DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 81N-0144]

RIN 0905-AA06

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that any topically applied hormone-containing drug product for over-the-counter (OTC) human 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 topically applied hormone-containing 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: March 9, 1994.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of January 5, 1982 (47 FR 430), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking that would classify topically applied hormone-containing drug products for OTC human use as not generally recognized as safe and effective and as being misbranded and would declare these products to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)). The notice was based on the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products (the 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 April 5, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by May 5, 1982.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

The agency's proposed regulation, in the form of a tentative final rule, for OTC topically applied hormone-containing drug products was published in the **Federal Register** of October 2, 1989 (54 FR 40618). Interested persons were invited to file by December 1, 1989, 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 January 30, 1990. New data could have been submitted until October 2, 1990, and comments on the new data until December 3, 1990. Final agency action occurs with the publication of this final rule on OTC topically applied hormone-containing drug products.

As discussed in the preamble to the agency's proposed rule for OTC topically applied hormone-containing drug products (54 FR 40618), the agency advised that the drug products covered by this regulation would be subject to the regulation effective 6 months after date of publication of the final rule in the **Federal Register**. On or after March 9, 1994, 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 application. If, in the future, any ingredient is determined to be generally recognized as safe and effective for use in an OTC topically applied hormone-containing drug product, the agency will promulgate an appropriate regulation at that time.

In response to the proposed rule, one comment from an individual was submitted. A copy of the comment is on public display in the Dockets Management Branch (address above). In proceeding with this final rule, the agency has considered the issues raised in the comment.

I. The Agency's Conclusions on the Comment

One comment expressed concern about the presence of steroids and steroid derivatives in OTC cosmetic drug products. The comment mentioned the recent purchase of two cosmetic products containing pregnenolone acetate. The comment stated that the name of the ingredient was listed in the labeling of both products, but expressed concern that the labeling of neither product indicated the chemical origin of the hormone ingredient. The comment stated that cosmetic manufacturers may use corticosteroids such as pregnenolone acetate as well as hormones (from an animal source) in the form of tissue extracts in "F.D.A. acceptable amounts" without truly informing the consumer. The comment mentioned that FDA regulations for cosmetic products require in the product's labeling a listing of all ingredients present, but complained that the source of a hormone ingredient is not required to be disclosed. The comment noted that people with major health concerns, as in the case of a cortisone-related disease such as Cushing's syndrome or an immunosuppressive disorder such as Lupus, might prefer to avoid corticosteroids from a hidden source. The comment contended that consumers who wish to avoid using such products have a right to know what they are using. The comment stated that a product's labeling is misleading when this information is not disclosed and suggested that the agency require disclosure of the chemical origin of a hormone in a cosmetic product's labeling.

There currently is no provision in sections 601 through 603 of the act (21 U.S.C. 361 through 363) that requires manufacturers of cosmetic products to disclose the chemical origin of a hormone ingredient in a cosmetic product's labeling. Nor is there currently any FDA regulation requiring this type of labeling.

In the notice of proposed rulemaking for topically applied hormone-containing drug products for OTC use (54 FR 40618 at 40620), the agency discussed the labeling of cosmetic products containing hormone ingredients. The agency stated that it considers the use of the word "hormone" in the text of the product's labeling or in the ingredient statement to be an implied drug claim, and that such labeling would cause the product to be regulated as a drug. The agency stated that if a manufacturer includes a hormone in its cosmetic product, it may designate this ingredient in the product's labeling by any appropriate name. The agency stated that the chemical name is preferable and mentioned that the chemical name for pregnenolone acetate is "3-hydroxypregn-5-ene-20-one acetate." This name would appear in a listing of all ingredients in the product in accordance with agency regulations in § 701.3 (21 CFR 701.3). Under this regulation, an ingredient must be declared in the product's labeling by the

name specified in the Cosmetics, Toiletries, and Fragrances Association Cosmetic Ingredient Dictionary or, if not in that dictionary, by the name specified in several alternative recognized compendia of chemical substances. The agency now urges cosmetic product manufacturers who include hormone ingredients (or substances containing hormones) in their products to identify these substances in their ingredient declaration using names that are most likely to be recognized by consumers. Following the sequence for designating cosmetic ingredients in § 701.3(c), the agency has now determined that the most appropriate names to use are those contained in the "USAN and the USP dictionary of drug names" listed in § 701.3(c)(2)(v). The names for hormone ingredients are currently not designated in agency regulations. Because the agency's cosmetic regulations specify a specific sequence of sources to be utilized to establish the name to be used for a cosmetic ingredient when the agency has not specified a name in § 701.30, elsewhere in this issue of the **Federal Register**, the agency is proposing to amend § 701.30 to establish the names that would be permitted to identify hormone ingredients in cosmetic product labeling.

