Exchange Act of 1934 (the "Act").[3] As part of those actions, the Commission is withdrawing certain proposals made earlier[4] relating to these matters. Specifically, for the reasons explained in the companion release, the Commission is announcing the following actions:

(1) Withdrawal of proposed Rule 3b–7, which would have defined the term "rule" of a self-regulatory organization for purposes of Sections 3(a)(27) and 3(a)(28) of the Act.

(2) Withdrawal of proposed amendments to Rule 19b–4 and related Form 19b–4A that would have provided summary effectiveness for certain proposed rule changes of a self-regulatory organization circulated, for pre-filing review, to the Commission and to persons who would be subject to the rules.

Further explanation of the above actions, and of other actions being taken concerning filings of proposed rule changes and other materials, is provided in the companion release issued today.

By the Commission.

George A. Fitzsimmons,

Secretary.

October 30, 1980.

[FR Doc. 80-34738 Filed 11-6-80; 8:45 am]

BILLING CODE 8010-01-M

ENVIRONMENTAL PROTECTION AGENCY

21 CFR Part 193

[FRL 1596-1; FAP 9H5196/P19]

Glyphosate; Proposed Food Additive Tolerances

Correction

In FR Doc. 80–26939, appearing at page 58494 in the issue for Wednesday, September 3, 1980, make the following corrections:

(1) In the **"Summary"** paragraph, in the seventh line, "isopropylsponic" should have read "isopropylamine".

(2) In the first paragraph under **"Supplementary Information"**, in the twelfth line, the word "the" should have read "from".

BILLING CODE 1505-01-M

[3] 15 U.S.C. 78a et seq.

[4] Securities Exchange Act Release No. 15838 (May 18, 1979), 44 FR 30924 (May 29, 1979).

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: Proposed rule.

SUMMARY: This document proposes that hair grower and hair loss prevention drug products be classified in Category II as being not generally recognized as effective and as being misbranded for over-the-counter (OTC) use. The document, based on the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products, is part of the ongoing review of OTC drug products conducted by the Food and Drug Administration (FDA).

DATES: Comments by February 5, 1981. Reply comments by March 9, 1981.

ADDRESS: Written comments to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFA–510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on December 10, 1979 a report on hair grower and hair loss prevention drug products from the Advisory Review Panel on OTC Miscellaneous External Drug Products.

Under § 330.10(a)(6) (21 CFR 330.10(a)(6)), the agency issues (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC hair grower and hair loss prevention drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

Because the Panel's recommendations on hair grower and hair loss prevention drug products for OTC use contain no Category I or Category III conditions, FDA is therefore issuing the Panel's recommendations as a notice proposing Category II classification of hair grower and hair loss prevention drug products for OTC use.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it. The Panel's findings appear in this document as a formal notice to propose classification of hair grower and hair loss prevention drug products as Category II and to obtain public comment before the agency reaches any decision on the Panel's recommendations. Should the agency accept the Panel's recommendation that the ingredients in hair grower and hair loss prevention drug products be classified as Category II, a regulation declaring the products to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 321(p)) will be proposed for inclusion in Part 310, Subpart E (21 CFR Part 310, Subpart E). The agency is including the proposed regulation in this notice to obtain full public comment at this time. After FDA has carefully reviewed the comments and reply comments, submitted in response to this notice, the agency will issue a tentative final order on hair grower and hair loss prevention drug products for OTC use.

Should FDA accept the conclusions and recommendations of the Panel, the agency would propose that hair grower and hair loss prevention drug products be eliminated from the OTC market, effective 6 months after the date of publication of a final order in the **Federal Register**, regardless of whether further testing is undertaken to justify their future use.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC hair grower and hair loss prevention drug products submitted for consideration by the Advisory Review Panel. All the submitted information will be put on public display at the Hearing Clerk's Office, Food and Drug Administration, after December 8, 1980, except to the extent that the person

submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD–510) (address above).

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, requests for data and information on all active ingredients used in OTC miscellaneous external drug products were issued in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179).

The Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report under § 330.10(a) (1) and (5) on the safety, effectiveness, and labeling of those products:

William E. Lotterhos, M.D., Chairman.
Rose Dagirmanjian, Ph. D.
Vincent J. Derbes, M.D. (resigned July 1976).
George C. Cypress, M.D. (resigned November 1978).
Yelva L. Lynfield, M.D. (appointed October 1977).
Harry E. Morton, Sc. D.
Marianne N. O'Donoghue, M.D.
Chester L. Rossi, D.P.M.
J. Robert Hewson, M.D. (appointed September 1978).

Representatives of consumer and industry interests served as nonvoting members of the Panel. Marvin M. Lipman, M.D., of Consumers Union, served as the consumer liaison. Gavin Hildick-Smith, M.D., served as industry liaison from January until August 1975, followed by Bruce Semple, M.D., until February 1978. Both were nominated by the Proprietary Association. Saul A. Bell, Pharm. D., nominated by the Cosmetic, Toiletry, and Fragrance Association, also served as an industry liaison since June 1975.

Two nonvoting consultants, Albert A. Belmonte, Ph. D., and Jon J. Tanja, R.Ph., M.S., have provided assistance to the Panel since February 1977.

The following FDA employees assisted the Panel: John M. Davitt served as Executive Secretary until August 1977, followed by Arthur Auer until September 1978, followed by John T. McElroy, J.D. Thomas D. DeCillis, R.Ph., served as Panel Administrator until April 1976, followed by Michael D. Kennedy until January 1978, followed by John T. McElroy, J.D. Joseph Hussion, R.Ph., served as Drug Information Analyst until April 1976, followed by Victor H. Lindmark, Pharm. D., until March 1978, followed by Thomas J. McGinnis, R.Ph.

The Advisory Review Panel on OTC Miscellaneous External Drug Products was charged with the review of many categories of drugs. Due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for hair grower and hair loss prevention drug products in this document. The review of other categories of miscellaneous external drug products will be continued by the Panel, and its findings will be published periodically in future issues of the **Federal Register**.

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings which dealt with the topic in this document were held on: October 29 and 30, 1978; January 14 and 15, March 11 and 12, May 18 and 19, August 3 and 4, September 28 and 29, October 28 and 29, and December 9 and 10, 1979.

The minutes of the Panel meetings are on public display in the Hearing Clerk's Office (HFA–305), Food and Drug Administration (address above).

At the Panel's request, Norman Orentreich, M.D., appeared before the Panel to express his views on hair grower and hair loss prevention drug products.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from an interested person, and has considered all pertinent information submitted through December 10, 1979 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed OTC hair grower and hair loss prevention drug products with respect to the following three categories:

Category I. Conditions under which OTC hair grower and hair loss prevention drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC hair grower and hair loss prevention drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel concludes that all hair grower and hair loss prevention active ingredients reviewed are safe, but none is effective for OTC use (Category II).

I. Submission of Data and Information

In an attempt to make this review as extensive as possible and to aid manufacturers and other interested persons, the agency compiled a list of ingredients recognized, either through historical use or use in marketed products, as hair growers and sebum hair loss (hair loss prevention) active ingredients. Thirteen hair grower ingredients were identified as follows: Amino acids, ascorbic acid, benzoic acid, essential oils, fatty acids, hormone constituents, lanolin, oil of eucalyptus, olive oil, proteins, tar oil, vegetable oil, and vitamins. Thirteen sebum hair loss prevention ingredients were identified as follows: Allantoin (5-ureidohydantoin), ammonium lauryl sulfate, dichlorophene, di-isobutyl-phenoxy-ethoxy-ethyl-dimethylbenzyl-ammonium chloride, estradiol, isopropyl alcohol, lauric diethanolamide, methyl ethyl ketone, polyethylene glycol, propytlene glycol, sulfonated vegetable and mineral oils, and tetracaine hydrochloride. Notices were published in the **Federal Register** of November 16, 1973 (38 FR 31679) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on these ingredients or any other ingredients used in OTC hair growers and sebum hair loss drug products.

