21 CFR Part 310

[Docket No. 79N-0177]

Sweet Spirits of Nitre for Over-the-Counter Human Use

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This document proposes that sweet spirits of nitre be classified in category II as being not generally recognized as safe and effective or as being misbranded for over-the-counter (OTC) use. This document, based on the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, is part of the ongoing review of OTC drug products conducted by the Food and Drug Administration (FDA). The agency, having reviewed the Panel's report, has determined that any drug product containing sweet spirits of nitre is misbranded and is a new drug for which an approved new drug application is required for marketing and that action to remove sweet spirits of nitre drug products from the market should be implemented expeditiously and not await the full procedural review that has been established for OTC drug products.

DATES: Comments by March 24, 1980.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on June 23, 1978, a report of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. Under § 330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner of Food and Drugs issues (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded (i.e., Category I); (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 (i.e., Category II); (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 (i.e., Category III); and (4) the conclusions and recommendations of the Panel. Because the Panel's recommendations on sweet spirits of nitre contain no Category I or Category III conditions, FDA is issuing a notice containing the Panel's recommendations proposing Category II classification for sweet spirits of nitre.

The Panel's report has been prepared independently of FDA, and 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 agency, however, has reviewed the Panel's report because the Panel's review of sweet spirits of nitre resulted from a report to FDA of a case of an infant death related to this product. The Panel concluded, and FDA concurs, that sweet spirits of nitre is not generally recognized as safe and effective for OTC internal use. Moreover, because of the potential for poisoning in infants and the lack of any beneficial use of the ingredients as a drug, the agency has determined that marketing of any drug product containing sweet spirits of nitre should cease. Accordingly, the agency proposes that any sweet spirits of nitre drug product offered for any use be classified as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)).

Under the provisions of this proposal, any drug product containing sweet spirits of nitre for any use in interstate commerce after the effective date of the final regulation is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352) and is 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 (21 U.S.C. 355) and Part 314 of the regulations (21 CFR Part 314) is required for marketing. In the absence of an approved new drug application such products in interstate commerce after the effective date of the final regulation will be subject to regulatory action.

Based on the Panel's conclusions and FDA's review of the data submitted to the Panel, the agency has determined that use of any drug product containing this ingredient for any purpose is contrary to the public interest and that action to remove all products containing sweet spirits of nitre from the market should be implemented expeditiously. Accordingly, the agency advises that it will not follow the full OTC rulemaking procedure set forth in § 330.10 (21 CFR 330.10). FDA will not publish a tentative final order, but will publish a final order after the receipt and consideration of comments on this proposal unless those comments raise substantial questions that cannot be immediately resolved. It is the agency's intention that the final order will become effective upon publication in the Federal Register. Interested persons have until March 24, 1980 to submit comments on this proposal.

Upon the effective date of the regulation, because of the risk associated with use of sweet spirits of nitre, the agency will request firms to recall to the retail level all drug products containing sweet spirits of nitre. In the interim manufacturers are requested to voluntarily discontinue manufacture of products containing this drug.

Although the Miscellaneous Internal Panel was concerned only with the internal use of sweet spirits of nitre, it did note the topical use of this ingredient, and it referred OTC drug products containing sweet spirits of nitre for external use to the OTC Miscellaneous Internal Panel for review. In view of the action taken in this document, FDA has concluded that any review by the OTC Miscellaneous Internal Panel of OTC drug products containing sweet spirits of nitre for external use unnecessary.

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 the Federal Register of August 27, 1975 (40 FR 38179), a further notice supplemented the initial notice with a detailed list of ingredients which did not include sweet spirits of nitre.

The Commissioner appointed the following Panel to review the information submitted and to prepare a report under § 330.10(a) (1) and (5) on the safety, effectiveness, and labeling of the ingredients in those products:

John W. Norcross, M.D., Chairman
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.
Samuel O. Thier, M.D. (resigned November 1975)
William R. Arrowsmith, M.D. (appointed March 1976)
Diana F. Rodriguez-Calvert, Pharm.D. (appointed July 1976)

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. 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.

