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; Proposed Rule

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

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

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by December 1, 1989. New data by October 2, 1990. Comments on the new data by December 3, 1990. Written comments on the agency's economic impact determination by January 30, 1990.

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

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of 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, 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 put on public display in the Dockets Management Branch (address above). In response to the advance notice of proposed rulemaking, one drug manufacturers' association, one law firm, and two manufacturers submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

In this proposed rule to amend part 310 by adding to subpart E new § 310.530 (21 CFR 310.530), FDA states for the first time its position on OTC topically applied hormone-containing drug products. Final agency action on this matter will occur with the publication at a future date of a final rule for OTC topically applied hormone-containing drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC topically applied hormone-containing drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final rule stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the proposed rule stage.

In the advance notice of proposed rulemaking, the agency stated that if it proposed to adopt the Panel's recommendation it would propose that 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 was undertaken to justify their future use. Based on all information available to date, the agency is proposing that OTC topically applied hormone-containing drug products be found not to be generally recognized as safe and effective. If the proposed finding is adopted in the final rule, the agency advises that the conditions under which the drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions) will be effective 6 months after the date of publication of the final rule in the **Federal Register**. On or after that date, no OTC drug products that are subject to the rule may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application (NDA). Further, any OTC drug product subject to the final rule that is repackaged or relabeled after the effective date of the final rule must be in compliance with the final rule regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the proposed rule at the earliest possible date.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Topically Applied Hormone-Containing Drug Products

1. One comment urged that § 310.530 be amended to limit it to the kind and type of hormone ingredients and products considered by the Panel in this rulemaking proceeding, i.e., skin creams and skin oils containing estrogens and progesterone that are marketed for topical use with claims for the improvement to or enhancement of the condition of the skin. Noting that estradiol was considered separately by the Panel under two dockets, hair grower and hair loss prevention drug products and hormone-containing drug products, the comment maintained that "the agency should separate the subject matter in the proposed monographs and new regulations."

The term "hormone" broadly describes 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 (ref. 1). There are many types of hormones (ref. 2). Standard reference texts, such as "Dorland's Illustrated Medical Dictionary," "AMA Drug Evaluations," and "The Pharmacological Basis of Therapeutics," use a number of similar terms to describe the various types of hormones. The terms "estrogens" and

"progestins" are generally used to describe the types of ingredients reviewed by the Panel (refs. 3 and 4). Estrogens include steroidal estrogens such as estradiol, estrone, conjugated estrogens, esterified estrogens, and ethinyl estradiol, and nonsteroidal estrogens such as dienestrol and diethylstilbestrol (ref. 5). Progestins include progesterone, esthisterone, and medroxyprogesterone acetate (refs. 6 and 7). Pregnenolone is a steriod closely related to progesterone in chemical structure, but it exerts an estrogen-like action on the skin when applied topically (ref. 8).

One of the call-for-data notices that listed ingredients in hormone creams for which data should be submitted to the Panel listed the ingredients estradiol, estrogen, estrogenic hormones, estrone, natural estrogens, pregnenolone acetate, and progesterone. (See the **Federal Register** of August 27, 1975; 40 FR 38179.) This list was intended to be a representative, but not all-inclusive, list of the types of hormones to be reviewed. Likewise, the list of hormones in this document is intended to be representative, but not all-inclusive.

Examples of other general types of hormones are adrenal corticosteroids and synthetic analogs, androgens, and anabolic steroids (ref. 9). Hydrocortisone is an adrenal corticosteroid. The synthetic analogs include dexamethasone, prednisone, prednisolone, and triamcinolone. Androgens include testosterone and methyltestosterone. Anabolic steroids include ethylestrenol, methandrostenolone, and oxymetholone.