A. *Submissions.* Pursuant to the above notices, the following submissions were received:

Firms and marketed products

Edwards Industrial Center, Inc., Matawan, NJ 07747—Hair and Scalp Treatment
Loesch Laboratory Consultants, Inc., Houston, TX 77006—Antiseptic Dressing, Deacidizing Scalp Conditioner, L–55–A Scalp Cleanser, Special Shampoo
Shepard D. Roberts, Brooklyn, NY 11203—Hair Stimulant and Grower

B. *Ingredients Reviewed by the Panel.*

1. *Labeled ingredients contained in marketed products submitted to the Panel.*

Ammonium lauryl sulfate
Ascorbic acid
Benzethonium chloride (di-isobutyl phenoxy ethoxy ethyl dimethyl benzyl-ammonium chloride, monohydrate)
Benzoaic acid
Coconut oil
Estradiol
Isopropanol
Lanolin
Lauric diethanolamide

Methyl ethyl ketone
Mineral oil
Polyethylene glycol 400
Polysorbate 80
Sodium hydroxide
Sulfonated vegetable oil
Tetracaine hydrochloride
Vegetable olive oil
Wheat germ oil (source of vitamin E and thiamine)

2. *Other ingredients reviewed by the Panel.*

Allantoin (5-ureidohydantoin)
Amino acids
Dichlorophen (dichlorophene)
Essential oils
Eucalyptus oil
Fatty acids
Hormone constituents
Olive oil
Propylene glycol
Proteins
Tar oil
Vegetable oil
Vitamins

C. *Classification of Ingredients.*

1. *Active ingredients.*

Ascorbic acid
Benzoic acid (benzoaic acid)
Estradiol
Lanolin
Tetracaine hydrochloride
Wheat germ oil (source of vitamin E and thiamine)

2. *Inactive ingredients.*

Ammonium lauryl sulfate
Benzethonium chloride (di-isobutyl phenoxy ethoxy ethyl dimethyl benzyl-ammonium chloride, monohydrate)
Coconut oil
Isopropyl alcohol (isopropanol)
Methyl ethyl ketone
Mineral oil
Polyethylene glycol 400
Polysorbate 80
Sodium hydroxide
Sulfonated vegetable oil
Vegetable olive oil

3. *Other ingredients.* The Panel was not able to locate nor is it aware of any data demonstrating the safety and effectiveness of the following ingredients when used as OTC hair grower and hair loss prevention active ingredients. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be discussed further in this document.

Allantoin (5-ureidohydantoin)
Amino acids
Dichlorophen (dichlorophene)
Essential oils
Eucalyptus oil (oil of eucalyptus)
Fatty acids
Hormone constituents
Lauric diethanolamide
Olive oil
Propylene glycol
Proteins
Tar oil
Vegetable oil
Vitamins

D. *Referenced OTC Volumes.* The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179). All the information included in these volumes, except for those deletions which are made in accordance with confidentiality provisions as set forth in § 330.10(a)(2), will be put on public display after December 8, 1980, in the Hearing Clerk's Office (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Discussion

The Advisory Review Panel on OTC Miscellaneous External Drug Products was given the responsibility to review the safety and effectiveness of single ingredients as well as combinations of such ingredients when used in OTC hair growers and sebum hair loss drug products. The Panel interpreted that request as a charge to evaluate products used for hair growers and seburm hair loss on that portion of the human head usually covered with hair. However, the Panel finds that the term "sebum hair loss" is too restrictive when OTC drug preparations for human hair loss are considered. Therefore, instead of the term "sebum hair loss," the term "hair loss prevention" was chosen by the Panel as a more general term to accurately describe any condition that contributes to the prevention of hair loss from the human scalp.

The common type of baldness, male-pattern alopecia, is inherited, as are hair color, texture, and curliness. A concern about the thinning of scalp hair resulting in hair loss may lead to the use of OTC "hair growth stimulants."

