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: Advance notice of proposed rulemaking.

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

DATES: Written comments by December 30, 1982 and reply comments by January 31, 1983.

ADDRESS: Written comments 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, National Center for Drugs and Biologics (HFD-510, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on July 21, 1979 a report on OTC aphrodisiac drug products for oral use from the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed rule containing (1) the monograph recommended by the Panel, which establishes conditions under which OTC aphrodisiac drug products are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The Panel's recommendations on OTC aphrodisiac drug products for oral use contain no Category I or Category III conditions, and FDA is issuing the Panel's recommendations proposing Category II classification of OTC aphrodisiac drug products for oral use.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations that the ingredients in OTC aphrodisiac drug products for oral use be classified as Category II. If the agency proposes to adopt the Panel's recommendations, a regulation declaring these products to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) will be proposed for inclusion in Part 310, Subpart E (21 CFR Part 310, Subpart E). The agency is including, in this advance notice of proposed rulemaking, a regulation based upon the Panel's recommendations in order to obtain full public comment at this time.

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

The agency invites public comment regarding any substantial or significant impact that this rulemaking would have on OTC aphrodisiac drug products for oral use. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC aphrodisiac drug products for oral use should be accompanied by appropriate documentation.

If FDA proposes to adopt the Panel's recommendations, the agency will propose that the final rule for OTC aphrodisiac drug products for oral use be effective 6 months after its date of publication in the **Federal Register**. Because the OTC aphrodisiacs have been found to be either ineffective or unsafe for OTC use and the Panel recommended that individuals with decreased libido or impaired sexual performance not self-medicate with these products, the agency believes 6 months to be a reasonable effective date for the final rule. On or after the effective date of the final rule, no OTC drug products that are subject to the rule may be initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the rule at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous internal drug products was issued in the **Federal Register** of November 16, 1973 (38 FR 31696). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect."

An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.' ") In the **Federal Register** of August 27, 1975 (40 FR 38179), a notice supplemented the initial notice with a detailed but not necessarily all-inclusive, list of active ingredients in miscellaneous internal drug products to be considered in the OTC drug review. The list, which included aphrodisiac ingredients, was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973, and August 27, 1975, informed OTC drug product manufacturers of their opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC drug review to all OTC drug products.

Under § 330.10(a)(1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients in these miscellaneous internal drug products:

Diana F. Rodriguez-Calvert, Pharm. D. (appointed July 1976), Acting Chairman
John W. Norcross, M.D., Chairman (resigned March 1979)
Ruth Eleanor Brown, R. Ph. (resigned May 1976)
Elizabeth C. Giblin, Ed. D.
Richard D. Harshfield, M.D.
Theodore L. Hyde, M.D.
Claus A. Rohweder, D.O. (deceased April 1979)
Samuel O. Thier, M.D. (resigned November 1975)
William R. Arrowsmith, M.D. (appointed March 1975)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Eileen Hoates, nominated by the Consumer Federation of America, served as the consumer liaison until September 1975, followed by Michael Schulman, J.D., Francis J. Hailey, M.D., served as the industry liaison, and in his absence John Parker, Pharm. D., served. Dr. Hailey served until June 1975, followed by James M. Holbert, Sr., Ph. D. All industry liaison members were nominated by the Proprietary Association.

The following FDA employees assisted the Panel: Armond M. Welch, R. Ph., served as the Panel Administrator. Enrique Fefer, Ph. D., served as the Executive Secretary until July 1976, followed by George W. James, Ph. D., until October 1976, followed by Natalia Morgenstern until May 1977, followed by Arthur Auer until October 1978. Roger Gregorio served as the liaison for the Office of New Drug Evaluation beginning November 1978. Joseph Hussion, R. Ph., served as the Drug Information Analyst until July 1976, followed by Anne Eggers, R. Ph., M.S., until October 1977, followed by John R. Short, R. Ph.

