DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 700 and 701

[Docket No. 91N-0245]

Cosmetic Products Containing Certain Hormone Ingredients; Notice of Proposed Rulemaking

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 identifying certain hormones that may appear in cosmetic products, specifying the upper concentration limits for those ingredients, and designating the source for naming those ingredients in product labeling. FDA is issuing this notice of proposed rulemaking in conjunction with the agency's final rule for topically applied hormone-containing drug products for over-the-counter (OTC) human use, published elsewhere in this issue of the **Federal Register**.

DATES: Written comments by November 8, 1993.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: John E. Bailey, Center for Food Safety and Applied Nutrition (HFS-440), Food and Drug Administration, 200 C St., SW., Washington, DC 20204, 202-205-4530.

SUPPLEMENTARY INFORMATION: Elsewhere in this issue of the **Federal Register** FDA is issuing a final rule establishing that any OTC drug product that is labeled, represented, or promoted as a topically applied hormone-containing product for drug use, with the exception of hydrocortisone and hydrocortisone acetate, is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act). In that final rule, the agency states that "hormone" includes estrogens, progestins, androgens, anabolic steroids, adrenal corticosteroids and synthetic analogs, progesterone, pregnenolone and pregneno- lone acetate, and hydrocortisone and hydrocortisone acetate.

Part 720 of FDA's regulations (21 CFR part 720) permits the voluntary filing of cosmetic product ingredient and cosmetic raw material composition statements. Section 720.4(c) requests that one or more of the categories listed in this section be cited to indicate the product's intended use. In the past, paragraph (12) of § 720.4(c) (skin care preparations) included the category hormone under paragraph (v). However, in the **Federal Register** of January 28, 1992 (57 FR 3128 at 3129), the agency removed from § 720.4(c)(12) the skin care categories "Hormone," "Skin lighteners," and "Wrinkle smoothing (removers)." The agency noted in its proposal to remove these categories (see the **Federal Register** of October 25, 1990, 55 FR 42993 at 42994) that these designations have been the subject of considerable regulatory controversy because such items can be both cosmetics and drugs under the act. These designations originally were included in the list of product categories when the regulation was published in the **Federal Register** of April 11, 1972 (37 FR 7151). At that time, it was the agency's intent to permit the registration of these types of products as cosmetics, but with the understanding that these products are legally both drugs and cosmetics. However, the original category designations have been interpreted by cosmetic manufacturers, and others, to mean that FDA considered these products to be exclusively cosmetics, which certainly is not the case. The agency expects the removal of these three category designations, and registration of such products, if they are also cosmetics, under the remaining category designations, to alleviate misunderstandings that have existed.

Elsewhere in this issue of the **Federal Register** the agency is completing the rulemaking for topically applied drug products containing hormone ingredients. While products containing hormone ingredients and making drug claims are drugs under the act, certain hormone-containing products not bearing drug claims could be cosmetics depending on the levels of hormones used and whether that level of use affects the structure or any function of the body. However, some hormones, such as anabolic steroids (e.g., methandrostenolone, stanozolol, and oxymetholone) and adrenal corticosteroids (e.g., betamethasone, prednisolone, and prednisone) would be inappropriate for use in a cosmetic product These hormone ingredients that are used in drug products do not at any level. These hormone ingredients that are used in drug products do not have any legitimate cosmetic uses. A review of cosmetic products registered voluntarily with the agency reveals that no product identifies any of these drug ingredients in its formulation.

The safety of certain hormone ingredients at specific concentration levels used for topical application has been established by many years of marketing of these products as OTC drugs. In the **Federal Register** of January 5, 1982 (47 FR 430 at 432), FDA published an advance notice of proposed rulemaking on OTC topically applied hormone-containing drug products. That document contained the results of a review of a number of marketed products containing hormone ingredients that was done by the Advisory Review Panel on OTC Miscellaneous External Drug Products (the Panel). The Panel recommended that FDA regard progesterone in a concentration up to 5 milligrams (mg)/ ounce (oz) is safe when used on the skin daily in a quantity not exceeding 2 oz per month. The Panel determined that this amount of topical progesterone does not produce systemic effects and has a low incidence of irritation or allergic local effects. The agency's adverse reaction files (Ref. 1) contain occurrences reported for topical hormone-containing products. None of the occurrences was classified as serious. The reports included two occurrences of vaginal hemorrhage, one of menorrhagia, and one of menstrual disorder. The other reports relate to contact dermatitis, urticaria, rash, and conjunctivitis and are considered less serious.

In the **Federal Register** of October 2, 1989 (54 FR 40618 at 40621), in the proposed rule on OTC topically applied hormone-containing drug products, FDA concurred with the Panel's conclusion that 5 mg/oz progesterone is safe for OTC use when used in an amount not exceeding 2 oz per month. As discussed below, the agency is proposing in new § 700.20(b)(2) to limit the use of progesterone in cosmetic products to these levels that have been found to be safe but lack effectiveness for drug use (do not affect the structure or any function of the body).

