DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 80N-0419]

Aphrodisiac Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administation (FDA) is issuing a notice of proposed rulemaking that would establish that aphrodisiac 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 Internal Drug Products and the public comment on an advance notice of proposed rulmaking 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 May 15, 1985. New data by January 15, 1986. Comments on the new data by March 17, 1986. 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 (21 CFR 330.10). Written comments on the agency's economic impact determination by May 15, 1985.

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

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of October 1, 1982 (47 FR 43572) FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking that would classify aphrodisiac drug products for OTC oral 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 Internal 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 December 30, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by January 31, 1983.

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 (HFA-305), Food and Drug Administration (address above) after deletion of a small amount of trade secret information. In response to the advance notice of proposed rulemaking, one consumer submitted a comment. This comment is on public display in the Dockets Management Branch.

In this proposed rule to amend Part 310 by adding to Subpart E new § 310.528 (21 CFR 310.528), FDA states for the first time its position on aphrodisiac drug products for OTC use. Final agency action on this matter will occur with the publication at a future date of a final rule relating to aphrodisiac drug products for OTC use.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC aphrodisiac drug products, based on the comment received and the agency's independent evaluation of the Panel's report. As discussed in the final rule revising the procedural regulations for reviewing and classifying OTC drugs, 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). (See the **Federal Register** of September 29, 1981; 46 FR 47730). 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 aphrodisiac drug products for OTC oral use 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 has broadened the scope of this rulemaking and is proposing that any aphrodisiac drug product for OTC use 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**. Upon the effective date of the final rule, OTC aphrodisiac drug products in interstate commerce will be regarded as unapproved new drugs and subject to regulatory action. Manufacturers are encouraged to comply voluntarily with the proposed rule at the earliest possible date.

I. The Agency's Tentative Conclusions on the Comment

The comment stated that yohimbine is known to be a workable aphrodisiac and that it has been tested at the Queens University in Canada as well as elsewhere. The comment contained a copy of a syndicated column that appeared in an unnamed newspaper (Ref. 1). The column responded to a reader who wrote that yohimbine, obtained in Mexico, had returned his potency to normal but that his doctor doubted that yohimbine was effective. The columnist stated that researchers at Queens University in Canada have reported that yohimbine may help some men who suffer from impotence, but the columnist did not provide any details of the study.

The agency telephoned the columnist and obtained the name of the publication that cited the Queens University study (Ref. 2). Subsequently, the agency obtained a copy of the journal in which the study was discussed.

The Queens University researchers reported on a number of studies, conducted during the late 1960's and mid 1970's using yohimbine in the treatment of impotence. The researchers stated that because of the variety of methodological problems the results are far from convincing and that the technologies used in the earlier studies did not provide for an accurate etiological diagnosis and for an objective assessment of therapeutic response. Accordingly, because of advances in diagnostic procedures and objective assessment, these researchers decided to reassess the value of yohimbine in a pilot study using 6 milligrams of yohimbine three times

daily in 23 highly selected patients in whom a firm diagnosis of primarily organic dysfunction was made. The researchers concluded that the results suggest that yohimbine may be beneficial in selected cases but that the number of satisfactory results is lower than the number given in previous reports. In addition, the researchers stated that, before pharmacological manipulation becomes established as an alternative to current surgical procedures for the treatment of erectile failure, controlled trials must be conducted to rule out a placebo effect.

The agency is aware that a 3-year study is being conducted at Queens University with the support of the Medical Research Council of Canada to determine the effectiveness of yohimbine as an aphrodisiac in highly selected cases and to resolve the question of diagnostic accuracy and objectivity frequently detracting from previous studies on the nonsurgical treatment or erectile dysfunction. Even if yohimbine were shown to be effective, the agency would concur with the Panel that individuals suffering from decreased libido and impaired sexual performance should not self-medicate, but should seek treatment under professional guidance. Therefore, at this time, the agency concludes that all aphrodisiac drug products, including yohimbine, are not appropriate for OTC use.

References

(1) Graedon, Joe, "Aphrodisiac May Really Work," *in* "The People's Pharmacy" (syndicated newspaper column, undated), Comment No. C–00001, Docket No. 80N–0419, Dockets Management Branch.

(2) Morales, A. et al., "Nonhormonal Pharmacological Treatment of Organic Impotence," abstract, *The Journal of Urology*, 128:45–47, The Williams and Wilkins Co., July 1982.

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

The Panel discussed the use of cantharides, don qual, estrogens, ginseng, golden seal, gotu kola, Korean ginseng, licorice, sarsaparilla, methyltestosterone, nux vomica, Pega Palo, sytrychnine, testosterone, yohimbine, and yohimbine hydrochloride as aphrodisiacs for OTC oral human use. FDA has considered the comment and other relevant data and information available at this time and concludes that it will tentatively adopt the Panel's report and recommendation.

