 330.10(a)(7) interested persons may file comments or objections and hearing requests on this proposal within 60 days. Within 12 months after publication of this proposed rule, interested persons may file new data; comments on the new data may be filed within 60 days after that 12 month period.

Thus, any interested person will have had several notices of the scope of the final rule and will have had several opportunities to submit data and information on any hair grower or hair loss prevention ingredient. There is no violation of the APA's procedural requirements in this rulemaking.

B. Comments on Hair Grower and Hair Loss Prevention Ingredients

7. One comment described a proposed pilot study of the effectiveness of an undisclosed ingredient derived from plant sources as a hair grower and requested that the ingredient be placed in Category III pending the outcome of this study. The comment provided general information about studies on the safety of the ingredient in animals and human subjects and concluded that no safety problems were observed.

Because the name of the ingredient was not provided, the agency is unable to fully assess it or to determine whether or not it is a new drug as defined in section 201(p) of the act (21 U.S.C. 321(p)). The comment did not provide adequate data for FDA to reach any conclusion on the safety of the ingredient to be studied. Data on the number of test animals used and their body weight, and the oral LD_{50} levels, as well as raw data, were lacking. Before proceeding to a limited human trial or pilot study, further animal toxicity studies should be conducted. Tests on the ingredient's topical irritancy and topical and systemic sensitivity in humans (e.g., the Draize test) then need to be conducted. Although the comment described use of the ingredient by subjects in many countries, no specific information on its use was provided. For example, data were lacking on the frequency of topical application and duration of use of the ingredient in human subjects, as well as on the method and frequency of observation of the subjects after testing was begun. If the duration of use of the ingredient is not short-term, chronic toxicity data also need to be obtained. The number of subjects—three—in the proposed pilot study is not sufficient to demonstrate statistically significant results.

The agency's detailed comments and evaluations on the information submitted are on file with the Dockets Management Branch (Ref. 1). Because the data and information provided by the comment were inadequate, and the ingredient is unknown, the agency cannot classify it at this time. Further, the agency's letter to the commenter seeking additional information (Ref. 1) was returned to FDA, marked "moved left no address." The undisclosed ingredient would be considered a "nonmonograph condition" at the time that the final regulation becomes effective.

Reference

(1) Letter from W. E. Gilbertson, FDA, to L. Imhotep, Imhotep Hair and Scalp Research Laboratories, coded LET010 to C00014, Docket No. 80N-0357, Dockets Management Branch.

8. Two comments advocated the use of orally ingested vitamin and mineral supplements to produce hair growth. One comment submitted information on a hair grower program that includes the use of oral vitamin and mineral supplements with the topical application of products containing certain B-vitamins (biotin, inositol, choline, pyridoxine, and niacin); amino acids (cystine, cysteine, and methionine); nucleic acids; jojoba oil; and aminobenzoic acid (formerly *para*-aminobenzoic acid).

The Panel's recommendations on OTC hair grower and hair loss prevention drug products addressed only active ingredients for external use (topical application). The Panel classified the topical use of vitamins and amino acids as Category II (45 FR 73957). The comments did not submit any data on the safe and effective use of B-vitamins, amino acids, jojoba oil, aminobenzoic acid, or nucleic acids for topical use as OTC hair growers or for hair loss prevention. The agency is not aware of any data that demonstrate the safety and effectiveness of any of these ingredients for topical hair grower or hair loss prevention use; therefore, the agency is proposing these ingredients as Category II.

Orally ingested vitamins and minerals are not considered within the purview of this rulemaking, which covers only products for external use. Although orally ingested vitamins and minerals are normally considered foods subject to the misbranding provisions of section 403 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 343), the intended use of a product determines whether it is a "drug," a "food," 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). An orally ingested product intended for drug use must be either generally recognized as safe and effective (21 U.S.C. 321(p)) or the subject of an approved new drug application (21 U.S.C. 355) and may not be misbranded (21 U.S.C. 352). Because no data were submitted regarding the use of orally ingested vitamins and minerals as hair growers or for hair loss prevention, the agency is unable to address this matter further at this time.

9. One comment noted that, at the dosage necessary to produce significant hair growth, the topical use of the female hormone estrogen produced female characteristics in males. These included breast enlargement, diminished growth of body and facial hair, and the appearance of a subcutaneous layer of fat. The comment concluded that treatments involving the use of topical hormones for hair growth necessitate a doctor's supervision and are not a viable alternative for the general public.