To expand its medical and scientific base, the Panel called upon the following consultants for advice in areas which required particular expertise:

Carol R. Angle, M.D. (pediatrics)
Jay M. Arena, M.D. (pediatrics)
William A. MacColl, M.D. (pediatrics)
Lynn R. Brady, Ph.D. (pharmacognosy)
Aruther E. Schwarting, Ph.D. (pharmacognosy)
Ralph b. D'Agostino, Ph.D. (statistics)

The Advisory Review Panel on OTC Miscellaneous Internal Panel Drug Products was charged with the review of many categories of drugs, but 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 recommenndations for sweet spirits of nitre for internal use in this document. The review of all other categories of miscellaneous internal drug products will be continued by the Panel, and its findings will be periodically published in the Federal Register during the Panel's deliberations.

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings were held on the following dates (the dates of those meetings which dealt with the topic of this document are in italics): February 23 and 24, March 23 and 24, April 27 and 28, June 22 and 23, September 21 and 22, November 16 and 17, 1975; February 8 and 9, March 7 and 8, April 11 and 12, May 9 and 10, *July 11 and 12, October 10 and 11,* 1976; February 20 and 21, April 3 and 4, May 15 and 16, July 9, 10 and 11, October 15, 16, and 17 December 2, 3, and 4, 1977; January 28, 29, and 30, *March 10, 11, and 12, May 5, 6, and 7, June 23, 24, and 25, August 4, 5, and 6,* September 29, 30, and October 1, November 17, 18, and 19, 1978; January 19 and 20, and *March 2 and 3,* 1979.

The minutes of the Panel meetings are on public display in the office of the Hearing Clerk (HFA–305), Food and Drug Administration (address given above).

No submissions were made for sweet spirits of nitre. However, sweet spirits of nitre came to the attention of the Panel as the result of a physician (Robert R. Chilcote, M.D.) reporting to FDA the case of an infant death. FDA performed an extensive followup and concluded that the incident described by Dr. Chilcote was unique or extremely rare (Ref. 1). nevertheless, the Advisory Review Panel on OTC Miscellaneous Internal Drug Products was informed of the incident and the results of the FDA followup. At the Panel's request, Dr. Chilcote was given an opportunity to appear before the Panel to describe the incident and to express his views on sweet spirits of nitre (see *Safety* below). Dr. Chilcote appeared before the Panel at its October 10, 1976 meeting. No other person requested an opportunity to appear before the Panel on this subject.

The Panel has thoroughly reviewed the literature and considered all pertinent data and information through June 23, 1978 in arriving at its conclusions and recommendations on sweet spirits of nitre for OTC internal use.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel considered sweet spirits of nitre for OTC internal use with respect to the following three categories:

Category I. Conditions under which sweet spirits of nitre is generally recognized as safe and effective and is not misbranded for OTC internal use.

Category II. Conditions under which sweet spirits of nitre is not generally recognized as safe and effective or is misbranded for OTC internal use.

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

The Panel concludes that sweet spirits of nitre is not safe or effective (Category II) for any OTC internal uses.

Reference

(1) OTC Volume 170163. (This volume is on display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857.)

Definition of Terms

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

1. *Antipyretic.* An agent that relieves or reduces fever.

2. *Antispasmodic.* An agent that relieves smooth muscle spasms.

3. *Diaphoretic.* An agent that promotes perspiration.

4. *Diuretic.* An agent that promotes the production and excretion of urine.

5. *Eructation.* A belch.

6. *Flatulent colic.* Acute abdominal pain characteristically intermittent and presumably due to spasm, obstruction, or distention of a portion of the gastrointestinal tract.