Hair growth is not continuous but rather cyclical. A hair follicle grows a hair for a specific period of time; this phase is called anagen. The hair then enters a transitional phase (catagen) and finally a resting phase called telogen. The telogen or resting hair sits in the hair follicle for several months; then it is shed. The cycle begins again with the new hair growing in the same follicle. A growing hair has specific characteristics, such as swelling and pigmentation at the tip. All growing hairs have external and internal root sheaths.

Several factors determine hair growth, i.e., the rate of growth, the duration of anagen, the duration of telogen, the thickness (diameter) of the hair, and the percentage of hairs in the growth (anagen) phase. For example, a scalp hair grows 3 to 5 years and has a much longer final length than an eyebrow hair, which grows for about 6 months. The growing cycle of body hair varies in length from site to site. Approximately 85 percent of the hair on the scalp is in the anagen phase. Because hairs in the anagen, telogen, and catagen phase can be distinguished morphically (by structure), a differential hair count can be done by looking at the roots (Ref. 1).

Hormones, with the exception of those topically applied, affect the hair cycle, the rate of hair growth, the diameter, and the pigmentation of hair. Topically applied hormones have no affect. At puberty many hairs change. A beard hair, for example, under the influence of the androgen dihydrotestosterone is converted from a very fine vellus hair, which has no pigment, is thin, and grows only to a very short length, to a coarse, long, terminal hair.

Male-pattern baldness is the exact opposite of what occurs in the development of a beard. A hair starts out coarse and goes to fine. This occurs in a certain pattern. First, there is a frontal "V" which male adolescents develop and which is really physiologic (Ref. 1). The hairline in women and children is usually straight across; adult males usually exhibit a M-shaped hairline. In people who inherit the gene for male-pattern baldness and who have a normal adult male androgen level, this frontal "V" continues to recede. The crown of the hair starts to go bald, and eventually the "V" connects with the crown. The result is a horseshoe pattern of hair. The follicle has not suddenly stopped producing a hair. Rather, the cycles of hair growth become shorter and shorter; terminal hairs are replaced by vellus hairs. Hamilton (Ref. 2) showed that baldness did not occur in the absence of male hormones, such as in men castrated before puberty, even though the tendency to baldness was inherited. When given androgens, the same subjects became bald.

Hair loss in women is not as great as that seen in men. There is some thinning of the hair in women who inherit the tendency to pattern alopecia (loss of hair) in later years, but hair loss never occurs to the extent found in men.

In certain body states, such as fever or childbirth, a conversion of a great many hairs from the anagen to the telogen phase occurs (Ref. 3). In 3 months (the duration of telogen on the scalp) these hairs are shed, and a sudden thinning of hair (diffuse alopecia) occurs. Then, new anagen hairs start to grow in the same follicle. It would be difficult to prove that this new hair growth occurred as a result of an

application of any substance to the scalp.

Diffuse hair loss can be produced by malnutrition (starvation, crash dieting, iron deficiency), exposure to radiation, and hormonal imbalance (hypothyroidism, hyperthyroidism, hypopituitarism) (Ref. 4). It is caused by a variety of drugs, especially those used for cancer chemotherapy. Alopecia areata (an inflammatory loss of hair in sharply defined areas), fungus infection, secondary syphilis, and lupus erythematosus can cause patchy or extensive baldness.

Nothing done to the hair shaft once it emerges from the surface of the scalp will influence the hair growth. Anything that would influence regeneration of the hair would have to work on the hair root. Pulling on the root, such as with tight ponytails, braids, or a great deal of hair teasing can damage the follicle and cause some alteration in hair growth. Permanent waving, bleaching, shaving, and other external trauma to the hair shaft, which does not affect the hair root, will not have a longterm effect on the hair.

Products which cling to the hair shaft will give extra bulk to the hair and make it seem thicker. The resulting effect is cosmetic and not a drug action intrinsically changing the hair. In order to demonstrate that an ingredient is a hair restorer, it must be proven that the substance gets into the hair root and causes stimulation of hair growth.

