**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 357**

**[Docket No. 79N-0378]**

## Anthelmintic Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

**AGENCY:** Food and Drug Administration.

**ACTION:** Proposed rule.

**SUMMARY:** This proposed rule would establish conditions under which over-the-counter (OTC) anthelmintic drug products, which destroy pinworms, are generally recognized as safe and effective and not misbranded. The proposed rule, 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).

**DATES:** Comments by December 8, 1980; reply comments by January 7, 1981.

**ADDRESS:** Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** William E. Gilbertson, Bureau of Drugs (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 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 drug products 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 these conditions under either (1) or (2) above (i.e., Category III); and (4) the conclusions and recommendations of the Panel. The Panel's conclusions on OTC anthelmintic drug products contained no Category III conditions.

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 it 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 as a formal proposal to obtain public comment before the agency reaches any final decision on the Panel's recommendations. FDA, however, has reviewed those ingredients which the Panel recommends should be placed in Category I for OTC anthelmintic drug products and considers that the potential risks from the use of gentian violet as an OTC anthelmintic outweigh its benefits and, therefore, intends to classify this ingredient in Category II at the tentative final monograph.

The Panel reviewed the information available to it regarding the safety of gentian violet and acknowledged both a scarcity of acute toxicity data and "a high incidence of undesirable side effects associated with its clinical use in children." The Panel also reviewed reports regarding the potential carcinogenicity of gentian violet and recommended "that further testing be performed to resolve the carcinogenic concerns." According to the Panel, however, these reports were not convincing when weighed against the lack of evidence of adverse effects reported during the long marketing history of gentian violet. The Panel, therefore, concluded that gentian violet was safe when used as directed.

After reviewing the available data relevant to the genetic toxicity of gentian violet (Refs. 1 through 4), FDA concludes that in bacterial and mammalian cells in culture, gentian violet in cytotoxic (having a deleterious effect on cells) and clastogenic (causing genetic damage). In addition, it has been shown to damage deoxyribonucleic acid (DNA) in *Escherichia coli* in vitro (Refs. 1 and 4). Gentian violet did not induce gene mutations in the Ames Assay (Ref. 4), but this may be a result of its cytotoxicity masking any mutagenic effect. In cultured mammalian cells gentian violet induced various chromosomal anomalies (Ref. 2). In a chick embryo assay and an in vivo mouse bone marrow assay, gentian violet did not induce chromosomal aberrations; however, it was toxic to the chick embryos at high doses (Ref. 4). The decreased genetic toxicity of gentian violet in vivo may be attributed to the presence of inactivating enzyme systems, a lack of penetration of the compound to the genetic material of the cell, or both. It is not known whether such protective mechanisms would be effective in preventing chromosomal and other genetic damage in humans receiving therapeutic doses of gentian violet.

The genetic toxicity data cited above indicate that gentian violet apparently interacts with and damages DNA in cultured cells. Since current theories of chemical carcinogenesis include the premise that active forms of chemical carcinogens may interact with DNA to initiate the neoplastic process (Ref. 5), this evidence is also suggestive of a potential carcinogenic effect of gentian violet. Moreover, gentian violet belongs to a class of dyes collectively referred to as di- and triaminophenylmethanes. A few of these dyes are known animal carcinogens; two of them, auramine and magenta, have been implicated as human carcinogens (Refs. 6, 7, and 8). The provisional listing of Food, Drug, and Cosmetic Violet Number 1, another dye of this same structural class, was revoked in the **Federal Register** of April 10, 1973 (38 FR 9077) on the basis of its possible carcinogenic activity. Review of one study on gentian violet itself suggests that long-term feeding to rats results in the induction of hepatocellular carcinoma (Ref. 9).

FDA recognizes that a definitive conclusion regarding the carcinogenic activity of gentian violet cannot be reached at this time. On the basis of the available evidence, the agency has nominated gentian violet for study in the newly formed National Toxicology Program. Prior to this nomination it was on the list of compounds to be included in the National Cancer Institute's Carcinogenisis Bioassay Program. In the meantime, the evidence that gentian violet interacts with DNA and belongs to the same structural class as known carcinogens necessitates a conservative policy regarding human exposure. Such exposure should be limited to situations where a clear-cut and unique beneficial effect of the drug can be expected.