Sweet Spirits of Nitre

The Panel concludes that sweet spirits of nitre is not generally recognized as safe and effective for use as a diaphoretic, diuretic, intestinal antispasmodic, or stimulant, for treatment of flatulent colic, or for any other OTC internal use.

Sweet spirits of nitre contains between 3.5 and 4.5 percent of ethyl nitrite in alcohol and is also known as spirit of nitre, spirit of nitrous ether, and ethyl nitrite spirit. It has been used in the past mainly as a diaphoretic to reduce fevers in children, as a diuretic, and as an intestinal antispasmodic to relieve colic in infants. The dose generally suggested for children younger than 10 years of age is less than 1 milliliter (mL).

Sweet spirits of nitre has also been used topically for cold sores and fever blisters. The Panel has deferred consideration of this OTC usage to the sory Review Panel on OTC ellaneous External Drug Products.

Safety. Severe methemoglobinemia may ensue if sweet spirits of nitre is ingested; two deaths due to ingestion have been reported to the Panel. Dreisbach (Ref. 1) cites a fatality from the ingestion of approximately 4 grams (g) of ethyl nitrite in a 3-year-old child, an amount approximately equivalent to 267 milligrams/kilogram (mg/kg) or 6.7 milliliters/kilogram (mL/kg) of a 4-percent ethyl nitrite spirit. Chilcote (Ref. 2) reports fatal methemoglobinemia occurring in a 4-month-old infant following the administration of an estimated dose of 5 mL of a 4-percent ethyl nitrite spirit (200 mg ethyl nitrite), which was given to control "fussiness."

The actual risk of severe poisoning in infants is unknown since it is thought that many cases of methemoglobinemia are not suspected or diagnosed as being related to ingestion of sweet spirits of nitre. From 1969 to 1973, the National Clearinghouse for Poison Control Centers received information on 16 nonfatal ingestions of sweet spirits of nitre by children (Refs. 3 through 7); this is believed to be a marked underestimation of those cases treated nationally. The risks of poisoning for infants due to some undeveloped me systems and to the increased of fetal hemoglobin (Ref. 2) are or factors in the Panel's assessment that sweet spirits of nitre is not safe for OTC use.

Effectiveness. A quantitative pharmacologic assay of the absorption and metabolic effects of oral sweet spirits of nitre is difficult due to its characteristic volatility and instability (Refs. 8 and 9). Sweet spirits of nitre deteriorates rapidly on storage, even under refrigeration. In an acid medium, such as gastric juice, the ethyl nitrite rapidly forms gaseous nitrous dioxide, which causes gastric irritation and copious eructations with the residual gas absorbed as nitrous acid (Refs. 8, 9, and 10).

There is some evidence that sweet spirits of nitre is a diaphoretic and possibly an antipyretic, secondary to the diaphoretic action. In the anesthetized dog and cat (Ref. 10), sweet spirits of nitre caused a decrease in body temperature of 1° to 4° C. As far back as 1893, however, Leech (Ref. 9) noted that the clinical effect on temperature "is inconsiderable unless toxic doses are given even though it does cause perspiration * * * particularly under umstances of external warmth * * *. After drachm [1¼ teaspoonsful] doses of a 2½ percent solution of ethyl nitrite in alcohol I have not infrequently seen the face bedewed with moisture in from ten to twenty minutes * * * but the diaphoretic value of ten to twenty minims [⅛ to ⅓ teaspoonful] of spirit of nitre as usually given medicinally is very problematic."

There is no evidence to support the effectiveness of ethyl nitrite as a diuretic. In dogs and cats (Ref. 10) and in humans (Ref. 9) ethyl nitrite causes an actual decrease in urine volume at first, followed by diuresis but with no net increase in volume.

Although the nitrites and nitrates seem to decrease the pain of intestinal spasm (Ref. 11), esophageal spasm (Ref. 12), and even ureteral and biliary colic (Ref. 13), there is insufficient current investigation of these effects to arrive at any determination of the effectiveness in relation to the benefit-to-risk ratio (Ref. 13). It must be noted that there is no evidence that any of these indications relate specifically to sweet spirits of nitre.