In order to expand its scientific base, the Panel called upon the following consultants for advice in areas which required particular expertise:

Lynn R. Brady, Ph. D. (pharmacognosy)
Arthur E. Schwarting, Ph. D. (pharmacognosy)
Ralph B. D'Agostino, Ph. D. (statistics)

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products was charged with the review of many categories of drugs. Due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations on aphrodisiac drug products for oral use in this document. The Panel's findings on other categories of miscellaneous internal drug products are being published periodically in the **Federal Register.**

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings at which aphrodisiac drug products were discussed were held on March 2 and 3, April 17 and 18, June 2 and 3, and July 21 and 22, 1979.

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

No individuals requested to appear before the Panel to discuss OTC aphrodisiac drug products for oral use, nor was any individual requested to appear by the Panel.

The Panel has thoroughly reviewed the literature and has considered all pertinent information available through July 21, 1979 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed OTC aphrodisiac drug products for oral use with respect to the following three categories:

Category I. Conditions under which OTC aphrodisiac drug products for oral use are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC aphrodisiac drug products for oral use are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed 15 active ingredients as OTC aphrodisiac drug products for oral use and classified all of the ingredients in Category II.

A. Ingredients Reviewed by the Panel

Although data were requested in the initial **Federal Register** notice of November 16, 1973 (38 FR 31696) and specific aphrodisiac ingredients were listed in the supplemental notice of August 27, 1975 (40 FR 38179), no submissions were received on aphrodisiac drug products. The Panel considered the six ingredients contained in the supplemental list as well as other ingredients with a history of aphrodisiac usage.

The following ingredients were listed in the **Federal Register** of August 27, 1975 (40 FR 38179):

Don qual
Golden seal
Gotu kola
Korean ginseng
Licorice
Sarsaparilla

Other ingredients reviewed by the Panel on its own initiative were as follows:

Cantharides
Estrogens
Ginseng
Methyltestosterone
Nux vomica
Pega Palo
Strychnine
Testosterone
Yohimbine

B. Definition of Terms

For the purpose of this document the Panel agreed on the following definitions:

1. *Androgenic.* Producing masculine characteristics.

2. *Androgens.* Any substance that possesses masculinizing activities, e.g., testosterone.

3. *Aphrodisiac.* Any drug which is claimed to arouse or increase sexual desire or improve sexual performance.

4. *Estrogens.* The female sex hormones.

5. *Libido.* Sexual desire.

6. *Virilism. The development of masculine physical and mental traits in the female.*

7. *Virility.* Possession of the normal primary sex characteristics in one of the male sex.

C. Evaluation of Aphrodisiacs

The literature is replete with a large number of substances which, at one

time or another, have been claimed to have aphrodisiac action (Refs. 1, 2, and 3). By contrast the list of aphrodisiac ingredients in the **Federal Register** of August 27, 1975 (40 FR 38179) is relatively limited. This discrepancy may be explained by the fact that the vast majority of so-called "aphrodisiacs" exist or existed as part of folkloric tradition. Very few of such substances are commercially marketed with claims of aphrodisiac action. Aphrodisiacs reviewed in this document are defined as drugs taken internally which are claimed to arouse or increase sexual desire (libido) or improve sexual performance. Occasionally, the term "tonic" is used somewhat synonymously with "aphrodisiac," in that a product may be claimed to restore enfeebled function and to promote vigor.

In humans with good general health who are not taking any drugs including alcohol, sexual drive (libido) and sexual performance are governed by multiple factors, the most common of which are physchological. Impotence and frigidity have often been successfully treated by psychotherapy. The Panel further concludes that the conditions of decreased libido and impaired sexual performance are not amenable to self-treatment with internal drugs.

Hormonal factors also affect libido. The androgens have been shown to change the sexual drive in both sexes. For example, testosterone, when given to women in repeated large doses (100 to 200 milligrams (mg) of testosterone propionate given three times per week) in the treatment of breast cancer, often causes intensified libido along with genital sensitivity and signs of virilism (Ref. 4). In men who have a testosterone deficiency, specific therapy (Ref. 5); whereas, in men who are physically normal and who have normal testicular function, the administration of androgens has not been documented convincingly to show either a change in libido or an improvement in sexual performance (Ref. 4). Also, the Panel is not aware of any data demonstrating that estrogens increase sexual responsiveness in the normal human female, but the Panel is aware that in the male high doses of estrogens, as used in the treatment of prostatic cancer and in attempts to reduce blood cholesterol, are powerful inhibitors of libido (Ref. 4).