FDA appreciates the different considerations noted by the Panel between lifetime exposure to gentian violet resulting from consuming residues of the drug in edible tissues of treated animals and the infrequent, intermittent exposure occasioned by use as a pinworm remedy. Nevertheless, the quantities ingested for treatment of pinworms are very large compared with the amounts individuals consume as

residues in meat. Thus the cumulative dose of gentian violet resulting from its use as an OTC anthelmintic may be comparable to the total exposure through the food supply for individual users.

With regard to effectiveness, FDA believes that under ideal conditons when gentian violet is used at proper doses for the full recommended 10-day course of treatment, it is effective against pinworms. In practice, however, the Panel recognized that its undesirable side effects (gastrointestinal disturbances) result in a considerable degree of noncompliance which "would obviously reduce the overall effectiveness of this ingredient." Individuals who discontinue treatment because of such side effects may experience no benefit from the gentian violet. In addition, gentian violet is unique among anthelmintics in having a recommended 10-day course of treatment. The length of the treatment by itself could lead to relatively lower patient compliance in relation to agents which are effective as the result of a single treatment or two widely spaced treatments.

One of the standards for determining that a drug is effective for OTC use as described in § 330.10(a)(4) (21 CFR 330.10(a)(4)) is "general recognition of effectiveness." In a letter to the Bureau of Drugs dated December 27, 1977 (Ref. 10), the Committee on Drugs of the American Academy of Pediatrics concluded that "because of the high incidence of adverse gastrointestinal effects (up to 50 percent), potential toxicity, low compliance, relatively low efficiency, and because of the availability of superior anthelmintics—gentian violet has no role in the treatment of enterobiasis." This opinion argues against a conclusion that gentian violet is generally recognized as safe and effective.

Gentian violet is currently the only active ingredient marketed OTC for pinworms. Other anthelmintic active ingredients are available on a prescription basis. The Panel found that pyrantel pamoate is effective for this indication and does not induce gastrointestinal side effects. The Panel recommended that pyrantel pamoate be moved from prescription-only to OTC status for the treatment of pinworms. If the agency accepts this recommendation, consumers would continue to have a pinworm remedy available OTC. FDA has made a tentative determination to accept the Panel's recommendations on the OTC use of pyrantel pamoate. Any persons marketing such an OTC product prior to the publication in the **Federal Register** of a final monograph will do so subject to the risk the agency may adopt a different position as detailed in § 330.13 (21 CFR 330.13).

FDA concludes that the rather modest health benefits associated with the continued OTC availability of gentian violet as an anthelmintic are outweighed by the risks, which are potentially quite serious. The agency invites specific comment on its intent to classify gentian violet in Category II at the tentative final monograph.

**References**

(1) Rosenkranz, H. S., and H. S. Carr, "Possible Hazard in Use of Gentian Violet," *British Medical Journal*, 3:702–703, 1971.

(2) Au, W., et al., "Cytogenetic Toxicity of Gentian Violet and Crystal Violet on Mammalian Cells in Vitro," *Mutation Research*, 58:269–276, 1978.

(3) Hsu, T. C., et al., "Cytogenetic Assays of Chemical Clastogens using Mammalian Cells in Culture," *Mutation Research*, 45:233–247, 1977.

(4) Au, W., et al., "Further Study of the Genetic Toxicity of Gentian Violet," *Mutation Research*, 66:103–112, 1979.

(5) Magee, P. N., "Extrapolation of Cellular and Molecular Level Studies to the Human Situation," *Journal of Toxicology and Environmental Health*, 2:1415–1424, 1977.

(6) Williams, M. H. C., and G. M. Bonser, "Induction of Hepatomas in Rats and Mice Following the Administration of Auramine," *British Journal of Cancer*, 16:87–92, 1962.

(7) International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Lyon, France, Vol. 4, pp. 57–64, 1974.

(8) Arcos, J. C., and M. F. Argus, "Chemical Induction of Cancer, Structural Basis and Biological Mechanisms," Academic Press, New York, Vol. II B, pp. 17–23, 1974.

(9) Weinberger, M. A., "Review of Slides from Old FDA Chronic Oral Toxicity Study with Gentian Violet," attached to FDA Memorandum dated February 1, 1978, in Panel Administrator's File (OTC Volume 17FPAII).

(10) Letter from Segal, S., to M. Freeman dated December 27, 1977, in Panel Administrator's File (OTC Volume 17FPAII).

