DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 310

[Docket No. 81N-0144]

Topically Applied Hormone-Containing Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of proposed rulemaking that would classify hormone-containing drug products for over-the-counter (OTC) oral human use as not generally recognized as safe and effective and as being misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by April 5, 1982, and reply comments by May 5, 1982.

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: William E. Gilbertson, Bureau of Drugs (HFD-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 15, 1980 a report on OTC topically applied hormone-containing drug products from the Advisory Review Panel on OTC Miscellaneous External Drug Products. FDA regulations (21 CFR 330.10(a)(6) provide that the agency issue in the **Federal Register** a proposed order containing: (1) The monograph recommended by the Panel, which establishes conditions under which OTC topically applied hormone-containing drug products 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 such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The Panel's recommendations on topically applied hormone-containing drug products for OTC use contain no Category I or Category III conditions, and FDA is issuing the Panel's recommendations proposing Category II classification of topically applied hormone-containing 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 to obtain public comment before the agency reaches any decision on the Panel's recommendations that the ingredients in topically applied hormone-containing drug products for OTC use be classified as Category II. If the agency proposes to adopt the Panel's recommendations, a regulation declaring these 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 310, Subpart E). The agency is including, in this advance notice of proposed rulemaking, a regulation based upon the Panel's recommendations in order to obtain full public comment at this time.

After reviewing all comments submitted in response to this document, FDA will publish in the **Federal Register** a notice of proposed rulemaking on topically applied hormone-containing drug products for OTC use. The agency's position on OTC topically applied hormone-containing drug products will be stated initially when that notice of proposed rulemaking is published in the **Federal Register.** In the notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part 25 (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC topically applied hormone-containing drug products. Types of impact may include, but are not limited to, the following: Increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any. Comments regarding the impact of this rulemaking on OTC topically applied hormone-containing drug products should be accompanied by appropriate documentation.

If FDA proposes to adopt the Panel's recommendations, the agency will propose that topically applied hormone-containing drug products be eliminated from the OTC market, effective 6 months after the date of publication of a final rule 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 topically applied hormone-containing drug products for OTC use submitted for consideration by the Panel. All this information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after February 4, 1982, except to the extent that the person submitting it demonstrates that it 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, a request for data and information on all active ingredients used in OTC miscellaneous external drug products was issued in the **Federal Register** of November 16, 1973 (38 FR 31697). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review pan[el] relied on their expertise and

understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.' ") In the **Federal Register** of August 27, 1975 (40 FR 38179) a notice supplemented the initial notice with a detailed, but not necessarily all-inclusive, list of active ingredients in miscellaneous external drug products to be considered in the OTC drug review. The list, which included hormone cream active ingredients, was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973, and August 27, 1975, informed OTC drug product manufacturers of the opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC review to all OTC drug products.

Under § 330.10(a)(1) and (5), the Commissioner appointed the following Panel to review the information submitted and to prepare a report on the safety, effectivenss, and labeling of the active ingredients in these miscellaneous external drug 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'Donohue, 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 topically applied hormone-containing drug products for OTC use in this document. The Panel's findings on other categories of miscellaneous external drug products are being published periodically in 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: January 28 and 29, 1978; November 7 and 8, and December 14 and 15, 1980.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above).

No individuals requested to appear before the Panel to discuss topically applied hormone-containing drug products for OTC use, nor was any individual requested to appear by the Panel.

The Panel has thoroughly reviewed the literature and data submissions, and has considered all pertinent information submitted through December 15, 1980 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed topically applied hormone-containing drug products for OTC use with respect to the following three categories:

Category I. Conditions under which topically applied hormone-containing drug products for OTC use are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which topically applied hormone-containing drug products for OTC use 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 reviewed three active ingredients in topically applied hormone-containing drug products and classified no ingredients in Category I, three ingredients in Category II, and no ingredients in Category III.

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, of hormone active ingredients contained in topically applied products (hormone creams). Notices were published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on these ingredients or any other ingredients used in OTC hormone cream drug products.

A. Submissions of Data and Information

Pursuant to the above notices, the following submissions were received:

Firms and Products

Helena Rubinstein, New York, NY 10022—Ultra Feminine Cream with Natural Estrogen and Progesterone, Ultra Feminine Beauty Oil with Natural Estrogen and Progesterone.