Using the names established by the agency, consumers who wish to avoid a particular cosmetic ingredient, for medical or other reasons, would be able to identify the ingredient contained in a product. Consumers may also contact manufacturers of cosmetic products if they are uncertain whether or not the product contains a specific hormone ingredient. The agency also suggests that consumers with medical conditions who wish to avoid topical corticosteroid products consult with a physician or pharmacist before using a cosmetic product that they believe contains a hormone ingredient.

Because certain hormone ingredients may be present in cosmetic products, the agency believes it would be appropriate to amend the cosmetic regulations to identify these hormones and to specify the upper concentration limits for those ingredients. Therefore, elsewhere in this issue of the **Federal Register**, the agency is proposing to amend Part 700 (21 CFR part 700) by adding new § 700.20 entitled "Use of certain hormones as ingredients in cosmetic products."

II. The Agency's Final Conclusions on OTC Topically Applied Hormone-Containing Drug Products

The agency has determined that all topically applied hormone-containing drug products for OTC human use are not generally recognized as safe and effective and are misbranded. This determination includes, but is not limited to, products that contain estrogens, progestins, androgens, anabolic steroids, and adrenal corticosteroids and synthetic analogs. The final regulation also covers pregnenolone and pregnenolone acetate, steroids that are closely related to progesterone in chemical structure and that exert an estrogen-like action on the skin when applied topically. However, the final regulation does not include hydrocortisone and hydrocortisone acetate labeled, represented, or promoted for OTC topical analgesic use in accordance with Part 348 (21 CFR part 348).

Except for drug products containing hydrocortisone or hydrocortisone acetate discussed above, any topically applied hormone-containing product bearing any drug claims is considered misbranded under section 502 of the act (21 U.S.C. 352) and is a new drug under section 201(p) of the act for which an approved application under section 505 of the act (21 U.S.C. 355) and Part 314 (21 CFR part 314) of the regulations is required for marketing. In appropriate circumstances, where there are adequate data to establish general recognition of safety and effectiveness, a citizen petition to establish a monograph for OTC topically applied hormone-containing drug products may be submitted under § 10.30 (21 CFR 10.30) in lieu of an application. Any OTC drug product subject to this final rule that is introduced or initially delivered for introduction into interstate commerce after the effective date of the 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 for specific comment on the economic impact of this rulemaking (54 FR 40618 at 40621 to 40622). 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 topically applied hormone-containing 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 topically applied hormone-containing drug products is not expected to pose such an impact on small businesses because there are a limited number of these types of products currently being marketed. As noted in the proposed rule (54 FR 40618 at 40620), there are only a few OTC skin care products containing hormones that are currently subject to new drug applications. The agency is aware of only a few other products that are currently marketed without new drug applications. These products would be able to remain in the market with some relabeling in accord with the notice of proposed rulemaking for cosmetic products containing certain hormone ingredients, published elsewhere in this issue of the **Federal Register**. 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, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

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

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. New § 310.530 is added to subpart E to read as follows:

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

(a) The term "hormone" is used broadly to describe a chemical substance formed in some organ of the body, such as the adrenal glands or the pituitary, and carried to another organ or tissue, where it has a specific effect. Hormones include, for example, estrogens, progestins, androgens, anabolic steroids, and adrenal corticosteroids, and synthetic analogs. Estrogens, progesterone, pregnenolone, and pregnenolone acetate have been present as ingredients in OTC drug products marketed for topical use as hormone creams. However, there is a lack of adequate data to establish effectiveness for any OTC drug use of these ingredients. Therefore, with the exception of those hormones identified in paragraph (e) of this section, 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. The intended use of the product may be inferred from the product's labeling, promotional material, advertising, and any other relevant factor. The use of the word "hormone" in the text of the labeling or in the ingredient statement is an implied drug claim. The claim implied by the use of this term is that the product will have a therapeutic or some other physiological effect on the body. Therefore, reference to a product as a "hormone cream" or any statement in the labeling indicating that "hormones" are present in the product, or any statement that features or emphasizes the presence of a hormone ingredient in the product, will be considered to be a therapeutic claim for the product, or a claim that the product will affect the structure or function of the body, and will consequently cause the product to be a drug.

(b) Any OTC drug product that is labeled, represented, or promoted as a topically applied hormone-containing product for drug use, with the exception of those hormones identified in paragraph (e) of this section, is regarded as a new drug within the meaning of section 201(p) of the act, for which an approved application or abbreviated 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 or abbreviated 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 use as a topically applied hormone-containing drug product 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 March 9, 1994, 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.

(e) This section does not apply to hydrocortisone and hydrocortisone acetate labeled, represented, or promoted for OTC topical use in accordance with Part 348 of this chapter.

Dated: September 2, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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