Although the androgens and estrogens have been shown to have both positive and negative effects on libido, they are powerful hormones and are not safe for use except under the supervision of a physician.

After a search of the available medical literature, the Panel was able to find only two studies which were designed to demonstrate a specific aphrodisiac action. In one double-blind crossover study, a combination prescription product containing methyltestosterone, yohimbine hydrochloride, and nux vomica (5 mg of each) was claimed to produce an "excellant or good response" in 31 out of 41 impotent male patients. Placebo produced only one "good" result (Ref. 6).

This study, as reported, has at least three major deficiencies. First, the "drugs" were coded "A" and "B" ("A" was the test medication and "B" the placebo); and, while each subject did not know the content of the "drug" he was receiving, he did know if it was "A" or "B." Such a code for the "drugs" could especially have been deciphered, thus destroying the blindness of the study. Second, since no details are given with regard to the outcome effectiveness measures ("excellent," "good," "fair," and "poor"), it is impossible to evaluate the appropriateness of these measures. Third, the study did not demonstrate a placebo effect because only 1 out of 41 individuals was classified as having a "good" response while on the placebo. In dealing with a phenomenon where psychological factors are so important, this low placebo success rate is highly unusual and suspect.

In the other study examined by the Panel (Ref. 7), an alcoholic extract of the Pega Palo plant (leaves and stems of *Rhynchosia pyramidalis)* was used in "50 cases of sexual impotence with partial or complete loss of libido and erections." The investigators reported that libido was increased in 41 individuals of whom 16 were restored to normal sexual activity during the test period. The study was not double-blind in that the investigators knew the drug the subjects were receiving. Further, while a placebo was said to be given "in many cases," no results were presented for the placebo. The study, as reported, does not meet the requirements of a well-controlled clinical study and cannot be considered as evidence toward the claims of effectiveness for Pega Palo.

Apart from these two studies which the Panel found to be highly inadequately, there was no substantive evidence whatever to support the claims of aphrodisiac action attributed to the various ingredients reviewd by the Panel. Such claims have been transmitted largely through folklore and exploited by manufactures who prey on the qullibility of people who most likely are in need of counsel or therapy.

Claims for cantharides and yohimbine have never been adequately supported. Cantharides (Spanish Fly) or cantharidin, the active constituent from the dried insect, causes irritation of the genitourinary tract, sometimes causing congestion of the tissue of the clitoris or penis. There is no evidence available to the Panel that this effect is accompanied by increased sexual desire or improved performance. Serious damage to the genitourinary tract has been reported, and there have been fatalities from shock associated with severe gastroenteritis. Yohimbine (from the bark of *Corynanthe yohimbe*), an alkaloid resembling reserpine, has been employed for centuries as an aphrodisiac, but there is not clinical evidence that it has any effect on either sexual desire or performance.

Ginseng (root of *Panax* species) has a long and popular folkoric use as an aphrodisiac. There are, however, no clinical studies or reports to support the often-repeated claim for effectiveness.

Nux vomica (seeds of *Strychnos nux-vomica*) and its active constituent, strychnine, have been used as sexual stimulants with claims of effectiveness based entirely on testimonials. There are no reports in the literature on clinical effectiveness. This plant-drug or its alkaloid is usually combined with other chemicals or products.

Of the six ingredients listed in the **Federal Register** of August 25, 1975 (40 FR 38179), gotu kola from *Centella asiatica,* licorice from glycyrrhiza species, sarsaparilla from smilax species, and Korean ginseng from *Panax* species, contain triterpenes. The panaxosides of ginseng, the asiatic acid-related compounds of gotu kola, and glycyrrhizic acid in licorice typify a group of constituents which may have a low level of androgenic action. The Panel is unaware of any proof that these compounds posses significant androgenic or aphrodisiac activity. The Panel could find no data in the literature of the last 20 years for the other two ingredients listed in the **Federal Register.** The Panel is not aware of the existence of the ingredient don qual and has not found it to be recorded in the indices of any major abstract service. Also, the Panel could find no information reporting the use of golden seal (Hydrastis canadensis) as an aphrodisiac.

