DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 80N-0357]

RIN 0905-AA06

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

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that any over-the-counter (OTC) hair grower or hair loss prevention drug product for external use is not generally recognized as safe and effective and is misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final rule, and all new data and information on hair grower and hair loss prevention drug products that have come to the agency's attention. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: January 8, 1990.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY 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 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 (Miscellaneous External 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 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 display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final rule, for hair grower and hair loss prevention drug products was published in the **Federal Register** of January 15, 1985 (50 FR 2190). Interested persons were invited to file by May 15, 1985, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by May 15, 1985. New data could have been submitted until January 15, 1986, and comments on the new data until March 17, 1986. Final agency action occurs with the publication of this final rule on OTC hair grower and hair loss prevention drug products.

As discussed in the proposed regulation for OTC hair grower and hair loss prevention drug products (50 FR 2190), the agency advised that the drug products covered by this regulation would be subject to the regulation effective 6 months after the date of publication of the final rule in the **Federal Register**. On or after January 8, 1989, no OTC drug products that are subject to this final 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).

In response to the proposed rule on OTC hair grower and hair loss prevention drug products, 218 consumers and 4 manufacturers submitted comments. No requests for oral hearing before the Commissioner were received. Copies of the comments received are on public display in the Dockets Management Branch. Additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

In proceeding with this final rule, the agency has considered all comments and changes in the procedural regulations.

I. The Agency's Conclusions on the Comments

A. General Comments

1. A number of comments agreed with the agency's proposal that currently *marketed* drug products containing active ingredients for OTC external use for hair grower and hair loss prevention are ineffective and should be eliminated from the OTC market. One comment said the proposal was long overdue and that purchasers of these drugs are bilked of millions of dollars each year. Another comment strongly supported the proposal in instances where manufacturers cannot substantiate their claims. Other comments stated that these drugs should either be shown to be effective before they are marketed or be taken off the market. Two comments pointed out that 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.

2. One comment suggested that the proposal to ban from the market all topical nonprescription products claiming to grow hair or prevent baldness should be extended to include vitamin or "food supplement" products claimed to restore hair, prevent hair loss, or provide nourishment to the hair. Another comment stated that the agency's proposal to ban hair loss products should include control of fraudulent claims.

As noted in the tentative final monograph, this rulemaking covers only products for external use, i.e., all active ingredients and labeling claims for OTC drug products marketed for external (topical) use as hair growers or for hair loss prevention. (See comment 8 at 50 FR 2193.) Upon the effective date of the final rule, any OTC drug product that is labeled, represented, or promoted for external use as a hair grower or for hair loss prevention will be a new drug within the meaning of section 201(p) of the act (21 U.S.C. 321(p)), for which an approved NDA under section 505 of the act (21 U.S.C. 355) is required for marketing. In the absence of an approved NDA, marketing of these products would be a violation of sections 505(a) and 301(d) of the act (21 U.S.C. 355(a) and 331(d)). Such products are also considered misbranded under section 502 of the act (21 U.S.C. 352). The marketing of unapproved new drugs or misbranded drugs subjects them to regulatory action.

The agency emphasizes that orally ingested products marketed for the same or similar hair grower or hair loss prevention indications are also subject to regulatory action. Such products are presently marketed as vitamins, "food supplements," or other orally ingested products. These products are frequently marketed with claims making them "drugs" within the meaning of section 201(g) of the act (21 U.S.C. 321(g)). (See *50 FR at 2193*). Any orally ingested drug product marketed for these indications

must be generally recognized as safe and effective (21 U.S.C. 321(p)) or the subject of an approved NDA. As with external drug products covered by this rulemaking, in the absence of an approved NDA, the marketing of these orally ingested drug products would be a violation of sections 505(a) and 301(d) of the act (21 U.S.C. 355(a) and 331(d)). Such products would also be misbranded under section 502 of the act (21 U.S.C. 352). Because orally ingested drug products for these indications are not covered by any OTC drug rulemaking, regulatory actions for these products will be handled on a case-by-case basis.

FDA Compliance Policy Guide 7132b.15 (Ref. 1) generally defers regulatory action for OTC drug products pending the establishment of a final monograph covering the products involved. On the effective date of this final rule, Compliance Policy guide 7132b.15 is revoked with respect to all OTC drug products, whether topical or orally ingested, that are marketed with hair grower, hair loss prevention, or similar claims.