In the same proposed rule (54 FR 40618 at 40621), the agency also tentatively concluded that pregnenolone acetate up to 0.5 percent is safe for OTC use. The agency's proposal was based on findings of the National Academy of Sciences/National Research Council, as part of the agency's Drug Efficacy Study Implementation. (The Panel did not review pregnenolone acetate.) A review of cosmetic products registered voluntarily with the agency reveals only two products formulated using pregnenolone acetate as an ingredient. One product is reported to contain

pregnenolone hemisuccinate in addition to pregnenolone acetate. Pregnenolone succinate is listed in the 1993 edition of "USAN and the USP dictionary of drug names" (Ref. 2), which is the authorized list of established names for drugs in the United States. Pregnenolone acetate is not listed in this reference. Based on its previous evaluation of the safety of pregnenolone acetate, the agency is proposing in new § 700.20(b)(1) to restrict the use of pregnenolone acetate in cosmetic products to no more than 0.5 percent, not to exceed 2 oz per month. At this level, the ingredient would not have a drug effect. However, the agency has not evaluated any safety and effectiveness data on pregnenolone hemisuccinate or pregnenolone succinate. Therefore, the agency is not proposing to include these ingredients in new § 700.20(b)(1), but invites comments and data to support the safe use of these ingredients in cosmetic products. The agency will announce in the final rule whether these ingredients will be included in § 700.20(b)(1).

This proposal specifies the hormone ingredients and their concentrations that may be used in the formulation of cosmetic products. The restrictions on the types and amount of hormone that may be used are based on agency determinations that these are safe levels which do not have any therapeutic effects or do not affect the structure or any function of the body (i.e., have no drug effect). Therefore, the agency is proposing that these levels of hormones be permitted for cosmetic conditions of use. At this time, the safety of hormones for inclusion in cosmetic products has been established only for progesterone at a concentration level up to 5 mg/oz and pregnenolone acetate at a concentration level up to 0.5 percent, when labeled for use not to exceed 2 oz per month. Any topically-applied products containing progesterone at concentrations of 5 mg/oz or less or pregnenolone acetate at concentrations of 0.5 percent or less are at this time regarded as cosmetics, provided the product labeling does not contain any drug claims as discussed elsewhere in this issue of the **Federal Register**.

The Panel reviewed a product containing "natural estrogens," i.e., a mixture of estrone and estradiol at a total concentration of 10,000 International Units (I.U.) per oz, and concluded that there were inadequate data to establish the safety of topically applied estrogens in concentrations up to 10,000 I.U. per oz. In the proposed rule for OTC topically applied hormone-containing drug products (54 FR 40618 at 40621), the agency stated that natural estrogens in concentrations up to 10,000 I.U. per oz are safe for topical application to the skin when used in amounts not to exceed 2 oz per month. However, the agency has no information on the concentration of individual estrogenic hormone chemicals (i.e., estradiol and estrone or any other estrogenic chemicals) present in natural estrogens. As a result, the agency is not currently able to establish the concentrations at which the individual estrogen hormone chemicals (which were found by the Panel to be safe for drug use) do not have therapeutic or other drug effects, i.e., at what levels it has been established that the ingredients do not affect the structure or any function of the body. Because insufficient information exists to allow the establishment of safe concentrations of individual estrogen hormone chemicals for use in cosmetic products, the agency is proposing at this time not to permit the use of natural estrogens, or any individual hormone chemicals that are constituents of natural estrogens, as ingredients for formulating cosmetic products. This use is not allowable because the agency is unable to establish at this time at what level of use of these hormone ingredients there is only a cosmetic effect and no drug effect. Therefore, the agency concludes at this time that any use of natural estrogens in cosmetic products makes the product an unapproved new drug. The conclusion is based on available data stating conclusively that at some levels the ingredients affect the structure or function of the body, and a concomitant lack of data establishing at what level, if any, the drug effect ceases. The agency invites comment on the qualitative and quantitative composition of natural estrogens that would allow the setting of safe levels for use in cosmetic products.

The agency is aware that estrogens and estrogen-containing substances have been used in cosmetic products. Manufacturers of such products are urged to submit data on the safety and exact chemical identity of such estrogens or estrogen-containing substances. The submission should also contain product labeling (current and historical) and provide information showing how long the cosmetic product containing this ingredient has been marketed. If adequate information is not provided to establish the chemical identity and composition of natural estrogens used in cosmetic hormone products, the agency will amend § 700.20 at the final rule stage to state that natural estrogens may not be used as ingredients for formulating cosmetic products. Thereafter, any use of natural estrogens in cosmetic products would make the product an unapproved new drug.

The agency has determined that 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 any function of the body. Such claims cause the product to be a drug.