Conclusion. Testosterone and methyltestosterone have a recognized influence on libido and sexual performance, but these drugs are powerful hormones with potentially serious untoward effects and must be used only under the supervision of a physician. Serious health risks are associated with alleged aphrodisiacs such as cantharides. There is no

conclusive scientific evidence demonstrating the safety or effectiveness of the large number of plant materials which have been used historically for aphrodisiac purposes. Individuals suffering from decreased libido and impaired sexual performance should not self-medicate, but should seek treatment under professional guidance. For these reasons, all OTC internal drug products with aphrodisiac claims are placed in Category II.

References

(1) Lewis, W. H., and M. P. F. Elvin-Lewis, "Medical Botany: Plants Affecting Man's Health," John Wiley and Sons, New York, pp. 326–332, 1977.

(2) Puri, H. S., "Vegetable Aphrodisiacs of India," *Quarterly Journal of Crude Drug Research*, 11:1742–1748, 1971.

(3) Wedeck, H. E., editor, "Dictionary of Aphrodisiacs," Peter Owen Ltd., London, 1961.

(4) Aaron, H., et al., "The Medical Letter on Drugs and Therapeutics," Drug and Therapeutic Information, Inc., New York, 5:45–46, June 7, 1963.

(5) Labhart, A., "Clinical Endrocrinology—Theory and Practice," Springer-Verlag, New York, pp. 468–469, 1976.

(6) Bruhl, D. E., and C. H. Leslie, "Afrodex: Double-Blind Test in Impotence," *Medical Record and Annals*, 56:22, 1963.

(7) Soba, J. G., E. E. Sanchez Molano, and F. Damrau, "Androgenic Action of Pega Palo. A Preliminary Report," *Journal of the National Medical Association*, 52:25–28, 1960.

Category II Labeling

The Panel concludes that all labeling claims for OTC aphrodisiacs or "placebo" aphrodisiacs are either false, misleading, or unsupported by scientific data. Claims such as those listed below and other similar terms which state or imply an aphrodisiac action are classified as Category II labeling when applied to OTC drug products:

a. "Acts as an aphrodisiac."

b. "Arouses or increases sexual desire and improves sexual performance."

c. "Helps restore sexual vigor, potency, and performance."

d. "Improves performance, staying power, and sexual potency."

e. "Builds virility and sexual potency."

f. "Creates an uncontrollable desire for immediate sexual gratification."

g. "Expands nature's gift of love."

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 as revised (see 47 FR 16010; April 14, 1982), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended in Part 310 by adding to Subpart E new § 310.528, to read as follows:

PART 310—NEW DRUGS

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

(a) Gotu kola, ginseng, licorice, sarsaparilla, cantharides, estrogens, methyltestosterone, nux vomica, Pega Palo, strychnine, testosterone, and yohimbine hydrochloride have been present as ingredients in drug products for internal 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 the safety and effectiveness of any of these ingredients for OTC use as an aphrodisiac. Labeling claims for OTC aphrodisiacs (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 OTC aphrodisiac drug products: "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 are no ingredients that can be generally recognized as safe and effective OTC for internal use as an aphrodisiac.

(b) Any OTC drug product labeled, represented, or promoted for internal use as an aphrodisiac is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act and is regarded as a new drug within the meaning of section 201(p) of the act for which an approved new drug application under section 505 of the act and Part 314 of this chapter is required for marketing.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD–1571), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted OTC as an aphrodisiac for internal use is safe and effective for the purpose intended.

(d) After the effective date of the final regulation, any such 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.

Interested persons may, on or before December 30, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one compy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before January 31, 1983. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: September 22, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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