The agency has reviewed the general labeling recommendations of the Panel for all OTC anthelmintic drug products. In particular, the Panel has recommended the following label warning: "Do not take this product if you are pregnant or ill, without first consulting a physician." The agency advises that this recommendation is inconsistent with the required labeling for pyrantel pamoate which is currently available only by prescription. The agency has further reviewed the Panel's report and concludes that there are insufficient data at this time to require a pregnancy warning for pyrantel pamoate. It is the agency's position that such a warning should only be required when medical and scientific evidence has demonstrated such need for the safe use of a product. Based upon the available data at this time, it is the agency's intent not to include such a pregnancy warning in the Tentative Final Order.

After FDA has carefully reviewed all comments submitted in response to both the Panel's and the agency's proposals, the agency will issue a tentative final regulation in the **Federal Register** to establish a monograph for OTC anthelmintic drug products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), the Panel and FDA have held as confidential all information concerning OTC anthelmintic drug products submitted for consideration by the Advisory Review Panel. All this information will be put on public display at the office of the Hearing Clerk, Food and Drug Administration, after October 9, 1980, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests of confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD–510) (address given above).

Based upon the conclusions and recommendations of the Panel, FDA proposes the following:

1. That the conditions included in the monograph, under which the drug products would be generally recognized as safe and effective and not misbranded (monograph conditions), be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

2. That the conditions excluded from the monograph either because they would cause the drug to be not generally recognized as safe and effective or to be misbranded or because the available data are insufficient to support the inclusion of such conditions in the monograph (nonmonograph conditions) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the **Federal Register**, regardless of whether further testing is undertaken to justify their future use.

FDA published in the **Federal Register** of May 13, 1980 (45 FR 31422) its proposal to revise the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug regulations (21 CFR 330.10) are unlawful to the extent that they authorize the marketing of Category III drugs after a final monograph. Accordingly, the proposed

regulations delete this provision and provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph (45 FR 31442).

Although it was not required to do so under *Cutler,* FDA has also decided to stop using the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" ( old Categories II and III). Any OTC drug product containing a "nonmonograph conditions" will be subject to regulatory action after the establishment of a final monograph. This document, however, retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

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 included anthelmintic ingredients.

The Commissioner appointed the following Panel to review the data and 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.S. (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.

In order 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)
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 for anthelmintic drug products in this document. The review of other categories of miscellaneous internal drug products will be continued by the Panel, and its findings will be published periodically in future issues of the **Federal Register.**

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, and *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,* and *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,* and *December 2, 3, and 4, 1977; January 28, 29, and 30, March 10, 11, and 12, May 5, 6, and 7,* and *June 23,* 1978.

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).

The following individuals were given an opportunity to appear before the Panel to express their views on OTC anthelmintic drug products either at their own or at the Panel's request:

Saul Bader, Ph. D.
Harold W. Brown, M.D.
Hugh C. Dillon, M.D.
Albert Eckian, M.D.
William Fiedelman, M.D.
George Goldstein, M.D.
Michael Hospador, Ph. D.
Harold Howes, Ph. D.
Edgar Martin, M.D.
Vernon W. Mayer, Ph. D.
John Penicnak, Ph. D.
Roger Sachs, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and the various data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through June 23, 1978 in arriving at its conclusions and recommendations for OTC anthelmintic drug products.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel considered OTC anthelmintic drug products with respect to the following three categories:

Category I. Conditions under which OTC anthelmintic drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC anthelmintic drug products 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.

## I. Submission of Data and Information

Pursuant to the notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on OTC miscellaneous internal drug products, the following firms made submissions related to anthelmintic drug products:

### *A. Submissions by Firms*

*Firms and Marketed Products*

Glenbrook Laboratories, New York, NY 10016, Jayne's P-W Vermifuge (for Children under 6 years), Jayne's P-W Vermifuge (for adults and children 6 years and older).

Pfizer Pharmaceuticals, New York, NY 10017, Pyrantel Pamoate Oral Suspension.

Scientific Associates, Inc., St. Louis, MO 63123, Piperazine Citrate Syrup, U.S.P.

*B. Ingredients Reviewed by the Panel*

*Labeled Ingredients Contained in Marketed Products Submitted to the Panel.*

Gentian violet
Piperazine citrate
Pyrantel pamoate

*C. Classification of Ingredients*

1. *Active ingredients.*

Gentian violet
Piperazine citrate
Pyrantel pamoate

2. *Inactive ingredients.*

None.

*D. Referenced OTC Volume Submissions*

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call for data notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179). All of the submitted information included in these volumes, except for those deletions made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after October 9, 1980, in the office of the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

**II. General Statements and Recommendations**

*A. Definition of Terms*

For the purposes of this document, the Panel adopted the following definitions:

1. *Anthelmintic.* An agent that is destructive to pinworms.