Sterling Drug, Inc., New York, NY 10016—Satura Moisture Cream with Hormones, Satura Moisture Lotion with Hormones, Moisturing Hormone Hand Cream, Cellogen Moisturizing Hormone Cream with Protein Hydrolysate.

USV Pharmaceutical Corporation, Tuckahoe, NY 10707—Hormonex Beauty Serum, Hormonex in Cream, Hormonex Hair and Scalp Serum.

In addition, FDA's Bureau of Drugs' Office of Compliance provided information to the Panel regarding potential hazards of topical skin and hair preparations containing various hormones (OTC Volune 160195). (See paragraph D. below—Referenced OTC Volumes.)

B. Ingredients Reviewed by the Panel

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

Estrone

Lanolin
Natural estrogenic hormones
Natural estrogens
Progesterone
Sesame oil
Vitamin A

2. *Other ingredients reviewed by the Panel.*

Estradiol
Estrogenic hormones
Estrogen
Pregnenolone acetate

C. Classification of Ingredients

1. *Active ingredients.*

Estrogens (estrogen, natural estrogens, estrogenic hormones, natural estrogenic hormones, estradiol, estrone)
Progesterone

2. *Inactive ingredients.*

Lanolin
Sesame oil
Vitamin A

3. *Other ingredient.* The Panel was not able to locate nor is it aware of any data demonstrating the safety and effectiveness of pregnenolone acetate, or any other ingredient, when used in topically applied hormone-containing drug products for OTC use. The Panel, therefore, classifies all such ingredients as Category II for this use, and they will not be discussed further in this document.

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 of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after February 4, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

E. General Discussion

The Panel has discussed topically applied hormone-containing drug products as a therapeutic class, as well as the two groups of active ingredients, the estrogens and progesterone, that are generally used in these products. The medical literature indicates that the topical application of hormone-containing drug products may affect the cellular structure of the skin but that these changes are observable only through a microscope.

Estrogenic hormones are responsible for the development of secondary sex characteristics in women at puberty. These hormones cause maturation of the internal and external genitals, enlargement of the breasts, and growth of pubic and axillary hair. Estrogens alone can produce proliferation of the uterine lining sufficient to cause menstrual bleeding; the normal ovulatory menstrual cycle results from the synergistic action of estrogens and progesterone. Pregnancy is associated with a large increase in levels of estrogens and progesterone. At the menopause, with declining levels of these hormones, menstrual cycles become irregular and then cease. Estrogen deficiency causes vasomotor disturbances (hot flashes) and atrophic vaginitis (Ref. *1*).

The ovary is the principal site of estrogen production in the nonpregnant premenopausal woman, and it secretes chiefly estradiol-17B (estradiol) and estrone. During pregnancy, the placenta produces more estrogens, primarily estradiol, than does the ovary. Estradiol is readily oxidized in the body to estrone, which in turn can be hydrated to estriol. These transformations take place mainly in the liver, where estrogens are also conjugated with sulfate of glucuronic acid. The conjugated estrogens are excreted by the kidney.

Natural estrogens for medicinal use are extracted from the urine of horses. A pregnant mare excrets over 100 milligrams (mg) of conjugated estrogens daily, more than any other mammal except a stallion.

Synthetic estrogens are often used therapeutically instead of natural estrogens. Alkylation of estradiol at the C17 position produces the orally potent estrogenic substances ethinyl estradiol and mestranol. Diethylstilbestrol and similar compounds have potent estrogenic activity although they do not have the steroidal configuration that estrogens have.

Progesterone is the ovarian hormone which changes the estrogen-primed lining of the womb into the secretory state necessary for pregnancy. In the mature menstrual cycle, a mature ovum is released; if it is not fertilized, a decline in the level of progesterone causes the lining of the womb to be shed—a change visible as menstrual bleeding. The activity of progesterone is determined by studying the cytology of vaginal smears and by measuring urinary pregnanediol, a metabolite of progesterone. Daily secretion of progesterone in a young woman ranges from a few milligrams during the early phase of the menstrual cycle to 10 to 20 mg in the latter half of the cycle to several hundred milligrams during the latter part of pregnancy, when progesterone is produced by the placenta as well as the ovary (Ref. *1*).

1. *Safety.* Estrogens are readily absorbed through the skin and mucous membranes, and systemic effects may result from topical application. In factory workers, gynecomastia (male breast development) followed the handling of diethylstilbestrol.