The agency agrees with the comment. The Panel discussed the side effects of topical estrogens and recommended a limit on the daily dosage of estradiol that would be safe for OTC use (45 FR 73956). The agency acknowledges that female characteristics have been produced in males using topical estrogens and finds that a product causing the side effects described by the comment is not suitable for OTC use. Further discussion of the use of topical estrogens as OTC hair growers is presented in comment 10 below.

10. One comment noted that the dose of estradiol classified by the Panel as ineffective was not specified in the listing of Category II active ingredients at 45 FR 73958. The comment requested that the dose be included in the listing to avoid confusion with larger doses that are used by clinicians and medical investigators and that may have an effect on hair growth.

The list of Category II ingredients at 45 FR 73958 is only a summary list. The paragraph preceding the list states that the Panel classified these hair grower and hair loss prevention ingredients as not generally recognized as effective for OTC use. The Panel subsequently discussed the topical use of estrogens and estradiol as hair growers and determined that the maximum daily dose of estradiol that is safe for OTC use is 5.5 micrograms per day (μg/day)

(i.e., 666 International Units per day (IU/day)). (See 45 FR 73958 and 73959.) However, doses of estradiol that are safe for OTC use were not found by the Panel to be effective. Although higher doses of estradiol are reported to have been used by clinicians and medical investigators, no data were presented to establish general recognition of safety or effectiveness for *OTC use*. The agency finds no reason to state a concentration for estradiol in the summary list because estradiol is not considered as safe and effective for OTC use at any concentration.

11. One comment complained that data and information on a hair grower drug product that had been submitted to the agency as part of the Drug Efficacy Study Implementation (DESI) review were *not made* available to the Panel, and therefore that the following statement in recommended § 310.527 is untrue: "Data or any other ingredient intended for use as a hair grower or for hair loss prevention in OTC drug products have not been submitted to the Food and Drug Administration for review for safety and effectiveness." The comment also expressed concern that, if the agency adopted the Panel's recommendation for Category II status of all OTC hair grower drug products, the approved NDA for this hair grower drug product would be revoked, thereby denying the manufacturer the right to a hearing under the DESI proceedings.

The drug product referred to by the comment consists of two topically applied preparations: an aqueous solution of sulfanilamide 0.25 percent (Formula A) and an aqueous solution of lanolin 1.5 percent (Formula B). This product has been the subject of an NDA that was approved for safety on February 26, 1948. It was reviewed for effectiveness by the National Academy of Sciences-National Research Council (NAS-NRC) under FDA's DESI review and was subsequently classified by FDA as "possibly effective." (See the **Federal Register** announcement, "Certain Sulfonamide-Containing Preparations for Topical, Ophthalmic, or Otic Use," published on September 25, 1970; 35 FR 14954.) The agency later issued a notice of opportunity for hearing in which the "possibly effective" indications were reclassified to "lacking substantial evidence of effectiveness" because no new data on effectiveness had been submitted within the period provided. (See the **Federal Register** of February 12, 1972; 37 FR 3196.)

The call for data for OTC miscellaneous external drug products (including hair grower and hair loss prevention drug products) was published in the **Federal Register** of November 16, 1973 (38 FR 31697), after the agency had announced in the **Federal Register** that the preparations containing sulfanilamide and lanolin, respectively, lacked substantial evidence of effectiveness. In response to the call for data, informationi on lanolin was submitted; the Panel concluded that there is no evidence to show that lanolin has an effect on hair growth (45 FR 73958).

In the **Federal Register** of April 28, 1981 (46 FR 23811), the agency announced a denial of hearing and withdrawal of approval of the NDA for the preparations in the DESI review proceeding. In that announcement, the agency extensively discussed the submitted data and information on the two preparations and concluded that there was a lack of substantial evidence that they have the effect represented under the conditions of use prescribed, recommended, or suggested in the labeling. The labeling contains the claims that the product softens the scalp, removes dandruff scales, and aids the scalp and hair. It is implied in advertisements for the product that it offers the user the expectation of diminished hair loss, hair regrowth in cases of baldness, and alleviation of dandruff. After considering all of the material submitted, the agency concluded that there was no genuine and substantial issue of fact requiring a hearing, and that the legal objections raised were without merit.