2. *Children.* Persons from 2 to under 12 years of age.

3. *Enuresis.* Urinary incontinence during sleep, i.e., bed wetting.

4. *Infants.* Persons under 2 years of age.

5. *Perianal.* In the region of the anus.

6. *Pruritus ani.* Itching in the region of the anus.

7. *Vermifuge.* Anthelmintic.

*B. General Discussion*

The Panel is aware that the term "anthelmintic" refers to therapeutic agents that are destructive to all worms. However, only the pinworm, *Enterobius vermicularis,* was considered in this document since it is the only intestinal worm which is amenable to self-diagnosis and treatment with an OTC drug product.

The Panel is also aware that another type of worm, *Ascaris lumbricoides* (large roundworm), is treatable by some of the same drug products which may be used for the treatment of pinworms; but since the *Ascaris* infestation can be much more serious, the Panel concludes that its diagnosis and treatment should be under the supervision of a physician.

The pinworm, *Enterobius vermicularis,* is the most common parasitic worm afflicting man. It occurs in all geographical areas within the United States, urban and rural. There is little socioeconomic difference in its incidence. Man is the only host for this usually benign but frequently irritating parasite. Infestation occurs more often in children than in adults.

Pinworms occur in humans only after pinworm eggs are ingested, and the adult worms live in the entire intestinal tract (the cecum, large and small bowel). When eggs are ingested, they hatch and mature in 15 to 28 days in the large bowel, and the worms live for 28 to 42 days (Ref. 1). During the night the female worm travels through the anus where it deposits approximately 11,000 eggs (Ref. 2).

Transmission of pinworms to the same or another host may be accomplished by several methods. Reinfestation can occur by transferring the eggs from the anal site to the mouth. The eggs can be harbored under the fingernails and transmitted to the mouth, where they are ingested. Pinworm eggs can contaminate food and drink and can survive for long periods of time without any host. Eggs can be present on clothing, bedding, bathroom fixtures, and other objects and can be readily transferred by handling the contaminated objects. The eggs are resistant to household disinfectants and can hatch after 2 to 3 weeks at room temperature (Ref. 2).

Most pinworm infestations cause no symptoms. Of the symptoms which do occur, the most frequent is perianal itching which may extend to the vulva in females. These symptoms are very disturbing to children and adults alike. It is occasionally the cause of secondary conditions, such as insomnia, enuresis, irritability, and secondary infection (due to localized scratching). Vague complaints of nausea and other gastrointestinal symptoms have also been associated with pinworm infestation.

It is noted in the literature that other complications of pinworm infestation such as appendicitis and vaginitis occur rarely (Ref. 3).

Diagnosis of pinworm infestation can be accomplished by either of two methods. One method is to cover the end of a swab or tongue depressor with scotch tape (sticky side out) and apply this end to the perianal area. The presence or absence of eggs is confirmed by examining the tape under the microscope. Although collection of eggs can be done at home, inspection and evaluation must be done in a laboratory or physician's office.

The other method of detection and identification for the consumer is to visually inspect the anal site (usually with a flashlight an hour or so after the child has gone to bed) for the presence of the female pinworm, which is one-fourth to one-half inch (6 to 13 millimeters (mm)) in length, and to see the worm actually move.

The primary goal of treating pinworm infestation is to completely eradicate the parasite and its eggs from the entire household. The eggs are extremely light in weight and can be airborne very easily and dispersed throughout the house.

The Panel is aware of a concern regarding the practice of treating all members of the household, and that the potential exists for the overuse of pinworm medication. In other words, those persons without confirmed infestations would also be recipients of therapy whether or not they exhibited the infestation or the symptoms of infestation.

The Panel believes that this practice will not present any hazard to those using pinworm medications, since the ingredients must be safe for general consumer use (when used as directed) in order to be marketed as an OTC drug product. Therefore, the Panel and its consultants concur with the widely accepted medical practice of treating all members of the household to eliminate the pinworm once one infested member has been identified. Such treatment extends to all members of a household except infants under two years of age, children weighing less than 25 pounds, or persons who are ill or pregnant, who should take such treatment only when so advised by a physician. If there is any question regarding the identification of the pinworm or the therapy for any member(s) of the household, a physician should be consulted before beginning treatment.