Masters (Ref. *2*) demonstrated an increased estrogen level in the urine and an estrogen-induced vaginal keratinization when two healthy postmenopausal women applied various estrogen creams topically. Five cream formulations were tested on each of the two women: Cream alone, cream plus 1 milligram per ounce (mg/oz) estrogen, cream plus 2 mg/oz estrogen, cream plus 4 mg/oz estrogen, and cream plus 1 mg/oz estrogen and 5 mg/oz progesterone. Haznam, Mahesh, and Greenblatt (Ref. *3*) reported similar vaginal keratinization effects in a 67-year-old woman from cutaneous application of estrogen creams containing 10,000 International Units per ounce (I.U./oz) and 50,000 I.U./oz estrogen. Greenblatt (Ref. *4*) treated an 18-year-old girl with Turner's Syndrome with an estrogen cream containing 10,000 I.U./oz estrone and 5 mg/oz progesterone. 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. *5* and *6*).

The Panel received three submissions for creams and oils claiming to improve the appearance of skin and hair (Refs. *7*, *8*, and *9*). These creams and oils contained 5,000 to 33,000 I.U./oz natural estrogen; in addition, one product contained progesterone 5 mg/oz.

Using 10,000 I.U./oz as an example for making calculations, and assuming for the calculation that the estrogen is estrone, the Panel calculated the concentration of estrogen in the reviewed OTC products as approximately 1 mg per 30 grams (g) or 0.003 percent, because 0.1 microgram (ug) of crystalline estrone is equivalent to 1 I.U. (Ref. *10*). One submission stated that the natural estrogen in its hormone cream is obtained from pregnant mares' urine and consists of 95 percent estrone with 17-estradiol and 5 percent miscellaneous female hormones (Ref. *9*). Bioassay is a better way of expressing estrogenic potency than weight because equal weights of chemically different estrogens differ markedly in their biologic effect. The estrogenic potency of estradiol is 12 times that of estrone

and 80 times that of estriol (Ref. *11*). Nevertheless, recent publications give estrogen content by weight.

The concentration of 10,000 I.U./oz estrogen was selected to achieve local cutaneous effects without significant systemic effects. The lack of systemic effects of this concentration is well documented in studies by Masters (Ref. *2*), Haznam, Mahesh, and Greenblatt (Ref.*3*), Karnaky (Ref. *12*), and Greenblatt (Ref. *13*). In the 30 years that these preparations have been marketed, only 3 cases of uterine bleeding (Ref. *14*) may be ascribed to their use (Ref. *15*). Adverse effects of systemic estrogen therapy, such as thrombotic disorders, nausea, edema, and breast tenderness and enlargement, have been reported from external use, due to the fact that when these products are purchased OTC it is possible for the user to disregard the instructions and apply far larger quantities than recommended (Ref. *16*). The incidence of irritation and allergic contact dermatitis using 10,000 I.U./oz is low. The Panel recognized that the data submitted are relatively old and concludes that there are inadequate data to establish that the use of estrogen is safe when used in amounts up to 2 oz/month in cream or oil. Therefore, the Panel recommends that estrogens in topically applied estrogen-containing OTC drug products be placed in Category III for safety.

Progesterone applied to the skin in concentrations similar to estrogen concentrations in marketed OTC cream and oil products seems free of systemic effects. Goldzieher and Baker (Ref. *5*), using a combination of estrogren 10,000 I.U./oz and progesterone 25 mg/oz, demonstrated no detectable increase in urinary pregnanediol. Karnaky (Ref. *12*) found no change in vaginal smears from the once-a-day use of cream containing estrogen 10,000 I.U. and progesterone 5 mg/oz. The Panel concludes that the topical OTC daily use of progesterone in a concentration up to 5 mg/oz is safe.

2. *Effectiveness.* The Panel was not presented any evidence or photographs showing any gross change, such as more even pigmentation or less wrinkling, to demonstrate that local application of estrogens improve the appearance of the skin. The only changes demonstrated have been histologic (microscopic review of sections of tissue) (Ref. *16*).