An increase in the rate of hair growth, an increase in the diameter of the hair shaft, or the duration of the anagen phase would be convincing evidence of hair growth stimulation. An easier measurement of hair growth would be the total weight of hair produced by stimulation as compared to a control over a period of time. These studies should be carried out on a portion of scalp with a matched, symmetrical area of scalp as simultaneous control, in order to allow for fluctuations of hair growth from systemic causes or from the season of the year.

Because a sudden excessive hair loss or an unusual pattern of hair loss may have an underlying medical cause, the Panel recommends that persons having such a problem consult a doctor.

References

(1) Transcript of Proceedings of the Advisory Review Panel on OTC Miscellaneous External Drug Products, January 14 and 15, 1979.

(2) Hamilton, J. B., "Male Hormone Stimulation is Prerequisite and an Incitant in Common Baldness," *American Journal of Anatomy*, 71:451–481, 1942.

(3) Kligman, A. M., "Pathologic Dynamics of Human Hair Loss," *Archives of Dermatology*, 83:175–198, 1961.

(4) Rook, A., D. S. Wilkinson, and F. J. G. Ebling, "Textbook of Dermatology," Vol. II, 2d Ed., Blackwell Scientific Publications, London, pp. 1559–1641, 1972.

III. Category II Active Ingredients

The Panel has classified the following hair grower and hair loss prevention ingredients as not generally recognized as effective and as being misbranded for OTC use.

Ascorbic acid
Benzoic acid
Estradiol
Lanolin
Tetracaine hydrochloride
Wheat germ oil

The Panel received three submissions for marketed products (Refs. 1, 2, and 3). One manufacturer submitted a formula for review for a product containing tetracaine hydrochloride, benzoaic acid [sic] (benzoic acid), and ascorbic acid. The manufacurer claimed that this product was for use as a "hair and scalp treatment product for preventing hair loss." However, neither data on the product nor the individual ingredients were submitted. The manufacturer merely stated that the tetracaine hydrochloride was employed for its vasodilatory properties and antipruritic action for aiding in developing hair follicles. Further, the manufacturer claimed that benzoic acid was used because of its antibacterial action and ascorbic acid for the claimed effect of strengthening hair roots by activating cellular respiration of the scalp and stimulating blood circulation (Ref. 1). The Panel reviewed this submission and concluded that there is no evidence that tetracaine hydrochloride, benzoic acid, ascorbic acid, or their combination applied topically to the scalp has any effect on hair growth. A search of the scientific literature did not yield any such evidence.

Another manufacturer submitted a laboratory report for a hair stimulant and grower. The manufacturer described the ingredients as lanolin, wheat germ oil, pure coconut oil, and pure vegetable olive oil, but no data on the effectiveness of the individual ingredients or the combination of ingredients were submitted (Ref. 2). The Panel reviewed the submission and concluded that there is no evidence that these ingredients or their combination applied topically to the scalp have any effect on hair growth. A search of the scientific literature did not yield any such evidence.

A third manufacturer submitted both safety and effectiveness data for a variety of products used for sebum hair loss. Treatment includes the sequential use of the following five products: (1) A deacidizing scalp conditioner (claimed for correcting, destroying, or neutralizing an acid), (2) a scalp cleanser, (3) a shampoo, (4) a hair growth stimulator, and (5) an antiseptic dressing. The manufacturer identified the active ingredients as: estradiol 666 International Units per day (IU/day) of 0.011 milligram per fluid ounce (mg/fl oz), providing a daily dose of 0.0055 mg/day, isopropanol, methyl ethly ketone, sulfonated vegetable and mineral oils, ammonium lauryl sulfate, and benzethonium chloride (di-isobutyl phenoxy ethoxy ethyl dimethyl benzyl-ammonium chloride, monohydrate). The manufacturer claimed that this system was a treatment for "sebum hair loss," defined as "the damage or destruction of the cells and tissues responsible for the holding and synthesizing of the hair shaft in the hair follicle by the epilating agents which have been shown to be present in human sebum."