Reference

(1) OTC Drugs—General Provisions and Administrative Procedures for Recognition as Safe and Effective, Office of Enforcement, Division of Compliance Policy, Associate Commissioner for Regulatory Affairs, Compliance Policy Guide No. 7132b.15, Food and Drug Administration, 1987.

3. A number of comments contained testimonials from consumers for several drug products labeled for hair growth and hair loss prevention. The comments wanted to continue using the products and did not want them taken off the market. Many of these comments supported a particular product which they claimed reduced or stopped hair loss, thickened hair, and in some cases stimulated hair growth. One comment considered the proposed FDA restriction too stringent and stated that it took away the right of choice. This comment contended that the most that should be done is to label herbal preparations as "not approved by the AMA or FDA as being of value in hair loss * * *". Two comments contended that it was unjust to prohibit the sale of products that perform as advertised or make a claim which a company can support, even though such products were not reviewed by the Panel or the agency. (See also comment 5 below for a discussion of one of these products.)

The agency discussed "freedom of choice" and statutory standards for marketing OTC drug products in the tentative final rule. (See 50 FR 2190 at 2191.) Agency regulations in 21 CFR 330.10(a)(4)(ii) state that standards for effectiveness 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. As mentioned in the tentative final rule, testimonials from consumers cannot be considered as adequate proof of effectiveness or safety (50 FR 2194 and 2195).

FDA has a statutory mandate to ensure that all OTC drug products are safe and effective for their intended use. The status of OTC topical hair grower and hair loss prevention drug products is being determined in this rulemaking. Such products have been found not to be generally recognized as safe and effective. Therefore, a labeling statement that the product has not been approved by FDA for a particular use, as one comment suggested, would be meaningless because under the act the products cannot be marketed in any event.

4. One individual submitted information on personal research performed on hair loss. The information included a discussion of the cause, prevention, and cure of male pattern baldness. According to the research theory, reduced circulation in the scalp is implicated in male pattern baldness. However, because the research did not include any information on specific products or ingredients, the agency cannot evaluate it as part of this rulemaking.

B. Comments on Hair Grower and Hair Loss Prevention Drug Products

5. One comment referred to a product that it claimed helped many individuals reduce excessive hair loss and in many cases allowed new hair growth for individuals affected by androgenic alopecia (male pattern baldness). The comment explained that the product was not developed until 1983 and, therefore, was not considered by the Panel. However, according to the comment, the ingredients were all approved by FDA for OTC human use. The comment stated that it had monitored a group of test subjects for periods ranging from 8 to 15 months, that all subjects showed no increased baldness, and that at least 60 percent of the subjects noticed varying degrees of new hair growth. The comment also submitted numerous signed testimonials from customers who claimed reduction of excessive hair loss and/or new hair growth while using the product. The comment informed the agency that it would submit a testing protocol for future planned testing of the product, by October 15, 1985. Subsequently, the comment indicated by letter (Ref. 1) that the submission of the protocol would be delayed.

The agency is unable to assess the safety and effectiveness of the product referred to by the comment because the comment did not identify the specific ingredient(s) contained in it. In addition, the comment did not submit sufficient data to support safety and effectiveness. As stated in comment 3 above, reports lacking the details that permit scientific evaluation, such as the 8- to 15-month monitoring of test subjects described by the comment, and consumers' testimonials are not adequate to establish effectiveness. Further, the testing protocol mentioned by the comment was never submitted. In the absence of any information regarding the active ingredient(s) and without safety and effectiveness data, the product cannot be evaluated for possible inclusion in a monograph.

Reference

(1) Comment No. LET00025, Docket No. 80N-0357, Dockets Management Branch.

6. One comment described two products, a shampoo and a scalp cleanser/conditioner, containing a surfactant that purportedly combines with excess oil in the hair and helps to stop hair fallout by removing excess oil and allowing normal hair growth to resume. The comment provided consumer testimonials containing statements that the product stopped abnormal hair fallout and in some cases caused regrowth of hair.

The comment did not identify the ingredient(s) present in the products and did not provide a copy of the products' labeling. The agency informed the company of the need for more information about the products, including ingredients, claims made on the labels, data from studies, and any other information relating to the safety and effectiveness of the ingredients (Ref. 1). No further information has been received from the company. In the absence of any information regarding the active ingredient(s) and without safety and effectiveness data, the products cannot be evaluated for possible inclusion in a monograph.