The Panel discussed topically applied hormone-containing drug products as a therapeutic class with emphasis on the two groups of active ingredients, the estrogens and progesterone, that are generally used in these products (47 FR 430 at 432). The Panel concluded that none of these ingredients is generally recognized as safe and effective for OTC drug use. The Panel also stated that it was not aware of any data demonstrating the safety and effectiveness of any other ingredient used in topically applied hormone-containing drug products for OTC use (47 FR 432). The agency is not aware of any estrogens, progestins, androgens, anabolic steroids, or adrenal corticosteroids that are currently generally recognized or proposed for general recognition as safe and effective for OTC topical drug use, except hydrocortisone preparations for topical use for the temporary relief of itching associated with minor skin irritations, inflammation, and rashes. (See the **Federal Register** of February 8, 1983; 48 FR 5852.)

As the comment pointed out, estradiol was also reviewed by the Panel in its report on hair grower and hair loss prevention drug products for OTC human use, published in the **Federal Register** of November 7, 1980 (45 FR 73955). The Panel concluded that there was a lack of evidence to establish effectiveness of estradiol and hormone constituents as hair growers or hair loss prevention OTC drug products and recommended that they be classified in Category II (45 FR 73959). The agency concurred with the Panel's recommendations in the proposed rule for these products that was published in the **Federal Register** of January 15, 1985 (50 FR 2190). More recently, in the **Federal Register** of July 7, 1989 (54 FR 28772), the agency concluded that estradiol is not generally recognized as safe and effective for claims of hair growth and hair loss prevention.

For the reasons stated above, the agency has determined that the title of the regulation that is the subject of this document should remain "topically applied hormone-containing drug products for OTC human use," as stated in the advance notice of proposed rulemaking. However, FDA has revised § 310.530(a) to state the scope of the regulation. Also, the agency is adding a new paragraph (e) in which it will list any hormone ingredients that are not covered by the regulation. This paragraph will include any hormone that is currently generally recognized or proposed for general recognition as safe and effective for OTC topical drug use. At the present time, the only hormones that are included in paragraph (e) are hydrocortisone and hydrocortisone acetate, which were proposed as Category I ingredients for the temporary relief of itching associated with minor skin irritations, inflammation, and rashes in the notice of proposed rulemaking for external analgesic drug products for OTC human use, published in the **Federal Register** of February 8, 1983 (48 FR 5852).

References

(1) "Webster's New World Dictionary," College Ed., Cleveland and New York, 1968, s.v. "hormone."

(2) "Dorland's Illustrated Medical Dictionary," 26th Ed., W.B. Saunders Co., Philadelphia, 1985, s.v. "hormone."

(3) "The Pharmacological Basis of Therapeutics," 7th Ed., edited by A.G. Gilman, L.S. Goodman, T.W. Rall, and F. Murad, Macmillan Publishing Co., Inc., New York, p. 1412, 1985.

(4) "Drug Evaluations," 6th Ed., American Medical Association, W.B. Saunders Company, Philadelphia, p. 689, 1986.

(5) "Drug Evaluations," 6th Ed., American Medical Association, W.B. Saunders Company, Philadelphia, pp. 703–705, 1986.

(6) "Drug Evaluations," 6th Ed., American Medical Association, W.B. Saunders Company, Philadelphia, pp. 705–706, 1986.

(7) "The Pharmacological Basis of Therapeutics," 7th Ed., edited by A.G. Gilman, L.S. Goodman, T.W. Rall, and F. Murad, Macmillan Publishing Co., Inc., New York, p. 1425, 1985.

(8) Silson, J.E., "Pregnenolone Acetate—A Dermatologically Active Steroid," *Journal of the Society of Cosmetic Chemists*, 8:129–137, 1962.

(9) "Drug Evaluations," 6th Ed., American Medical Association, W.B. Saunders Company, Philadelphia, pp. 661–687, 1986.