The scientific evidence cited in the third manufacturer's submission to the Panel consisted of studies, published in 1951 and 1952, showing that human sebum or squalene (a chemical in sebum) applied to the skin of rats produced epilation; no more recent studies and no human studies were available (Ref. 3).

The theory that sebum can cause hair loss is not today generally accepted by the medical profession (Ref. 4). One text described studies which measured 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 and found no quantitative difference in sebum between these groups. It was concluded that balding men did not have abnormally oily scalps and that no quantitative chemical difference existed between the sebum of balding subjects and balding men. Male pattern baldness may occur coincidentally with increased scalp oiliness. Except for the fact that hair loss and the stimulation of sebaceous glands are both caused by dihydrotestosterone, hair loss and increased scalp oiliness probably are otherwise unrelated.

Pochi and Strauss (Ref. 5) in 1974 reviewed the endocrinologic control of the human sebaceous gland. Estrogen given systemically reduces the size and secretion of sebaceous glands in both men and women. Ethinyl estradiol applied to the forehead of normal men was shown to reduce sebum production; however, the concentration required (1 percent or greater) to reduce sebum

production produced signs of feminization from systemic drug absorption. Attempts to inhibit sebum production with topical estradiol 17B, which is a weaker estrogen, have been unsuccessful.

Because estrogens are readily absorbed through the skin and mucous membranes, the systemic effects resulting from topical application frequently may be observed. For example, in factory workers, gynecomastia (excessive development of the male mammary glands) resulted from handling of diethylstilbestrol (Ref. 6). Masters (Ref. 7) demonstrated increased estrogen in the urine and estrogen-induced vaginal keratinization when two healthy post-menopausal women applied estrogen cream to their skins. Haznam, Mahesh, and Greenblatt (Ref. 8) reported similar effects from cutaneous application of estrogen to a 67-year-old woman. Greenblatt (Ref. 9) treated an 18-year-old girl with Turner's Syndrome with estrogen cream; she developed vaginal keratinization, breast enlargement, and an increase in pubic hair. After applying radioactive estrogen under plastic or aluminum foil to women's backs radioactive metabolites were promptly detected in their urine (Refs. 10 and 11).

Therefore, because of the risk of systemic effects, the amount of estrogen applied topically should be limited. OTC estrogen preparations are labeled with instructions not to exceed a measured amount, which contains 666 IU/day which is approximately 20,000 IU/month. The Panel agreed that estradiol in a dose of 5.5 micrograms per day (μg/day), which equals 666 IU/day, is safe. The lack of systemic effects from this dose is well documented in studies by Masters (Ref. 7), Haznam (Ref. 8), Karnaky (Ref. 12), and Greenblatt (Ref. 13). In the 30 years that these preparations have been marketed, only 3 cases of uterine bleeding (Refs. 14, 15, and 16) may be ascribed to their use. Other adverse effects of systemic estrogen therapy, such as thrombotic disorders, nausea, edema, and breast tenderness and enlargement, have not been reported at this dosage. This is in spite of the fact that when creams are purchased OTC, the user can disregard the instructions and apply far larger quantities than recommended.

The manufacturer of the estrogen-containing product further stated that "this system does purport to be effective in the treatment of male pattern baldness and was not designed for that purpose." However, the data included in this report show that in a random sample of men and women with thinning hair, at least 50 percent of the patients were helped by this treatment (Ref. 3). To support the use of the product for sebum hair loss, the manufacturer submitted a variety of animal safety data for the individual active components of the various marketed products. Effectiveness data included controlled and uncontrolled studies, documented case reports, and references to the scientific literature. The manufacturer stated that four clinical tests demonstrated effectiveness. Three uncontrolled tests were conducted by 44 dermatologists on 230 patients treated from 2 to 11 months during the years 1965 through 1971. Of the patients treated, 88 percent had their hair loss reduced to normal loss or the loss was significantly decreased; 82 percent showed an improvement in the general condition of the scalp, 58 percent showed evidence of new hair growth, and 51.6 percent showed noticeable hair thickening (Ref. 3). One controlled clinical study, conducted in a southwestern medical school, indicated that 33 percent of the patients had a significant decrease in hair loss compared with their control period. Forty-five percent of the patients showed significant evidence of new hair growth as shown by physician examination and corroborated by actual hair count. In addition, 57.5 percent of the patients reported a significant increase in hair density compared to their control period. The manufacturer claims that the studies demonstrate that the treatment "has been shown to be effective for controlling and treating sebum hair loss" (Ref. 3).