The agency is tentatively adopting the following conclusions set forth by the Panel (45 FR 43574–43575): (1) that testosterone and methyltestosterone have a recognized influence on libido and sexual performance, but that these drugs are powerful hormones with potentially serious untoward effects and must be used only under the supervision of a physician; (2) that serious health risks are associated with alleged aphrodisiacs such as cantharides; (3) that there is no conclusive scientific evidence demonstrating the safety or effectiveness of any of the plant materials that have been used historically for aphrodisiac purposes; (4) and that individuals suffering from decreased libido and impaired sexual performance should not self-medicate, but should seek treatment under professional guidance.

In addition, the agency is aware that there are currently marketed products labeled as vitamins and minerals for OTC use as aphrodisiacs. Although the Panel did not address the use of vitamins and minerals as aphrodisiacs, the agency is aware of no data or information to support the safety and effectiveness of any vitamin or mineral for this use. Therefore, § 310.528(a) of the proposed rule includes vitamins and minerals among the ingredients that are not generally recognized as safe and effective for use as aphrodisiacs.

Whereas the Panel (the Advisory review Panel on OTC Miscellaneous Internal Drug Products) limited its deliberation to oral products, the agency believes that this rulemaking appropriately should apply to any ingredient labeled for use as an OTC aphrodisiac (any drug which is claimed to arouse or increase sexual desire or improve sexual performance). The agency is unaware of any data to support the oral or topical use of any OTC aphrodisiac drug product. Therefore, the agency tentatively concludes that any aphrodisiac for OTC use is classified as Category II.

The agency is also revising § 310.528(b) to clarify that a product covered by the regulation is a new drug for which an approved NDA is required for marketing, and that in the absence of an approved NDA the product would also be misbranded under section 502 of the act.

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 aphrodisiac drug products for OTC use, is a major rule.

For purposes of the Regulatory Flexibility Act, the economic assessment concluded that, while the average economic impact of the overall OTC drug review on small entities will not be significant, the possibility of larger-than-average impacts on some small firms in some years might exist. Therefore, the assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose a significant impact on a substantial number of small entities. The analysis identified the possibilities of reducing burdens on small firms through the use of (a) relaxed safety and efficacy standards or (b) labels acknowledging unproven safety or efficacy. However, the analysis concluded that there is no legal basis for any preferential waiver, exemption, or tiering strategy for small firms compatible with the public health requirements of the Federal Food, Drug, and Cosmetic Act. Nevertheless, to avoid overlooking any problems or feasible possibilities of relief peculiar to this group of products, the agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC aphrodisiac drug products. Comments regarding the economic impact of this rulemaking should be accompanied by appropriate documentation. The agency previously invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on aphrodisiac drug products for OTC oral use. 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 May 15, 1985. 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 that under 21 CFR 25.24(d)(9) (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR 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 it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 310 by adding to Subpart E new § 310.528, to read as follows:

PART 310—NEW DRUGS

§ 310.528 Drug products containing active ingredients offered over-the-counter (OTC) for human use as an aphrodisiac.

(a) Cantharides, don qual, estrogens, ginseng, golden seal, gotu kola ginseng, licorice, sarsaparilla, methyltestosterone, minerals, nux vomica, Pega Palo, strychnine, testosterone, vitamins, yohimbine, and yohimbine hydrochloride have been present as ingredients in drug products for use as an aphrodisiac. Androgens (e.g., testosterone and methyltestosterone) and estrogens are powerful hormones when administered internally and are not safe for use except under the supervision of a physician. There is a lack of adequate data to establish general recognition of the safety and effectiveness of any of these ingredients, or any other ingredient, for OTC use as an aphrodisiac. Labeling claims for aphrodisiacs for OTC use (any drug which is claimed to arouse or increase sexual desire or improve sexual performance) are either false, misleading, or unsupported by scientific data. The following claims are examples of some that have been made for aphrodisiac drug products for OTC use: "acts as an aphrodisiac;" "arouses or increases sexual desire and improves sexual performance;" "helps restore sexual vigor, potency, and performance;" "improves performance, staying power, and sexual potency;" "builds virility and sexual potency;" "creates an uncontrollable desire for immediate sexual gratification;" and "expands nature's gift of love." Based on evidence presently available, there is no ingredient that can be generally recognized as safe and effective for OTC use as an aphrodisiac.

(b) Any OTC drug product that is labeled, represented, or promoted for use as an aphrodisiac 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) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FDA –1571) (OMB Approval No. 0910–0014), 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 OTC as an aphrodisiac is safe and effective for the purpose intended.

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

Interested persons may, on or before May 15, 1985, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville MD 20857, 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. The agency has provided this 120 day period (instead of the normal 60 days) because of the number of OTC drug review documents being published concurrently. Written comments on the agency's economic impact determination may be submitted on or before May 15, 1985. 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 January 15, 1986, 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 March 17, 1986. 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 March 17, 1986. 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.

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

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