Reference

(1) Letter from W.E. Gilbertson, FDA, to R. Tepper, Growth Plus Laboratories, coded LET00022, Docket No. 80N-0357, Dockets Management Branch.

7. One manufacturer submitted data (Ref. 1) to support the effectiveness of a

scalp hygiene regimen for sebum hair loss that listed a number of ingredients, including estradiol. The data included a protocol and information on hair fall counts from a preliminary study; a protocol, information on hair fall counts, and photographs related to hair density and hair growth measurements from the main study; and a summary of two clinical studies involving ingredients other than estradiol and comparing hygiene regimen treatments with placebos. The instructions provided by the manufacturer for the treatment regimen also claimed that hair growth is stimulated.

The Miscellaneous External Panel reviewed and evaluated data on estradiol and the other ingredients in the manufacturer's products for "sebum hair loss" (45 FR 73955 at 73958 and 73959). The Panel concluded that the available data failed to demonstrate the effectiveness of the ingredients, and classified estradiol as not generally recognized as being effective and as being misbranded for OTC use (45 FR 73958). In the tentative final monograph, the agency noted that doses of estradiol that were safe for OTC use were not found by the Panel to be effective (50 FR 2190 at 2194) and tentatively adopted the Panel's recommendation that all OTC drug products labeled for external use as a hair grower or for hair loss prevention be classified Category II (not generally recognized as safe and effective) (50 FR 2196).

Regarding the manufacturer's claim that its scalp regimen was for "sebum hair loss," the Panel noted that the theory that sebum can cause hair loss is not generally accepted by the medical profession today. The Panel stated that studies have shown no quantitative difference in the normal amount of sebum and the hourly production of sebum on the bald scalp, the hairy scalp of balding men, and the scalp of men who showed no baldness (45 FR 73955 at 73958). In the notice of proposed rulemaking for OTC hair grower and hair loss prevention drug products, the agency agreed with the Panel that hair loss has not been shown to be related to the production of sebum (50 FR 2190 at 2195, comment 13). Data to show that sebum causes hair loss have not been submitted since the notice of proposed rulemaking was published. Further, Orentreich, a leading dermatologist, indicated that sebum contains very high concentrations of dihydrotestosterone, which is associated with hair loss (Ref. 2). However, he noted that although the androgen in sebum has been measured, it has not been shown that dihydrotestosterone is the sebum can partition out of the sebum into the skin. Moreover, no scientific study has shown that shampooing the scalp frequently, to reduce sebum on the scalp, has any effect in reducing dihydrotestosterone and thereby reducing hair loss.

Daily shampooing and cleansing of the scalp with the manufacturer's treatment as well as placebo appeared to reduce shedding of hair in the submitted studies (Ref. 1). The Panel noted that daily shampooing with any nonmedicated shampoo would remove surface oil, scale, and loose hairs (45 FR 73955 at 73959). This phenomenon was discussed at one of the Panel's meetings (Ref. 2) in a presentation by Orentreich, who indicated that normally 100 hairs are shed per day, 700 a week. On the first day of shampooing, 300 hairs will be shed, the next day 25, the next day 50, the next day 75, then back to 100 hairs a day. The more often the hair is shampooed, the less hair loss occurs per shampoo. For example, if an individual shampoos once a week, 700 hairs will be shed; if an individual shampoos once in 2 weeks, 1,400 hairs will be shed. Another important factor discussed by Orentreich as affecting hair shedding is seasonal cycles, with October, November, and December being months of greater shedding, with shedding heaviest in November. As stated by Orentreich, awareness of these two factors (shampooing and seasonal shedding cycles) is important in any evaluation of a product claiming hair loss prevention. The agency notes that some subjects were evaluated during the months of October, November, December, while some subjects were evaluated in other months. There is no indication that the manufacturer considered seasonal shedding cycles in any of its data analyses. There is also no showing of the impact that the failure to consider this factor had on the results obtained.

The data in the preliminary tests consisted of daily counts of hair loss in three groups, each using a different regimen (estradiol, hygiene, and placebo) during pretreatment and treatment phases. The scalps of the subjects in the estradiol and hygiene groups were treated daily with a conditioner, cleanser, shampoo, and antiseptic dressing. The estradiol group received an application of a lotion containing estradiol 0.011 milligram per fluid ounce. The hygiene group received a lotion without estradiol. The third group received a placebo regimen and was the control group. The preliminary tests were done to check study parameters before beginning the main study.