The Panel has reviewed the data submitted and concludes that the uncontrolled clinical studies were too subjective to be convincing, because they consisted of only favorable testimonials by dermatologists, as well as men and women with hair loss. Daily shampooing with any nonmedicated shampoo would remove surface oil, scale, and loose hairs. No descriptions, photographs, or quantitative data on the hair loss of individual patients were given. Since the telogen phase on the scalp averages 3 months, it would be surprising to have a real decrease in hair loss in 2 months.

The one controlled quantitative study was very well planned, but so poorly carried out that the results are not significant. Thirty-four subjects (8 women and 26 men) complaining of hair loss of either male pattern or generalized type were studied during a 2-month control period and 3 to 5 months of use of the combination treatment. Photographic assessment and telogen counts were attempted, but the results of these tests were inadequate because the photographs were unclear. Collections of hair loss were also unreliable because of changes in shampooing frequency.

The Panel has reviewed all the information submitted and concludes that the ingredients are safe when used as specified, but that the data fail to demonstrate the effectiveness of these ingredients. Based upon a review of all of the data available to the Panel, and on the fact that no data are available in the literature demonstrating the effectiveness of ingredients reviewed as hair growers and hair loss prevention drug products, the Panel concludes that all claimed hair grower and hair loss prevention active ingredients reviewed are not effective for OTC external use.

References

(1) OTC Volume 160118.

(2) OTC Volume 160232.

(3) OTC Volume 160018.

(4) Rook, A., "Common Baldness and Alopecia Areata" *in* "Recent Advances in Dermatology," Vol. 4, Churchill Livingstone, New York, pp. 223–245, 1977.

(5) Pochi, P. E., and J. S. Strauss, "Endocrinologic Control of the Development and Activity of the Human Sebaceous Gland," *The Journal of Investigative Dermatology*, 62:191–201, 1974.

(6) Murad, F., and A. G. Gilman, "Estrogens and Progestins," *in* "Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman, and A. Gilman, MacMillan Publishing Co., Inc., New York, pp. 1423–1450, 1975.

(7) Masters, E. J., "The Percutaneous Absorption of Estrogens," *Proceedings of the Scientific Section of the Toilet Goods Association*, 33:5–11, 1960.

(8) Haznam, M. W., V. B. Mahesh, and R. B. Greenblatt, "Absorption of Topically Applied Estrogen Preparations," *Dermatologia Internationalis*, 4:86–91, 1965.

(9) Greenblatt, R. B., "Report on Helena Rubinstein Estrogen-Progesterone Cream Study," Draft of unpublished paper, in OTC Volume 160095.

(10) Goldzieher, J. W., and R. E. Baker, "The Percutaneous Absorption of Estradiol-17B and Progesterone," *The Journal of Investigative Dermatology*, 35:215–218, 1960.

(11) Baker, R. E., and J. W. Goldzieher, "A Simple Method for the Measurement of Total Urinary Radioactive Steroid Metabolites and its Application to the Study of Percutaneous Absorption." *Acta Endocrinologica*, 38: 276–284. 1961.

(12) Karnaky, K. J., "An Investigation of Possible Gynecological Changes Resulting From the Topical Use of an Estrogen-Progesterone Cream With Special Emphasis on Vaginal Epithelial Cell Height and pH," *Tri-State Medical Journal*, March, 1960.

(13) Greenblatt, R. B., et al., "Physiologic and Clinical Aspects of Ovarian Hormones," *Archives of Dermatology* 89:846–857, 1964.