The comment submitted to this rulemaking provided no new data or information for the agency to consider with respect to the Panel's conclusion on lanolin or the agency's conclusion previously reached through the DESI review on the two preparations. Based on the Panel's recommendation and on the agency's analysis set forth in the **Federal Register** at April 28, 1981 (46 FR 23811), the agency proposes that sulfanilamide and lanolin be classified in this tentative final regulation as Category II for use as OTC hair growers or for hair loss prevention.

The concerns expressed by the comment (i.e., denying the right to a hearing and possible revocation of the product's NDA) have already been addressed by the agency in the DESI review proceeding and need not be addressed in this rulemaking. The agency points out that the comment to this rulemaking was submitted before the April 28, 1981 **Federal Register** announcement was published.

The statement in § 310.527, "Data on any other ingredient intended for use as a hair grower * * * have not been submitted to the Food and Drug Administration for review * * *," was intended by the Panel to refer to data submitted to the agency's OTC drug review, pursuant to the call-for-data notice for OTC miscellaneous external drug products. Because this statement is not a necessary part of the regulation, it is not being included in this tentative final regulation.

12. Four comments submitted data and information to support their contention that topically applied biotin, a B-vitamin, is an effective OTC hair grower and hair loss prevention ingredient. One comment opposed the marketing of biotin-containing products as hair growers and described them as frauds, stating that these products were the subject of an April 1980 Florida court case involving the U.S. Postal Service. Of the comments supporting Category I status of biotin, one comment requested that further action on the advance notice of proposed rulemaking be delayed until the results of a double-blind study have been submitted. One comment submitted 10 volumes of data and information from a "retrospective" study in support of the safety and effectiveness of biotin 0.005 to 0.1 percent, which included log books, records on patients, photographs, and data summaries (Ref. 1) and a supplement to the data (Ref. 2). Another comment suggested that a prospective controlled study be conducted to show whether biotin-containing products are effective for this use because the quality of the photographs in the data submitted prevented any conclusions from being reached.

The agency is aware that the mail-order sale of a biotin hair grower product was halted as the outcome of an administrative proceeding completed in 1980 by the U.S. Postal Service. Actions taken by the U.S. Postal Service, however, are separate from actions taken under the Federal Food, Drug, and Cosmetic Act. In addition, data and information not available in 1980 may now be available for submission to FDA.

The comments provided information that included brochures on biotin products, a description and a copy of an article by Settel (Ref. 3), and a statement from a consumer on the effectiveness of biotin as a hair grower. A reference on dihydrotestosterone-A, cited by one comment, could not be obtained either from libraries or from the comment source (Ref. 4). The product brochure and the article by Settel provided no data for the agency to review on biotin's safety and effectiveness. In addition, statements from consumers cannot be

considered as adequate proof of effectiveness or safety.

The submitted study (Ref. 1) was not controlled and therefore is inadequate. The agency agrees with the comment that the photographs included in these data prevent any conclusions from being reached; the photographs display such variability in technique that they provide inadequate data for assessment. Other data were also inadequate: questionable methods of evaluating hair root viability, the use of untrained observers, and the use of drugs in addition to biotin in the course of treatment preclude reliance on those studies.

The agency agrees with the coment that a prospective controlled study on biotin is the preferred approach to study design. The agency's detailed comments and evaluations on the data submitted are on file in the Dockets Management Branch (Ref. 5).

The comment's request to delay action on the advance notice of proposed rulemaking was made in December 1980. Since that time the person who made the comment has submitted no new data or information. The agency will not delay its OTC drug rulemaking proceedings to allow additional time for further research. In accordance with agency regulations, new data may be submitted within 12 months following publication of this proposed rule (21 CFR 330.10(a)(7)).

After reviewing the data and information submitted by the comments, the agency is proposing that biotin be classified in Category II because the data are inadequate to demonstrate this ingredient's safety or effectiveness as an OTC hair grower and hair loss prevention drug ingredient.

References

(1) Comment No. C00022, Volume I through Volume X, Docket No. 80N-0357, Dockets Management Branch.

(2) Comment No. SUP002, Docket No. 80N-0357, Dockets Management Branch.

(3) Settel, E., "Control of Excessive Hair Loss Through Topical Enzyme Therapy," *Drug and Cosmetic Industry*, 121:34-37 and 156-158, 1977.

(4) Comment No. C00013, Docket No. 80N-0357, Dockets Management Branch.

(5) Letter from W. E. Gilbertson, FDA, to E. Settel, coded LET012 to C00022, Docket No. 80N-0357, Dockets Management Branch.