The main study of prevention of hair loss was a double-blind test designed to evaluate the effectiveness of estradiol in an isopropyl alcohol vehicle after the hair was treated with a conditioner, cleanser, and shampoo. The data for this study consisted of raw data on sheets containing the test subjects' hair fall counts, hair density counts from a photographic technique, and photographs of scalp test areas designed to evaluate changes in the number of hairs per square centimeter of scalp, changes in the morphology of the hair in the study site, and changes in linear growth. Initially, the manufacturer indicated that estradiol played an important role in controlling hair loss, and the test objectives included determining the effectiveness of estradiol treatment for reducing hair fall and possibly stimulating hair growth. After completing the studies, the manufacturer concluded that most of the effects on hair fall and any resulting change in scalp hair densities were due mostly to the scalp hygiene regimen tested along with the estradiol treatment. However, the agency notes that the statistical analysis of the study, dated June 21, 1988, and prepared by the manufacturer's consultant (Ref. 3), does not support the company's conclusion. This analysis indicated that while there was improvement with all three of the regimens tested, hair fall counts decreased at a faster rate in the estradiol group.

As part of the main study, the three regimens were tested in subjects with hair loss less than and greater than 80 hairs per day. The manufacturer indicated that in the group with low hair fall the estradiol regimen results were not significantly different from the results for the other two regimens, and in the group with high hair fall, the subjects did not stay in the study long enough to provide a sufficient number of subjects for proper analysis of the results. Although stated to be statistically insignificant by the manufacturer, the consultant's analysis of the exact hair counts, based on pictures of scalp areas, indicated that some improvement occurred with all three regimens used but that there was no clear differentiation among the groups.

The consultant's statistical analysis is based on a linear least squares fit of log transformed average weekly hair fall counts as a function of week since the beginning of the study. Using this type of analysis, the slope of a linear regression line which is significantly less than zero would imply an overall decreasing trend in hair fall over time. The agency agrees

with this concept. However, as discussed below, the agency has determined that simple linear regression models are not the appropriate method of analysis for the data obtained from these studies.

The consultant's method of analysis compared the following treatment groups in the preliminary tests: (1) Low order daily hygiene plus placebo, (2) high order daily hygiene plus placebo, and (3) high order daily hygiene plus estrogen. The method of analysis used in the main study compared the following treatment groups: (1) Full regimen plus estrogen, high hair fall group, (2) full regimen plus estrogen, low hair fall group, (3) full regimen plus placebo, high hair fall group, (4) full regimen plus placebo, low hair fall group, (5) low order regimen plus placebo, high hair fall group, and (6) low order regimen plus placebo, low hair fall group. (High hair fall denotes an average of at least 80 hairs per day before treatment, and low hair fall signifies less than 80 hairs.) The agency finds that this method of analysis is valid provided the data in each of the treatment groups can be adequately modeled by a simple linear regression model. However, the agency points out that a simpler and more direct comparison of the treatment groups with respect to decreasing hair fall could be accomplished by just analyzing change from baseline scores at the end of the treatment period after adjusting for baseline differences between the treatment groups (if any).

The agency has reanalyzed the data from both the preliminary tests and the main study. The agency has determined that simple linear regression models are not the best fit of the data in the treatment groups. Specifically, investigation of the scatter plot of the high order daily hygiene plus estrogen data (average daily hair fall (AHF) vs. week) indicates a definite change in the trend of the data between week 7 and 8. Conventional statistical model-building techniques dictate use of a piecewise linear model, i.e., a model which fits separate linear regression models to both pieces of the data. For both the high and low order daily hygiene plus placebo data, scrutiny of residual plots reveals a curvilinear trend in the residuals over time. Again, statistical model-building methods imply that the high and low order daily hygiene plus placebo data require at least a quadratic regression model. When these (nonlinear) models are fit to the data, the slope comparison criterion proposed by the manufacturer's consultant is not feasible. Similarly, the single model (i.e., log (AHF) = week) used by the manufacturer's consultant for all six subsets of the data in the main study is not the model that best fits the data. The agency finds that the statistical significance of estradiol over placebo has not been demonstrated. The agency concludes that these data do not establish that estradiol is effective for hair loss reduction.