In the proposed rule for OTC topically applied hormone-containing drug products, the agency stated that use of the chemical name of a hormone ingredient in labeling is preferable (54 FR 40618 at 40620). Based on a comment received in response to that proposal, as discussed elsewhere in this issue of the **Federal Register** the agency acknowledges that the chemical name may not be readily recognized by consumers. The agency is designating generally recognized established names to be used to identify these hormone ingredients in cosmetic product labeling, and is including these names in § 701.30.

The agency's cosmetic regulations (21 CFR 701.3(c)) 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. Under that sequence, "USAN and the USP dictionary of drug names" is not the first source to be utilized. Progesterone is found in USAN (Ref. 3), but pregnenolone acetate is not. Therefore, the agency is proposing to amend § 701.30 to establish progesterone and pregnenolone acetate as the names that are to be used to identify these ingredients in cosmetic product labeling.

The agency is aware that some consumers may wish to avoid using a cosmetic product containing a hormone ingredient for medical or other reasons. The establishment of uniform names to be used in all cosmetic product labeling should aid consumers in identifying those ingredients. Consumers may contact manufacturers of cosmetic products if they are uncertain whether or not the product contains a hormone ingredient. Consumers may also want to consult with a physician or pharmacist before using a cosmetic product that they believe contains a hormone ingredient.

References

(1) Department of Health and 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.

(2) "USAN and the USP dictionary of drug names," 30th ed., United States Pharmacopeial Convention, Inc., Rockville, MD, p. 524, 1993.

(3) "USAN and the USP dictionary of drug names," 30th ed., United States Pharmacopeial Convention, Inc., Rockville, MD, p. 529, 1993.

The agency has determined under 21 CFR 25.24(a)(11) that this proposed 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.

In accordance with Executive Order 12291, FDA has carefully analyzed the economic effects of this proposal and has determined that the final rule, if promulgated, will not be a major rule as defined by the Order. The agency is not aware of any cosmetic hormone products that contain pregnenolone acetate or progesterone in an amount above the levels being proposed in § 700.20(b). Thus, no product reformulations appear to be necessary. Some product relabeling may be necessary if the cosmetic product currently uses the word "hormone" or makes an implied drug claim in its labeling. However, because of the limited number of products affected, the agency concludes that this proposed rule is not a major rule.

FDA, in accordance with the Regulatory Flexibility Act, has considered the effect that this proposal would have on small entities including small businesses and has determined that, based on the limited number of affected products, no significant impact on a substantial number of small entities will derive from this action.

Interested persons may, on or before November 8, 1993, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two 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. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 700

Cosmetics, Packaging and containers.

21 CFR Part 701

Cosmetics, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR Parts 700 and 701 be amended as follows:

PART 700—GENERAL

1. The authority citation for 21 CFR part 700 continues toread as follows:

Authority: Secs. 201, 301, 502, 505, 601, 602, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331,352, 355, 361, 362, 371, 374).

2. New § 700.20 is added to read as follows:

§ 700.20 Use of certain hormones as ingredients in cosmetic products.

(a) Pregnenolone acetate and progesterone have been used as ingredients in both cosmetics and in cosmetics that are also drugs, depending on the claims made for the product. There are currently no approved over-the-counter hormone drug products except those identified in § 310.530(e) of this chapter.

(b) Pregnenolone acetate and progesterone may be safely used in cosmetic products at certain concentration levels. These ingredients may be included as single ingredients in cosmetic products when the product is formulated to contain up to the following amounts and is labeled with directions for use not to exceed 2 ounces of the product applied topically per month:

(1) Pregnenolone acetate 0.5 percent.

(2) Progesterone 5 milligrams per ounce.

(c) Any cosmetic product that contains pregnenolone acetate or progesterone in an amount exceeding that stated in paragraph (b) of this section or labeled with directions for use that exceed 2 ounces of the product applied topically per month is regarded as an unapproved new drug in accord with § 310.530 of this chapter and is subject to regulatory action under sections 502 and 505 of the act.

(d) Any cosmetic product using the word "hormone" in the text of its labeling or in its ingredient statement is considered as making 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. Any cosmetic product labeled as a "hormone cream" or with any statement in its labeling that "hormones" are present in the product or with any claim that the product will affect the structure or function of the body is subject to regulatory action under sections 502 and 505 of the act.

PART 701—COSMETIC LABELING

3. The authority citation for 21 CFR Part 701 continues to read as follows:

Authority: Secs. 201, 502, 601, 602, 603, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 352, 361, 362, 363, 371, 374); secs. 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1454, 1455).

4. Section 701.30 is amended by adding two new entries to the table to read as follows:

§ 701.30 Ingredient names established for cosmetic ingredient labeling.

* * * * *

Chemical name or description	Chemical formula	Established label name
*	*	*
3-Hydroxypregn -5-ene-20-one acetate.	$C_{23}H_{34}O_3$	Pregnenolone acetate.
Pregn-4-ene-3,20- dione.	$C_{21}H_{30}O_22$	Progesterone.

Dated: September 2, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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