13. Several comments defended the use of topical preparations that are used to treat hair loss attributed to accumulation of sebum, the secretion of the sebaceous glands. One comment stated that sebum collects around the hair shaft at the follicle and hardens, choking off the follicle, and that topical preparations are especially effective in dissolving sebaceous accumulations. The comments provided statements from consumers on the effectiveness and safety of these products. One comment, from a hair grower consultant firm, stated that the firm's submission to the Panel was mistakenly reviewed for the claim of treating male pattern baldness, rather than for sebum hair loss. The comment argued that the ingredients in its products (i.e., estradiol, isopropanol, methyl ethyl ketone, sufonated vegetable and mineral oils, ammonium lauryl sulfate, and benzethonium chloride) should at least have been classified as Category III by the Panel and requested that FDA delay final classification of the ingredients in its products for not less than 18 months to allow time to submit "confirmatory efficacy data." One comment described as "successful" a hair loss prevention product containing the chemical dinitrochlorobenzene.

The Panel noted that the theory that sebum can cause hair loss is not generally accepted by the medical profession today and that studies have shown no quantitative difference in the amount of sebum present on the bald scalp, the hairy scalp of balding men, and the scalp of men who showed no baldness (45 FR 73958). The agency agrees with the Panel that hair loss has not been shown to be related to the production of sebum. No data have been submitted by the comments to show that sebum causes hair loss.

With regard to the statement made in one comment, that a company's submission was not reviewed for a claim for sebum hair loss, the agency notes that the Panel thoroughly discussed this submission and claim in its report, prefacing its discussion with the following statement: "A third manufacturer submitted both safety and effectiveness data for a variety of products used for sebum hair loss" (45 FR 73958). The comment submitted information on a variety of products used to treat sebum hair loss and identified several ingredients in the product as active ingredients: estradiol 0.011 milligram per fluid ounce (mg/fl oz), isopropanol, methyl ethyl ketone, sulfonated vegetable and mineral oils, ammonium lauryl sulfate, and benzethonium chloride. The agency tentatively concurs with the Panel that these ingredients are safe when used as labeled in the submission, but that the data fail to demonstrate the effectiveness of these ingredients for hair loss prevention. As stated in comment 12 above, statements from consumers cannot be regarded as adequate proof of safety and effectiveness of these products. Furthermore, the agency concurs with the Panel's classification of estradiol 0.011 mg/fl oz as the only active ingredient among these ingredients, when used in OTC hair grower and hair loss prevention drug products. The product containing benzethonium chloride is labeled as an "antiseptic dressing for the hair and scalp" that "helps to destroy and control bacteria * * * and aids in combing or 'setting' the hair." The Panel classified benzethonium chloride as an inactive ingredient. The comment did not present any evidence that the product has any effect on hair growth or hair loss prevention; thus, there is no basis to consider benzethonium chloride an active ingredient for these uses.

The firm's request for an 18-month delay was dated February 5, 1981. The firm has submitted no new data subsequent to its request. As discussed in comments 4 and 12 above, action on the advance notice of proposed rulemaking is not being delayed; data may be submitted following the publication of this proposed rule (21 CFR 330.10(a)(7)) or in accordance with the NDA procedures (21 CFR Part 314).

No data were submitted on the safety and effectiveness of dinitrochlorobenzene. One company commenting on this ingredient described its use by West German researchers in treating alopecia areata, a type of baldness that is unrelated to male pattern baldness (Ref. 1). The company also stated that dinitrochlorobenzene produces contact dermatitis, which can be severe enough to warrant discontinuation of treatment. Thus, the agency concludes the information is inadequate to consider dinitrochlorobenzene as generally recognized as safe and effective for OTC use as a hair grower or for hair loss prevention.

Reference

(1) "Checkup on Medicine: Elaboration on a Baldness Cure," *Science Digest*, 85:83, February 1979.

14. One comment included data and information on a product containing "sulfur at 1 percent on carbon in a fraction of paraffinic hydrocarbons" (Refs. 1 and 2) and requested that FDA consider the entire formula of the product as active and classify it as safe and effective for OTC use for the prevention of hair loss.

FDA has reviewed the data and information and determined that the comment did not provide adequate data to establish the safety and effectiveness of the active ingredients. The description of the active ingredients as

"sulfur at 1 percent on carbon in a fraction of paraffinic hydrocarbons" is inadequate for the agency to fully assess the ingredients or to determine whether any of the ingredients is a new drug as defined in section 201(p) of the act (21 U.S.C. 321(p)). The agency has requested that the firm submit the chemical names and descriptions of the active ingredients as well as their concentrations, and also requested clarification of the confidentiality status of a section of the safety data (Ref. 3). To date, no reply has been received from the firm.