(14) OTC Volume 160055.

(15) OTC Volume 160195.

(16) Goldberg, M. B., and F. Harris, "Use of Estrogen Creams," *Journal of the American Medical Association*, 150:790–791, 1952.

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.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 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 authority delegated to the Commissioner (21 CFR 5.1), 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 new § 310.527 to Subpart E, to read as follows:

§ 310.527 OTC drug products containing active ingredients offered for external use as hair growers or for hair loss prevention.

(a) Ascorbic acid, benzoic acid, estradiol, lanolin, tetracaine hydrochloride, and wheat germ oil have been present as ingredients in over-the-counter (OTC) drug products marketed for use as hair growers or for hair loss prevention. There is a lack of adequate data to establish the effectiveness of these ingredients as hair growers or hair loss prevention OTC drug products. Data on any other ingredient intended for use as a hair grower or for hair loss prevention in OTC drug products have not been submittted to the Food and Drug Administration for review for safety and effectiveness. Therefore, any OTC drug product 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 labeled, represented, or promoted for use as a hair grower or hair loss prevention agent is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act and is regarded as a new drug within the meaning of section 201(p) of 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.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD–1571), 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 use as a hair grower or hair loss prevention agent is safe and effective for the purpose intended.

(d) After the effective date of the final regulation, any such drug product introduced in interstate commerce that is not in compliance with this section is subject to regulatory action.

Interested persons are invited to submit their comments in writing (preferably in four copies and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before February 5, 1981. Comments should be addressed to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replying to comments may also be submitted on or before March 9, 1981. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: October 16, 1980.

Mark Novitch,

Acting Commissioner for Food and Drugs.

[FR Doc. 80-34724 Filed 11-6-80; 8:45 am]

BILLING CODE 4110-03-M

---

21 CFR Parts 700, 710, 720, and 730

[Docket No. 80N-0346]

Modification in Voluntary Registration of Cosmetic Industry Data

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to reduce the reporting burden of the persons voluntarily participating in the registration of cosmetic product establishments and the filing of cosmetic product formulations, raw material compositions, and consumer adverse reactions. The proposed reductions will have no significant effect on the quality of the cosmetic registration programs.

DATES: Written comments by January 6, 1981. The proposed effective date of the final rule based on this proposal is 30 days after its date of publication in the **Federal Register.**

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's office) (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Earl L. Richardson, Bureau of Foods (HFF–444), Food and Drug Administration, 200 C ST. SW., Washington, DC 20204, 202–245–1094.

SUPPLEMENTARY INFORMATION: Regulations issued in 1972 and 1973 in response to petitions received from the Cosmetic, Toiletry and Fragrance Association, Inc., provide for the voluntary registration of cosmetic product establishments (21 CFR Part 710), voluntary filing of cosmetic product ingredient and cosmetic raw material composition statements (21 CFR Part 720), and voluntary filing of cosmetic product experiences (21 CFR Part 730).

A recently conducted review of the reporting requirements and impact of the reported information on the quality of the voluntary registration and filing programs has demonstrated that several items may be eliminated without significantly affecting the respective data files. Exclusion of these items will reduce the reporting burden of the firms currently participating in the programs and may motivate others to become participants.

The following changes in the voluntary reporting of cosmetic industry data are being proposed. These changes will not require resubmission of previously registered data.

Voluntary Registration of Cosmetic Product Establishments

It has been determined that disclosure of the kind of ownership or operation of an establishment (e.g., individually owned, partnership, or corporation) is not pertinent to the registration of manufacturers or packers of cosmetics. The purpose of this registration program is to provide FDA with information on the existence and location of an establishment. Ownership information does not help to identify establishments subject to factory inspection or support the enforcement of the Federal Food, Drug, and Cosmetic Act. FDA therefore proposes that the designation of the kind of ownership be deleted in § 710.4 (21 CFR 710.4).

FDA also proposes to delete from § 710.4 any reference to establishments which merely distribute cosmetics. Such