Goldzieher (Ref. *17*) biopsied the thighs and forearms of five elderly women before and after topical application of estrogen 10,000 I.U./oz. He found upon microscopic examination that the thin, senile epidermis thickened, both because of an increased number of cell layers and also because of the increased size of individual epidermal cells, and that the dermal-epidermal junction (rete ridges) returned to normal. A similar study using estrogen 5,000 to 15,000 I.U./oz on 28 elderly women, 6 elderly men, and 4 young women showed similar changes in the elderly people of both sexes but no change in the young women (Ref. *18*). Microscopic improvement was first evident histologically 10 days after starting treatment, and by the thirtieth day of treatment the epidermis has doubled in thickness and was better differentiated. Eller and Eller (Ref. *19*) did serial biopsies on 36 adults of both sexes and various ages treated with estrogen cream containing 7,500 and 15,000 I.U./oz and reached the same conclusion. Brown (Ref. *20*) instructed women aged 30 to 75 to apply estrogen cream to one side of their faces and the cream base alone to the other side for 45 days. The cream contained either 10,000 I.U. estrogen with 5 mg progesterone per ounce or 50,000 I.U./oz estrogen. Twenty-six post-treatment facial biopsies were submitted to expert dermatopathologists, who could not detect any histologic difference between the estrogen-treated and cream base-treated sides. In this study, Brown (Ref. *20*) noted a clinical (visual) impression of moderate improvement in appearance and wrinkling on the estrogen-treated side. This was also noted by Spoor (Ref. *21*) in double-blind half-face studies on eight women aged 22 to 64 treated for 30 days with cream containing 10,000 I.U./oz estrogen and 5 mg/oz progesterone.

Peck (Ref. *22*) performed a modified McClure-Aldrich test by injecting 0.05 milliliter (mL) of normal saline intradermally and measuring the time required for the visible and palpable wheal to disappear. This test measures the ability of the dermis to absorb additional fluid and therefore the saturation of the dermis which fluid prior to the injection. Peck (Ref. *22*) tested the cheeks of 4 women who used 10,000 I.U./oz estrogen cream daily. He found that the absorption time of the saline was increased in every case after 6 weeks of treatment. He did not report McClure-Aldrich tests after using the cream base alone. The Panel believes that it is possible that the mild dermal edema, which was difficult to demonstrate histologically, may be produced equally well by a moisturizing cream which does not contain hormones.

The use of progesterone on the skin is thought to increase skin surface oil by stimulating sebaceous glands. Animal experiments have shown that progesterone increased the size and rate of secretion of sebaceous glands in castrated male and female rats (Ref. *23*). A qualitative study by Spoor (Ref. *21*) using osmic acid staining of surface fat was interpreted as showing an increase in sebum production from local application of progesterone. However, quantitative gravimetric and histologic studies by Pochi and Strauss (Ref. *24*) demonstrated no effect on sebaceous gland secretion or size from the intramuscular administration of 50 mg/day progesterone in prepubertal girls and boys, young adult women, and aged women.

The physiologic stimulus to sebaceous gland growth and secretion is testosterone (Ref. *24*). In 1961, Strauss (Ref. *25*) demonstrated an appreciable increase in sebum production in aged females after the daily administration of 100 mg of methyltestosterone orally. Accordingly, Strauss (Ref. *25*) believed that some of the synthetic progestational agents, such as 17-*alpha*-ethynyl-nortestosterone, have and rogenic activity and stimulate sebaceous glands. However, more recent medical opinion (1975 to 1980) is that progesterone has no effect on human sebaceous glands (Refs. *16* and *26*).

The Panel notes that estrogen and progesterone hormones are often included in products that make cosmetic claims only. The Panel recognizes that evidence submitted demonstrating safety of estrogens not exceeding 10,000 I.U./oz and progesterone not exceeding 5 mg/oz is relatively old data. Additionally, the Panel knows of no objective data that show these levels are effective. The Panel believes that inclusion of estrogen and progesterone in these products misleads the consumer into believing that using the ingredient will give the user a more youthful appearance when in fact the changes that occur cannot be seen with the naked eye.

3. *Evaluation.* The Panel concludes that there are inadequate data to establish the safety of topically applied estrogens in the concentration reviewed, up to 10,000 I.U./oz, and that progesterone, in a concentration up to 5 mg/oz, is safe when used on the skin daily in a quantity not exceeding 2 oz/month. These amounts of topical estrogens and progesterone do not produce systemic effects and have a low incidence of irritation or allergic local effects. Higher concentrations of topical estrogens produce systemic effects and should not be available OTC. Higher concentrations of progesterone have not been tested for safety for OTC use.