The Panel is aware of other pinworm drug products in current prescription status, and it urges FDA and drug manufacturers to review these new drug applications (NDA's) with an eye towards switching from prescription to OTC status, when appropriate.

**References**

(1) OTC Volume 170068.

(2) Hebeler, J. R., "Pinworms: A Nocturnal Nuisance," *Continuing Education,* pp. 1–3, February 1975.

(3) "Parasitic Infections," *in* "Textbook of Pediatrics," 10th Ed., Edited by Vaughan, V. C., R. J. McKay, and W. E. Nelson, W. B. Saunders Co., Philadelphia, pp. 754–755, 1975.

*C. Labeling*

The Panel believes that all labeling should be clear, concise, and easily read and understood by most consumers so that the medication can be properly used. The Panel has followed these concepts in the development of the Category I labeling. The Panel is also concerned about the size and color of the print used in the labeling of these and all drug products, and it recommends that the industry make the necessary effort to design labeling which can be read easily by consumers.

Due to the complexity of the pinworm identification, the dosage involved in treatment, and the hygiene procedures to be followed to reduce reinfestation, the Panel recommends that the packaging of OTC pinworm drug products contain a package insert for the consumer. This insert should contain: (1) a detailed description of how to find and identify the pinworm; (2) commentary on the life cycle of this parasite; (3) the ways in which it may spread from person to person and hygienic procedures to curtail such spreading; (4) all other Category I labeling information contained in the monograph.

The indications for use should be simply and clearly stated; the directions for use should provide the user with enough information for the safe and effective use of the product; and the label should include a statement that the product is only intended to eradicate pinworm infestation and should not be used to treat other types of worm infestation. Instructions for product usage (e.g., "Shake Well Before Using") should be prominently displayed on all appropriate package labeling.

The Panel feels that any statements suggesting prophylactic use of an anthelmintic drug product are entirely unwarranted and should not appear on any OTC anthelmintic labeling.

The Panel concurs with the current OTC labeling regulation dealing with warning statements (21 CFR 330.1(g)) and recommends that labeling for anthelmintic drug products contain a "Warnings" section which contains the following warnings in addition to any drug-specific warnings: "Keep this and all drugs out of the reach of children" and "In case of accidental overdose, seek professional assistance or contact a poison control center immediately."

Since both gentian violet and pyrantel pamoate have the potential for causing gastrointestinal side effects, the Panel has recommended a warning alerting the consumer to discontinue its use and consult a physician if these side effects occur. OTC pinworm medication is not recommended for infants, children who weigh less than 25 pounds, or persons who are ill or pregnant unless advised otherwise by a physician.

Since OTC drug products can be purchased by anyone, it is the view of the Panel that the public generally does not regard these products as medicines which, if used improperly, can result in injurious or potentially serious consequences. The public needs to be continually alerted to the idea that these products, like all medicine, carry some risk and should be treated with respect. The consumer should also be informed of any possible signs of known toxicity or any symptom requiring discontinuation of the use of the drug so that appropriate steps may be taken before more severe consequences become apparent.

The Panel believes that the label should contain a listing of all ingredients and that it should clearly indicate which are active and which are inactive. Active ingredients must be listed by their established names, and the label should state the quantity of the active ingredient in the recommended dosage.

**III. Anthelmintic Drug Products**

*A. Category I Conditions*

The following are Category I conditions under which anthelmintic drug products are generally recognized as safe and effective and not misbranded.

1. *Category I active ingredients.*

Gentian violet.

Pyrantel pamoate

a. *Gentian violet.* The Panel concludes that gentian violet (also known as methylrosaniline chloride) is safe and effective for OTC use as an anthelmintic when used as specified in the dosage and labeling sections below.

(1) *Safety.* Very little data are available on the acute toxicity of gentian violet, but the Panel has found the following information. Hodge et al. (Ref. 1) reported that the administration of gentian violet in propylene glycol resulted in a 7-day oral $LD_{50}$ (median lethal dose) of 600 milligrams/kilogram (mg/kg) for mice and a 7-day oral $LD_{50}$ of 250 mg/kg for rats. For guinea pigs and cats, a propylene glycol solution of gentian violet was used intraperitoneally, and results showed an approximate lethal dose of 100 to 150 mg/kg. In rabbits the intraperitoneal adminsitration of a propylene glycol solution of gentian violet gave a lethal dose from 125 to 250 mg/kg. The minimum lethal dose in rabbits given gentian violet orally in capsules for 6 days was 22 mg/kg daily for a total dose of 132 mg/kg. In two dogs treated orally with enteric-coated tablets of gentian violet for 18 days, one dog died at 40.1 mg/kg daily, whereas the second dog survived a dose of 35.4 mg/kg daily. Since the human dose is 2 mg/kg daily for a 10-day treatment, the authors concluded that the total dose would be "* * * less than one-fifth the [acute] lethal doses for the various species, so that the margin of safety seems adequate in consideration of the conditions of use."