The summary of the two clinical studies described double-blind, comparative tests on individuals with varying degrees of daily hair loss. These studies appear to be adjuncts to the main study because they involved evaluation of various daily hygiene regimes. In one study, a daily hygiene regimen involved treatment with a mixture of isopropyl alcohol and methyl ethyl ketone, a sulfonated oil mixture, and a strong shampoo with ammonium lauryl sulfate base. That regimen was compared with a placebo regimen in which placebos replaced the treatment ingredients and a shampoo of moderate strength with an amphoteric base replaced the strong shampoo. The second study was similar except that a strong shampoo was used 4 days a week, and the results were compared to a placebo regimen using a weak shampoo 3 days a week. The treatment regimen included a sulfonated oil mixture, a strong shampoo with an ammonium lauryl sulfate base (4 days a week), and a mild amphoteric base shampoo (3 days a week). The placebo regimen consisted of only three shampoos a week with use of a placebo oil mixture, placebo shampoo (water and dye), and a mild amphoteric base shampoo.

The results of these two clinical studies appeared to show that daily shampooing over a long period of time, regardless of ingredients, reduced hair fall, but there were no significant differences in hair loss reduction between the two groups in both studies. The summary of the two clinical studies lacks the detail necessary for the agency to evaluate any significant effectiveness of the different regimens. In addition, the number of subjects participating in the studies was not given. The agency concludes that these studies do not provide sufficient data to demonstrate that daily shampooing, using either a drug or cosmetic product, affects hair loss reduction.

After reviewing the available data, the agency concludes that the studies are not sufficient to support Category I status for the claims of hair loss prevention or hair growth. The claim for hair growth is not well-documented because the study model is short and poorly controlled. Regarding the claim for hair loss prevention, there appeared to be a trend to reduce shedding of hair based on increased shampooing and cleansing of the scalp with the products tested: cleanser, plus estradiol and placebo. There was a slight indication in the study that estradiol, with the cleansing agents, could be more helpful. However, to fully establish the claim of decreased hair loss (rather than prevention), it would be necessary to conduct a controlled 6- to 12-month double-blind study, preferably with crossover, with adequate numbers of patients (in the hundreds) in order to generate data sufficient for appropriate statistical review.

In conclusion, the agency has determined that estradiol is not generally recognized as safe and effective for claims of hair loss prevention and hair growth. Accordingly, estradiol is a nonmonograph ingredient. The other ingredients in the manufacturer's scalp hygiene regimen were determined to be inactive ingredients by the Panel (45 FR 73955 at 73957). The agency concurs that these ingredients are not active drug ingredients for these claims. Further, shampoos and scalp cleansers used to cleanse the hair (and not labeled with any claims relating to hair loss prevention or hair growth) are cosmetics and are not covered by this rulemaking proceeding.

The agency recommends that in order to establish the general recognition of safety and effectiveness of a potential OTC hair grower drug product, studies similar to those performed for the evaluation of the safety and effectiveness of the only agency-approved hair growth drug product would be appropriate (Ref. 4). Although that particular product is marketed as a prescription drug product, the methods used to study it would be applicable for an OTC hair grower drug product.

There are no agency-approved OTC hair loss prevention drug products. The agency recommends that any person wishing to study the safety and effectiveness of such a drug product submit a protocol for agency review before beginning such studies.

References

(1) Comments No. C00254, C000268, RPT00002, and RPT00003, Docket No. 80N–0357, Dockets Management Branch.

(2) Transcript of Twenty-Ninth Meeting of the Advisory Review Panel on OTC Miscellaneous External Drug Products, January 14, 1979, pp. 63, 65, and 93–98.

(3) Comment No. RPT00003, Docket No. 80N–0357, Dockets Management Branch.

(4) NDA 19–501, Food and Drug Administration.

8. One comment submitted a protocol (Ref. 1) for a double-blind study of a hair treatment product containing biotin (versus placebo) to determine the comparative effects on excessive hair fall out and hair regrowth. At least 50 subjects with male pattern alopecia were to be evaluated.

The agency reviewed the protocol and found it deficient in a number of aspects: (1) The randomization procedure was not mentioned in the protocol. (2) The sample size was not a fixed number, but was a vague goal of more than 50, and the statistical rationale for a particular sample size was not given. (3) Statistical methods to analyze the hair loss data were not described in the protocol. (4) Procedures to rate the pictures of balding areas were not mentioned in the protocol. (Such a rating scheme for evaluating new hair growth needs to be clearly defined and validated across different blinded observers. However, nonparametric methods to be used for analyzing the photographic data were not presented in the protocol.) (5) Because the duration of the study was 1 year, incomplete observations were expected, yet the protocol did not mention how missing data and drop-outs from the study would be handled in the analysis. The agency concluded that without the above-listed information the protocol was not acceptable from a statistical viewpoint.