2. Two comments stated that the Panel's proper function was to evaluate the safety and effectiveness of hormone-containing products intended for OTC drug use, and not those intended for cosmetic use. One comment from a manufacturer pointed out that the drug/cosmetic status of a product presents legal rather than scientific questions, that the labeling of its products contains only cosmetic claims, and therefore that the products are not drugs. The comments maintained that it is the intended use of a product, rather than its physical properties, that determines whether the product is a drug or a cosmetic. To support this contention, one comment cited several court cases, including *National Nutritional Foods Association* v. *Mathews*, 557 F.2d 325 (2d Cir. 1977); *National Nutritional Foods Association* v. *FDA*, 504 F.2d 761 (2d Cir. 1974); *United States* v. *"Sudden Change,"* 409 F.2d 734 (2d Cir. 1969). The comments added that "FDA's own regulations explicitly recognize that articles represented as hormone skin care products are cosmetics" and cited 21 CFR 720.4(c)(12)(v). One comment concluded that FDA acted properly in not incorporating into § 310.530 the Panel's discussion concerning the cosmetic use of hormone ingredients. The comments requested that the agency clarify that any regulation adopted as part of the OTC drug review applies to OTC drug products and not to cosmetic products for which no drug claims are made. One specific suggestion was that the agency revise the title for proposed § 310.530 to read "Topically Applied Hormone-Containing Products for Over-the-Counter (OTC) Human Drug Use."

The agency agrees that this regulation applies only to topically applied hormone-containing drug products that fall within the statutory definition of a drug. A "drug" is principally defined in the act as an article "intended for use in the diagnosis, cure, mitigation,

treatment, or prevention of disease" or "intended to affect the structure or any function of the body * * *." (See 21 U.S.C. 321(g)(1)(B), (C).) A "cosmetic," on the other hand, is defined primarily as an article intended to be "* * * applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance * * *." (See 21 U.S.C. 321(i).) The intended use of a product, therefore, determines whether it is a "drug," a "cosmetic," or both. This intended use may be inferred from the product's labeling, promotional material, advertising, and any other relevant factor. See, e.g., *National Nutritional Foods Ass'n* v. *Mathews*, 557 F.2d 325, 334 (2d Cir. 1977). A manufacturers' subjective claims of intent may be pierced to find its actual intent on the basis of objective evidence. *National Nutritional Foods Ass'n* v. *FDA, supra*, 504 F.2d at 789.

The agency believes that the title of § 310.530 clearly states that the regulation covers drug products. However, paragraph (a) has been changed to clarify that this regulation pertains only to products that are intended for use as drugs.

The agency has reviewed the labeling in current NDAs for skin care products that contain estrogen, progesterone, and pregnenolone acetate (refs. 1, 2, and 3). One product with labeling submitted by the comment contains estrogen and progesterone and makes the following labeling claim: "This cream (or oil) is scientifically prepared with natural estrogen and progesterone. Contains lubricants and moisturizers to help counteract dryness. Gives the skin a softer, smoother, more supple look." The other product identifies itself as a cosmetic cream. Although it does not explicitly make any claims that would be considered drug claims, its labeling does identify the hormone ingredient as "pregnenolone acetate."

Skin care products that contain hormones are solely cosmetics if the claims in the labeling, promotional material, advertising, and other relevant materials are only cosmetic in nature (e.g., to promote attractiveness), and no actual or implied therapeutic claims, or claims that the product will affect the structure or function of the body, are made. The agency considers the use of the word "hormone" in the text of the labeling (e.g., "This cream (or oil) is scientifically formulated to contain a hormone") or in the ingredient statement to be 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 that "hormones" are present 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.

If a manufacturer includes a hormone in its product, it may denominate this ingredient in the labeling by any appropriate name. However, use of the chemical name is preferable. For example, for progesterone, the chemical name is "pregn-4-ene-3,20-dione;" and for pregnenolone acetate, the chemical name is "3-hydroxypregn-5-ene-20-one acetate." Nevertheless, the agency cautions that any statement on the label of a cosmetic product of the presence of a hormone ingredient, e.g., "contains natural estrogen and progesterone," must be consistent with 21 CFR 701.1 and must not be given undue prominence.

While § 720.4(c)(12)(v) does list hormone skin care preparations as a cosmetic product category, such recognition does not preclude regulation of such products as drugs. See also 36 FR 16934; August 26, 1971. A product that contains hormone ingredients can be either a cosmetic or a drug, or both, depending on the intended use of the product. If the skin care products that contain estrogen, progesterone, and pregnenolone acetate, which are currently subject to new drug applications (refs. 1, 2, and 3), were to be relabeled as discussed above (i.e., no reference to the term "hormone"), the products could properly be regulated as cosmetics alone. Upon promulgation of a final regulation for OTC hormone-containing drug products, the agency will publish a notice of opportunity for a hearing on a proposal to withdraw approval of the NDAs for those products that presently have NDAs but that are determined not to be safe and effective or that are no longer marketed as drugs.