Evaluation. Ethyl nitrite as a 3.5 to 4.5 percent solution in alcohol (sweet spirits of nitre) has been used for several centuries as a diaphoretic, diuretic, and intestinal antispasmodic (Ref. 8). The Panel is aware of no scientific evidence supporting its effectiveness, and there is a definite concern as to its safety. Therefore, the Panel places sweet spirits of nitre in Category II for any OTC internal human medicinal use.

References

(1) Dreisbach, R. H., "Handbook of Poisoning: Diagnosis and Treatment," 8th Ed., Lange Medical Publications, Los Altos, CA, p. 338, 1974.

(2) Chilcote, R. R., et al., "Sudden Death of an Infant from Methemoglobinemia After Administration of 'Sweet Spirits of Nitre'," *Pediatrics*, 59:280–282, 1977.

(3) Poison Control Statistics, Food and Drug Administration, p. 167, 1969.

(4) Poison Control Statistics, Food and Drug Administration, p. 164, 1970.

(5) Poison Control Statistics, Food and Drug Administration, p. 167, 1971.

(6) Poison Control Statistics, Food and Drug Administration, p. 165, 1972.

(7) Poison Control Statistics, Food and Drug Administration, p. 160, 1973.

(8) Atkinson, G. A., "The Pharmacology of the Nitrites and Nitroglycerine," *Journal of Anatomy and Physiology*, 22:225–239 and 351–371, 1888.

(9) Leech, D. J., "Pharmacological Action and Therapeutic Uses of the Nitrites and Allied Compounds—Lecture II Continued," *Lancet*, 2:76–79, 1893.

(10) Thompson, M. R., M. J. Andress, and C.T. Ichniowski, "The Pharmacologic Activity of Chemically Assayed Spirit of Ethyl Nitrite, USP, Including pH Value," *Journal of the American Pharmaceutical Association*, 22:487–495, 1933.

(11) Beams, A. J., "The Effect of Nitrites on Pain and on the Motility of the Gastrointestinal Tract," *Archives of Internal Medicine*, 49:270–275, 1932.

(12) Orlando, R. Z., and E. M. Bozymski, "Clinical Manometric Effects of Nitroglycerin in Esophageal Spasm," *New England Journal of Medicine*, 289:23–25, 1973.

(13) Nickerson, M., "Vasodilator Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S., and A. Gilman, The MacMillan Co., New York, pp. 731–733, 1975.

Note.—The Food and Drug Administration has determined that this document is exempt from the requirement of preparing an Environmental Impact Statement as specified under 21 CFR 25.1(f)(4).

Therfore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 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 authority delegated to the Commissioner (21 CFR 5.1), 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 new § 310.525, to read as follows:

§ 310.525 Sweet spirits of nitre drug products.

(a) Historically, sweet spirits of nitre has been present as an ingredient in over-the-counter (OTC) drug products for various uses. Based upon the lack of adequate data to establish effectiveness for any use and the adverse benefit-to-risk ratio, sweet spirits of nitre drug products cannot be considered generally recognized as safe and effective. The benefit from using sweet spirits of nitre for any use is insignificant when compared to the risk.

(b) Any drug product containing sweet spirits of nitre is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act and is 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 preparation containing sweet spirits of nitre for any use is safe and effective for the purpose intended.

(d) Any such drug product in interstate commerce after the effective

date of the final regulation that is not in compliance with this section is subject to regulatory action.

Interested persons are invited to submit their comments in writing (preferably in four copies and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before March 24, 1980. Comments should be addressed to the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments may be seen in the above office between 9 A.M. and 4 P.M., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment suporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: February 12, 1980.

William F. Randolph,

Acting Associate Commissioner, Regulatory Affairs.

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