Subsequently, the comment submitted a protocol addendum (Ref. 2) addressing the agency's five comments. The agency reviewed the protocol addendum and concluded that the revised protocol also was not statistically acceptable until the following revisions were made:

(1) Revision of the randomization procedure for assigning successive subjects as they are accepted into the study;

(2) Analysis of the data using the method of analysis of covariance, adjusting for baseline values, to compare treatment groups with respect to the number of hairs lost;

(3) Revision of the method for comparing the proportion of successes in each treatment group.

The company's proposed "binomial test" was determined not to be appropriate because this was a parallel group study and there was no matching. The agency recommended using Fisher's exact test or the chi-square test.

Without these revisions, the agency concluded that the protocol was not acceptable from a statistical viewpoint. The agency's detailed comments are on file in the Dockets Management Branch (Ref. 3).

The agency did not receive any further response from the comment regarding this study protocol, nor has it received any study results from the comment. No other data were submitted for biotin. Accordingly, biotin is a nonmonograph ingredient.

References

(1) Comment No. LET016, Docket No. 70N–0357, Dockets Management Branch.

(2) Comment No. LET019, Docket No. 80N–0357, Dockets Management Branch.

(3) Letter from W.E. Gilbertson, FDA, to M.H. Shapiro, Kleinfeld, Kaplan and Becker, coded LET021, Docket No. 80N–0357, Dockets Management Branch.

II. The Agency's Final Conclusions on OTC Hair Grower and Hair Loss Prevention Drug Products

Although the Panel recommended that the hair grower and hair loss prevention active ingredients ascorbic acid, benzoic acid, estradiol (not to exceed 5.5 micrograms per day), lanolin, tetracaine hydrochloride, and wheat germ oil were safe, it did not find sufficient data to determine that any of these ingredients were generally recognized as effective for these uses in an OTC drug product. The agency has determined that none of these ingredients or any other hair grower or hair loss prevention active ingredient, including biotin, has been found to be generally recognized as safe and effective and not misbranded for use as a hair grower or for hair loss prevention. Therefore, all hair grower and hair loss prevention ingredients, including amino acids, aminobenzoic acid, ascorbic acid, benzoic acid, biotin and all other B-vitamins, dexpanthenol, estradiol and other topical hormones, jojoba oil, lanolin, nucleic acids, polysorbate 20, polysorbate 60, sulfanilamide, sulfur 1 percent on carbon in a fraction of paraffinic hydrocarbons, tetracaine hydrochloride, urea, and wheat germ oil, are considered nonmonograph ingredients and misbranded under section 502 of the act (21 U.S.C. 352) and are new drugs under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved NDA under section 505 of the act (21 U.S.C. 355) and Part 314 of the regulations (21 CFR Part 314) is required for marketing. As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in a citizen petition to establish a monograph. (See 21 CFR 10.30.) Any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule that is not in compliance with the regulation is subject to regulatory action.

No comments were received in response to the agency's request on January 15, 1985 (50 FR 2190 at 2197) for specific comment on the economic impact of this rulemaking. The agency has examined the economic consequences of this final rule 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 final rule for OTC hair grower and hair loss prevention drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96–354). That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC hair grower and hair loss prevention drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

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.

List of Subjects in 21 CFR Part 310

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations is amended in Part 310 *to read* as follows:

PART 310—NEW DRUGS

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

Authority: Secs. 501, 502, 503, 505, 701, 704, 705, 52 Stat. 1049–1053 as amended, 52 Stat. 1055–1056 as amended, 67 Stat. 477 as amended, 52 Stat. 1057–1058 (21 U.S.C. 351, 352, 353, 355, 371, 374, 375); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

2. Section 310.527 is added to Subpart E 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, dexpanthenol, estradiol and other topical hormones, jojoba oil, lanolin, nucleic acids, 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 OTC drug products for external use as hair growers or for hair loss prevention. There is a lack of adequate data to establish general recognition of the safety and effectiveness of these or any other ingredients intended for OTC external use as a hair grower or for hair loss prevention. Based on evidence currently available, all 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 (the 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) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC external use as a hair grower or for hair loss prevention is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in Part 312 of this chapter.

(d) After January 8, 1990, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

Dated: April 28, 1989.

Frank E. Young,

Commissioner of Food and Drugs.

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