In clinical use, the side effects of nausea, vomiting, abdominal pain, or diarrhea may occur in as many as one-third of the children treated with gentian violet (Refs. 1 and 2). Although the Panel acknowledges a high incidence of undesirable side effects affecting patient compliance, it considers gentian violet to be generally recognized as safe when properly used as an OTC anthelmintic in humans.

The Panel is aware of both the recent concern that gentian violet may be a carcinogen and the recently published and unpublished data regarding its potential carcinogenicity (Refs. 3 through 6). The Panel recognizes the propriety of the FDA Bureau of Foods' position that the present weight of the evidence regarding the toxicity of gentian violet indicates that gentian violet may be carcinogenic and that the question of carcinogenicity cannot be unequivocally answered based on the available data. No decision on the safety of gentian violet residues in the edible parts of animals can be made until appropriate data resolving the question of carcinogenicity are submitted to FDA.

The Panel was also made aware of concerns expressed by a physician from the Division of Anti-Infective Drug Products of the Bureau of Drugs about the continued OTC status of gentian violet, namely, that more effective and better-tolerated drugs for treating pinworm infestations are available and that questions regarding the carcinogenic, mutagenic, and embryotoxic potential of gentian violet have not been resolved.

The Panel has considered the concerns of both the Bureau of Foods and the Division of Anti-Infective Drug Products. However, the Panel recognizes that safety considerations regarding the short-term use of a compound as a drug in humans differ significantly from safety considerations regarding low-level, long-term human exposure to that compound in food. In this context, the data on the potential carcinogenicity of

gentian violet remain a concern but do not preclude the short-term, effective use of gentian violet as an anthelmintic in humans. The Panel recommends that further testing be performed to resolve the concerns about carcinogenicity associated with gentian violet. Because there is no conclusive proof that gentian violet is a carcinogen, the Panel concludes that it is safe for OTC use as an anthelmintic when used as directed.

The Panel was also made aware of one report that gentian violet may cause contact sensitization (Ref. 7). The Panel knows of no other such reports and concludes that the demonstrated benefits of gentian violet as an OTC anthelmintic in humans outweigh the risks of contact sensitization.

In evaluating the safety of gentian violet, the Panel was made aware of the reported high incidence of gastrointestinal distress associated with ingestion of the drug. Although it is generally recognized as an effective anthelmintic, therapeutic doses of the drug may produce side effects such as nausea, vomiting, diarrhea, and abdominal pain as a result of a direct irritant effect of the drug on the mucosa of the stomach and small intestine (Ref. 8). The Panel concludes that while these side effects are annoying, they are not deemed to be dangerous.

The Panel recommends that gentian violet for use as an anthelmintic be marketed only as an enteric-coated tablet. By delaying release of the drug until it reaches the small intestine, the incidence and severity of direct gastrointestinal irritation may be lessened, and patient compliance may be improved.

(2) *Effectiveness.* Gentian violet is an aniline dye that has been used for many years as an OTC anthelmintic. It is currently the only anthelmintic available for OTC use. Because of a lack of interest in the ingredient, very few studies have been performed to demonstrate its effectiveness in treating pinworm infestations. The effectiveness studies which have been performed were conducted 25 to 40 years ago under considerably less stringent standards than are applicable today, but the results are still informative.

In one study (Ref. 9) conducted on 20 children who were given gentian violet orally as sugar-coated tablets in doses of 11 mg (for every year of life)/day for a 7-day treatment (and repeated after 7 days), 70-percent effectiveness was demonstrated.

Another study (Ref. 2) performed on children and adults resulted in 92-percent effectiveness. In this study enteric-coated gentian violet tablets were administered to children in doses of 10 mg (for every year of life)/day and to adults in a dose of 64 mg before meals three times daily. Of the 122 patients who completed the treatment (36 did not), 107, of whom 85 were 16 years of age or younger, were given the treatment for 10 days, while the remaining individuals (all children) received the drug over a period of 8 days, rested 7 days, and then repeated the 8-day treatment. A total of 112 patients of the 122 showed no pinworm eggs on post-treatment swab examinations.