The safety data submitted with the comment included photographs of histologic examinations in animals; however, these photographs were poorly reproduced and could not be evaluated. Although the data contained an evaluation of carcinogenicity, the Ames test for mutagenicity was not conducted. The agency notes that a number of the study subjects stated that the test preparation and the placebo lotion caused stinging and burning. However, in the absence of details on the product's formulation, the agency is unable to assess the significance of this information in relation to the overall safety of the ingredients. The data also included an effectiveness study; however, the efficacy criteria were arbitrarily defined and difficult to interpret. The statistical methodologies used to evaluate hair loss were not appropriate and there were various numerical inconsistencies in the sponsor's tables. The efficacy end-points used to evaluate hair growth were not based on objective criteria, and the significance level for multiple comparisons was not adjusted when subjective responses were evaluated. In addition, the length of time that the study was conducted was not adequate to show persistence of results. In view of these inadequacies, the agency cannot consider the data submitted by the comment as adequate to establish safety or effectiveness. Thus, the agency proposes to classify sulfur 1 percent on carbon in a fraction of paraffinic hydrocarbons as Category II for OTC use for the prevention of hair loss.

The agency's detailed comments and evaluations on the data and information submitted are on file with the Dockets Management Branch (Ref. 4).

References

(1) Comment No. RPT, Volume I through Volume IV, Docket No. 80N-0357, Dockets Management Branch.

(2) Comment No. SUP, Docket No. 80N-0357, Dockets Management Branch.

(3) Comment No. LET005, Docket No. 80N-0357, Dockets Management Branch.

(4) Letter from W.E. Gilbertson, FDA, to W. Pendergast, attorney for Fortkan International, Inc., coded LET015, Docket No. 80N-0357, Dockets Management Branch.

15. Four comments included data and information, which included a copy of a product brochure and statements by a consumer and a physician, to show that effectiveness of certain hair grower products that appear to contain polysorbate 20 or polysorbate 60 (a nonionic surface active ingredient), urea, biotin, and pantothenol. Two of the comments each included seven volumes of data and information on the product's safety and effectiveness (Refs. 1 and 2). Another comment cited a report on a hair preparation that included information on studies conducted on the safety and effectiveness of "certain non-ionic surface-active agents" when applied to the human scalp and skin (Ref. 3).

The data and information submitted with two comments (Refs. 1 and 2) contained histograms, pictures, and tables that were not readily discernible. In particular, the reproduced photographs were of such poor quality that an assessment of hair regeneration could not be made. The agency subsequently requested that the firms that filed the comments submit original versions of these data and that the names of the active incredients and the confidentiality status of the product formulations be clarified (Refs. 4 and 5). No communications have been received from the firms; thus, the agency is unable to consider further the data and information provided by the comments. The agency's detailed comments and evaluations on the information submitted are on file with the Dockets Management Branch (Refs. 6 and 7).

The report cited by one comment (Ref. 3) described only the results of studies; data from observations were not presented. In addition, the formulation (including identification of the active ingredients) of the hair preparation used in the studies was not revealed. The brochure provided by one comment provided no data for evaluation, and, as stated in comments 12 and 13 above, statements from consumers do not constitute adequate evidence of safety or effectiveness.

The agency concludes that the data and information submitted with the comments are inadequate for the agency to classify the ingredients in the products discussed above as generally recognized as safe and effective for use as OTC hair growers or for hair loss prevention. The agency's conclusions on biotin are presented in comment 12 above.

References

(1) Comment No. C00015, Volume I through Volume VII, Docket No. 80N-0357, Dockets Management Branch.

(2) Comment No. C00016, Volume I through Volume VII, Docket No. 80N-0357, Dockets Management Branch.

(3) Setalla, K., and I. Schreck-Purola, "Baldness and Its Cure: Safety and Mode of Effect of Hair Preparation," The First Department of Pathology, University of Helsinki, Finland, 1977.

(4) Letters from W.E. Gilbertson, FDA, to K. Cox, Florida Nutrition Center, Inc., coded LET007 and LET008, Docket No. 80N-0357, Dockets Managment Branch.