References

(1) FDA-approved labeling from NDA 10-766, copy in OTC Volume 16GTFM, Docket No. 81N-0144, Dockets Management Branch.

(2) FDA-approved labeling from NDA 11-539, copy in OTC Volume 16GTFM.

(3) FDA-approved labeling from NDA 12-603, copy in OTC Volume 16GTFM.

B. Comments on Hormone Ingredients

3. Two comments disagreed with the Panel's conclusions on the safety of estrogen and progesterone when applied to the skin and objected to the Panel apparently basing its conclusions on the safety of topically applied estrogen on its judgment that the safety data are "relatively old" (47 FR 430 at 433). One comment claimed that there is no evidence showing that the studies to which the Panel referred are less valid now than when they were completed, adding that its products, which contain 10,000 International Units per ounce (I.U./oz) of estrogen, have been marketed OTC under effective new drug applications for approximately 24 years with an extremely low incidence of adverse reactions. Noting that such proof of safety is included as part of the standards for the safety of an OTC drug in 21 CFR 330.10(a)(4)(i), the comment stated that it appears that the Panel ignored these standards in reaching its conclusions about the safety of topically applied estrogens at a level of 10,000 I.U./oz. The comment added that its products were reviewed by the National Academy of Science/National Research Council (NAS/NRC) as part of the FDA Drug Efficacy Study Implementation (DESI) review, and that this group of experts did not raise any questions regarding the safety of these products.

The other comment maintained that the Category III classification is inappropriate in view of the evidence cited by the Panel that estrogen does not produce systemic effects and has a low incidence or irritation and allergic effect when used at a concentration of 10,000 I.U./oz. The comment also objected to the Panel's failure to recognize the safety of progesterone at a concentration of 5 milligrams per ounce (mg/oz). Citing the Panel's statements on the safety of progesterone at this concentration (47 FR 430 at 433), the comment asked that the agency recognize the safety of progesterone in a concentration of 5 mg/oz in the next FDA **Federal Register** publication on this subject.

The comment added that the regulation should be revised to specify that high level estrogen and progesterone concentrations (exceeding 10,000 I.U./oz estrogen and 5 mg/oz progesterone) have not been shown to be generally recognized as safe and effective for OTC drug use, and that such concentrations of hormone ingredients in a product intended for topical OTC drug use would require an effective NDA. The comment asserted that such action would protect the public without depriving manufacturers and consumers of effective products.

The Panel concluded that inadequate data were submitted to establish the safety of topically applied estrogens in concentrations up to 10,000 I.U./oz when used in amounts not to exceed 2 oz per month (47 FR 430 at 433). It also pointed out that the lack of systemic effects of

concentrations up to 10,000 I.U./oz is well documented in studies, and that these estrogen concentrations have a low incidence of irritation or allergic local effects. The agency has reviewed all of the data submitted to the Panel, considered the data for these products evaluated as part of the DESI review, considered the OTC marketing history of these products for over 25 years, and evaluated the adverse reaction reports submitted for these products for the last 16 years (ref. 1). The agency concludes that estrogens in concentrations up to 10,000 I.U./oz are safe for topical application to the skin when used in amounts not to exceed 2 oz per month.

The Panel recognized the safety of progesterone at a concentration of 5 mg/oz when used in amounts not to exceed 2 oz per month, but concluded "that there was 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" (47 FR 430 at 433). The agency concurs with this conclusion. The comments did not submit sufficient data to establish the effectiveness of either ingredient for OTC drug use. While the agency concurs with the comments that up to 10,000 I.U./oz estrogen and 5 mg/oz progesterone are safe for OTC use, these ingredients are classified in Category II because of a lack of effectiveness for drug use at these concentrations.