As noted earlier, about one-third of the patients treated with gentian violet experience adverse reactions, and these reactions result in a considerable incidence of noncompliance with the 10-day course of treatment. In the study cited immediately above (Ref. 2), there was a 23-percent dropout rate. The low compliance would obviously reduce the overall effectiveness of this ingredient, but the effectiveness rate for those who complete the 10-day course of therapy is sufficient enough for the Panel to conclude that gentian violet is generally recognized as effective when used as directed.

(3) *Dosage.* The usual daily dose of gentian violet for adults and children is 2 mg/kg daily divided into two or three administrations as enteric-coated tablets (Ref. 10). Treatment should continue for a complete 10-day course with a maximum of 150 mg/day (Ref. 11). The Panel believes that gentian violet should not be used for children who are less than 2 years of age, who weigh less than 25 pounds, or those who cannot swallow the tablet whole, except under the supervision of a physician. The manufacturer should include dosage information on the labeling in such a manner that persons can readily determine how much of the drug product to take in relation to their body weight.

(4) *Labeling for gentian violet.* The Panel recommends that in addition to the Category I labeling recommended for OTC anthelmintic drug products in general, the labeling for gentian violet should contain the following warning, direction and other information. (See part III paragraph A.2 below—Category I labeling.)

(a) *Warnings.* "Because of the staining properties of this preparation, do not bite, chew, or suck the tablets."

(b) *Directions.* "Tablets should be swallowed whole and taken with water."

(c) *Other information.* (i) "If vomiting occurs with this medication, the vomitus may be colored purple."

(ii) "This medication will cause your stools to be colored purple. This is harmless."

References

(1) Hodge, H. C., et al., "Acute Oral Toxicity of Methylrosaniline Chloride," *Toxicology and Applied Pharmacology,* 22:1–5, 1972.

(2) Wright, W. H., and F. J. Brady, "Studies on Oxyuriasis," *Journal of the American Medical Association,* 114:861, 1940.

(3) Rosenkranz, H. S., and H. S. Carr, "Possible Hazard in Use of Gentian Violet," *British Medical Journal,* 3:702–703, 1971.

(4) Au, W., et al., "Cytogenetic Toxicity of Gentian Violet on Mammalian Cells in Vitro," *Mutation Research,* 58:269–276, 1978.

(5) Hsu, T. C., et al., "Cytogenetic Assays of Chemical Clastogens Using Mammalian Cells in Culture," *Mutation Research,* 45:233–247, 1977.

(6) Weinberger, M. A., "Review of Slides from Old FDA Chronic Oral Toxicity Study with Gentian Violet," attached to FDA Memorandum dated February 1, 1978, in Panel Administrator's File (OTC Volume 17FPAII).

(7) Bielicky, T., and M. Novak, "Contact-Group Sensitization to Triphenylmethane Dyes," *Archives Dermatology* 100:540–543, 1969.

(8) Gleason, M. N., et al., "Clinical Toxicology of Commercial Products," 3d Ed., The Williams and Wilkins Co., Baltimore, p. 73, 1969.

(9) White, R. H. R., and O. D. Steinden, "Piperazine in the Treatment of Threadworms in Children," *British Medical Journal,* 2:755–757, 1953.

(10) Shirkey, H. C., "Pediatric Therapy," 4th Ed., The C. V. Mosby Co., St. Louis, p. 1108, 1972.

(11) OTC Volume 170024.

b. *Pyrantel pamoate.* The Panel concludes that pyrantel pamoate is safe and effective for OTC use as an anthelmintic when used as specified in the dosage and labeling sections below.

(1) *Safety.* The safety of pyrantel pamoate seems well established because of the paucity of adverse reactions reported since its introduction as a prescription drug in 1972 (Ref. 1). There have been no reports of significant toxicity due to accidental overdosage.

The Panel has evaluated data submitted by a manufacturer and considers it of sufficient importance to this document to be included in toto (Ref. 2):

Pyrantel pamoate at doses of 50, 250, and 500 mg/kg/day was administered to the rat for 30 days without adverse symptoms. Postmortem examination and histologic examination revealed no morphologic changes attributable to the treatment.

In another study, rates were given 100, 300, or 600 mg/kg/day for 13 weeks. Apart from a slight reduction in growth rate and food consumption in rats receiving 600 mg/kg/day there were no adverse symptoms observed. No gross

or histopathologic changes attributable to the drug were observed.