The Panel further concludes that there is no evidence that using a hormone-containing drug product at the levels which are safe for OTC use will do

anything more than using the cream vehicle alone. Therefore, the Panel concludes that these products are ineffective for OTC drug use. Further, the Panel recognizes an inherent fallacy in marketing a cosmetic product which contains a medication regardless of the nonmedical intention of the label claim. If the medication affects the structure or function of the skin, then the purported cosmetic is, in fact, a medication. If the medication is present in such small amounts that neither the structure or function of the skin is altered, then its presence in the cosmetic is misleading because of lack of effectiveness, and the product should be considered misbranded.

References

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

(2) Masters, E. J., "The Percutaneous Absorption of Estrogen," *Proceedings of the Scientific Section of the Toilet Goods Association, No. 33, May 1960,* contained in OTC Volume 160095.

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

(4) Greenblatt, R. B., "Report on Helena Rubinstein Cream Study," contained in OTC Volume 160095.

(5) Goldzieher, J. W., and R. E. Baker, "The Percutaneous Absorption of Estradiol-17B and Progesterone," *The Journal of Investigative Dermatology,* 35:215–218, 1969.

(6) 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.

(7) OTC Volume 160055.

(8) OTC Volume 160057.

(9) OTC Volume 160095.

(10) Harvey, S. C., and C. D., Withrow, "Hormones," *in* "Remington's Pharmaceutical Sciences," A. Osol et al., editors, 16th Ed., Mack Publishing Co., Easton, PA, p. 928, 1975.

(11) Guyton, A. C., "Medical Physiology," 5th Ed., W.B. Saunders Co., Philadelphia, p. 1091, 1976.

(12) Karnaky, K. J., "An Investigation of Possible Gynecological Changes Resulting from Topical Use of an Estrogen-Progesterone Cream with Special Emphasis on Vaginal Epithelial Cell Height and pH," Preliminary Report contained in OTC Volume 160095.

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

(14) OTC Volume 160105.

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

(16) "Estrogens and Progestins," *in* "AMA Drug Evaluation," 4th Ed., John Wiley & Sons, Inc., New York, p. 679, 1980.

(17) Goldzieher, M. A., "Effects of Estrogen on Senile Skin," *Journal of Gerontology,* 1:196–201, 1946.

(18) Goldzieher, J. W., "Direct Effect of Steroids on Senile Human Skin: A Preliminary Report," *Journal of Gerontology,* 4:104, 1949.

(19) Eller, J. J., and W. D. Eller, "Estrogenic Ointments. Cutaneous Effects of Topical Applications of Natural Estrogens, With Report of Three Hundred and Twenty-One Biopsies," *Archives of Dermatology and Syphilology,* 59:449–462, 1949.

(20) Brown, R. K., "Evalution of Dermatologic Creams Containing Female Hormones," *Journal of the American Medical Women's Association,* 21:493–499, 1966.

(21) Spoor, H. J., "Measurement of Natural Skin Oil: Influence of Topically Applied Hormones Upon Its Production," *American Practitioner and Digest of Treatment,* 11:497–505, 1960.

(22) Peck, S. M., "Hormone Cosmetics," *The Practitioner,* 173:159–165, 1954.

(23) OTC Volume 160195.

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

(25) Strauss, J. S., "Effect of Progesterone on the Human Sebaceous Gland," *Journal of Investigative Dermatology,* 36:309–319, 1961.

(26) Hurley, H. J., "Permeability of the Skin," *in* "Dermatology," Volume I, edited by S. L. Moschella, D. M. Pillsbury, and J. J. Hurley, W. B. Saunders Co., Philadelphia, p. 64–68, 1975.

PART 310—NEW DRUGS

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 (see 46 FR 26052; May 11, 1981), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended in Part 310 by adding to Subpart E new § 310.530, to read as follows:

§ 310.530 Topically applied hormone-containing drug products for over-the-counter (OTC) human use.

(a) Estrogens and progesterone have been present as ingredients in over-the-counter (OTC) drug products marketed for topical use as hormone cream. There is a lack of adequate data to establish the safety and effectiveness of these ingredients as OTC topically applied hormones. Data on any other ingredients intended for use as a topically applied hormone in OTC drug products have not been submitted 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 topically applied hormone 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 topically applied hormone-containing drug product 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 topically applied hormone-containing drug product 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 may, on or before April 5, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before May 5, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: December 17, 1981.

Richard S. Schweiker,

Secretary of Health and Human Services.

[FR Doc. 82-6 Filed 1-4-82; 8:45 am]

BILLING CODE 4160-01-M