Reference

(1) Department of Health Human Services, Food and Drug Administration, Adverse Reaction Summary Listings, pertinent pages for the years 1969–1985, copy in OTC Volume 16GTFM, Docket No. 81N–0144, Dockets Management Branch.

4. One comment objected to the Panel's statement that it could not locate, nor was it aware of, any data demonstrating the safety and effectiveness of pregnenolone acetate used in topically applied hormone-containing drug products for OTC use (47 FR 430 at 432). According to the comment, safety data on this ingredient are included in an NDA, and the Panel could have reviewed these data. The comment added that annual reports on adverse reactions filed with FDA show a low incidence of adverse reactions to pregnenolone acetate. The comment requested that FDA's preamble and record in this rulemaking proceeding note the existence of an effective NDA for a product containing this ingredient. The comment also requested that § 310.530(b) be revised to clarify that drug products containing hormones are misbranded unless they are covered by [illegible]s.

There is an effective NDA (12–603) for a product containing pregnenolone acetate. However, NDAs were not available to the Panel for review unless the holder of the NDA specifically submitted the data it contained to the Panel for evaluation in the OTC drug review. NDA 12–603 became effective before 1962. Thus, it was approved for safety only and not for effectiveness. The product covered by the NDA contains 0.5 percent pregnenolone acetate and was reviewed by the NAS/NRC as part of the FDA DESI review (ref. 1). The agency published the NAS/NRC findings in the **Federal Register** of October 2, 1969 (34 FR 15389), stating that the products were possibly effective for their labeled indications. The agency considers concentrations up to 0.5 percent pregnenolone acetate as safe for OTC use, but that there is a lack of evidence that this ingredient is effective at these concentrations. The agency is revising § 310.530(b) to clarify that a product covered by the regulation is a new drug under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)) for which an approved NDA under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314) is required for marketing, and in the absence of an approved NDA the product would be in violation of section 505 and also would be misbranded under section 502 of the act (21 U.S.C. 352). With respect to NDA 12–603, if the product covered by the NDA is relabeled as discussed above, the product could be regulated as a cosmetic and the NDA withdrawan. (See comment 2 above.)

Reference

(1) National Academy of Sciences/National Research Council, Drug Efficacy Study, ACC 1907, copy in OTC Volume 16GTFM, Docket No. 81N–0144, Dockets Management Branch.

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

As discussed above, the agency has clarified that the scope of this rulemaking applies to all topically applied hormone-containing drug products for OTC human use, to include, but not limited to, estrogens, progestins, androgens, anabolic steroids, and adrenal corticosteroids and synthetic analogs. The 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. With the exception of hydrocortisone and hydrocortisone acetate used in external analgesic drug products, the agency is not aware of any hormone that is generally recognized or proposed for general recognition as safe and effective for OTC topical drug use. FDA is revising § 310.530(a) to clarify the scope of the regulation and is adding a new § 310.530(e) to identify hormones that are not covered by the regulation.

The agency is also revising § 310.530(b) to clarify that a product covered by the regulation is a new drug under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved NDA under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314) is required for marketing, and in the absence of an approved NDA the product would be in violation of section 505 and also would be misbranded under section 502 of the act (21 U.S.C. 352). As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in a citizen petition to establish a monograph. (See 21 CFR 10.30.)

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for 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. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invited public comment in the advance notice of proposed rulemaking regarding any impact that

this rulemaking would have on OTC topically applied hormone-containing drug products. No comments on economic impacts were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by January 30, 1990. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined 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.

Interested persons may, on or before December 1, 1989, submit to the Dockets Management Branch written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before January 30, 1990. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before October 2, 1990, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before December 2, 1990. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final rule, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on December 2, 1990. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final rule is published in the **Federal Register,** unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 310

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that subchapter D of chapter I of title 21 of the Code of Federal Regulations be amended as follows:

PART 310—NEW DRUGS

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

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

2. Section 310.530 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 that "hormones" are present 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 Federal Food, Drug, and Cosmetic Act, for which an approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) 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 the effective date of the final regulation, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

(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: August 26, 1989.

Frank E. Young,

Commissioner of Food and Drugs.

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