(5) Letters from W.E. Gilbertson, FDA, to C. Richardson, Standard Research Laboratories, coded LET006 and LET009, Docket No. 80N-0357, Dockets Management Branch

(6) Letter from W.E. Gilbertson, FDA, to K. Cox, Florida Nutrition Center, Inc., coded LET011, Docket No. 80N-0357, Dockets Management Branch.

(7) Letter from W.E. Gilbertson, FDA, to C. Richardson, Standard Research Laboratories, coded LET013, Docket No. 80N-0357, Dockets Management Branch.

II. The Agency's Tentative Adoption of the Panel's Report

The Panel discussed the use of ascorbic acid, benzoic acid, estradiol, lanolin, tetracaine hydrochloride, and wheat germ oil for OTC use as hair growers or for hair loss prevention. Based on the comments, the agency has also considered the ingredients amino acids, aminobenzoic acid, biotin and all other B-vitamins, topical hormones, jojoba oil, nucleic acids, pantothenol, polysorbate 20, polysorbate 60, sulfanilamide, sulfur 1 percent on carbon in a fraction of paraffinic hydrocarbons, and urea for these uses. FDA has considered the Panel's recommendations, the comments, and other data and information available at this time and concludes that it will tentatively adopt the Panel's report and recommendation that all OTC drug products labeled for external use as hair growers or for hair loss prevention be classified Category II.

The agency is also revising § 310.527(b) to clarify that a product covered by the regulation is a new drug for which an approved NDA is required for marketing, and in the absence of an approved NDA the product would also be misbranded under section 502 of the act.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these

economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for ORC hair grower and hair loss prevention drug products for external use, is a major rule.

For purposes of the regulatory Flexibility Act, the economic assessment concluded that, while the average economic impact of the overall OTC drug review on small entities will not be significant, the possibility of larger-than-average impacts on some small firms in some years might exist. Therefore, the assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose a significant impact on a substantial number of small entities. The analysis identified the possibilities of reducing burdens on small firms through the use of (a) relaxed safety and efficacy standards or (b) labels acknowledging unproven safety or efficacy. However, the analysis concluded that there is no legal basis for any preferential waiver, exemption, or tiering strategy for small firms compatible with the public health requirements of the Federal Food, Drug, and Cosmetic Act. Nevertheless, to avoid overlooking any problems or feasible possibilities of relief peculiar to this group of products, the agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC hair grower and hair loss prevention drug products for external use. Comments regarding the economic impact of this rulemaking 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 hair grower and hair loss prevention drug products for external use, 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 that under 21 CFR 25.24(d)(9) (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 310

New drugs.

PART 310—[AMENDED]

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 310 by adding to Subpart E new § 310.527, to read as follows:

§ 310.527 Drug products containing active ingredients offered over-the-counter (OTC) for external use as hair growers or for hair loss prevention.

(a) Amino acids, aminobenzoic acid, ascorbic acid, benzoic acid, biotin and all other B-vitamins, estradiol and other topical hormones, jojoba oil, lanolin, nucleic acids, pantothenol, polysorbate 20, polysorbate 60, sulfanilamide, sulfur 1 percent on carbon in a fraction of paraffinic hydrocarbons, tetracaine hydrochloride, urea, and wheat germ oil have been marketed as ingredients in over-the-counter (OTC) drug products for external use as hair growers or for hair loss prevention. There is a lack of adequate data to establish the effectiveness of these or any other ingredients intended for external use as OTC hair growers or for hair loss prevention. Based on evidence presently available, labeling claims for OTC hair grower and hair loss prevention drug products for external use are either false, misleading, or unsupported by scientific data. Therefore, any OTC drug product for external use containing an ingredient offered for use as a hair grower or for hair loss prevention cannot be considered generally recognized as safe and effective for its intended use.

(b) Any OTC drug product that is labeled, represented, or promoted for external use as a hair grower or for hair loss prevention is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which an approved new drug 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, such product is also misbranded under section 502 of the act.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FDA–1571) (OMB Approval No. 0910–0014), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for external use as a hair grower or for hair loss prevention is safe and effective for the purpose intended.

(d) After the effective date of the final regulation, 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.

Interested persons may, on or before May 15, 1985, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, 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. The agency has provided this 120 day period (instead of the normal 60 days) because of the number of OTC drug review documents being published concurrently. Written comments on the agency's economic impact determination may be submitted on or before May 15, 1985. 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 January 15, 1986, 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 March 17, 1986. 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 (HFA–305) (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, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on March 17, 1986. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

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