An inconsistent hepatotoxicity has been observed in dogs. Male beagle dogs were given 500, 250, or 50 mg/kg/day for 30 days. Transaminase elevations were seen in 2 (out of 4) which received the top dose and liver changes were observed histologically in one. In an identical, but separate, study in female dogs these same effects appeared at both 500 and 250 mg/kg/day. In a third study in male and female beagle dogs serum transaminases and liver biopsy specimens were normal after 14 and 30 days of 250 or 50 mg/kg/day.

Pyrantel pamoate administered to beagle dogs in daily doses of 100, 300, or 600 mg/kg for 13 weeks caused no toxic symptoms or effect on body weight. In three of four dogs receiving 300 mg/kg and two of four receiving 600 mg/kg, transaminase levels were raised after 13 weeks' treatment. A slight, apparently dose-dependent lymphocytosis was observed in dogs after 13 weeks. There were no histopathologic changes attributable to the drug. It should be noted that these effects were not observed in dogs which were given the better absorbed tartrate salt of pyrantel.

Those dose levels represent approximately 27 times the recommended dose in man of 11 mg/kg [5 milligrams/pound (mg/lb)].

Reproductive and teratologic studies were carried out to investigate the effects of pyrantel pamoate on fertility, pregnancy, the developing fetus, and the newborn in rats and rabbits. These consisted of reproduction studies in three parts, all according to the protocol recommended in the 1966 FDA Guidelines.

Pyrantel pamoate at dose levels of 260 or 25 mg/kg/day had no effect on fertility, reproduction, organogenesis, parturition, or lactation in rats or organogenesis in rabbits.

In clinical studies of children given a single dose of 5 mg/lb, there was a documented incidence of transient elevation of the serum glutamic-oxaloacetic transaminase (SGOT) in 1.2 percent of 571 subjects from several institutions. In undocumented cases without baseline values, the SGOT was mildly elevated at 24 or 48 hours after therapy in 20 percent of 155 children (Ref. 2).

In humans side effects due to pyrantel pamoate (as the suspension) at the recommended doses of 5 mg/lb (base activity) of body weight have occurred infrequently, and even at high doses (up to 3,500 mg) the side effects were still infrequent (Ref. 2). The most frequently reported side effects were specific to the gastrointestinal tract and may be related to the clearing of worms (Ref. 2). The most frequent gastrointestinal disturbances are nausea, vomiting, abdoiminal cramps, and diarrhea. Other side effects encountered include headache, dizziness, anorexia, drowsiness, and rashes.

Information on the absorption of pyrantel pamoate is incomplete. The Panel is aware of one study in which single oral doses of 5 mg/lb yielded low plasma levels of less than 0.05 to 0.13 microgram/millimeter (μg/ml) of unchanged drug. This study of 14 subjects showed a maximum absorbance (urinary excretion) of 6.7 percent. This low level of absorption may contribute to the paucity or reported adverse reactions (Ref. 3).

During an oral presentation at a Panel meeting, the Panel was reminded of some adverse reactions which have previously been reported (Ref. 4), including one case each of ototoxicity, optic neuritis, and hallucinations with confusion and paresthesias. The Panel considered this information in depth and concluded that, in the absence of information to support cause and effect, these reports were not evidence of a pyrantel pamoate reaction.

The Panel has reviewed the information available to it (Refs. 5 and 6) regarding an incident in Egypt in which 12 of 37 children treated with pyrantel pamoate developed severe reactions and two children died. In view of the scanty information available now or likely to be available in the future and considering the vast experience with pyrantel pamoate, which is estimated at over 100 million persons treated without any reported incidence of death, the Panel concludes that these reactions and deaths were not due to pyrantel pamoate.

The Panel concludes that pyrantel pamoate is generally recognized as safe of OTC human use an an anthelmintic in the dosages discussed below.

(2) *Effectiveness.* Pyrantel pamoate works like succinylcholine chloride in that it depolarizes muscle thereby paralyzing the worm's contractile hold on the intestinal wall. Both the pinworm *(Enterobius vermicularis)* and the large roundworm *(Ascaris lumbricoides)* are particularly sensitive to the effect of the drug.

Numerous studies document the high degree of effectiveness of pyrantel pamoate. Pitts and Migliardi (Ref. 3) determined that the overall effectiveness in three groups totalling 1,506 patients (mainly children) was 97.2 percent. The dose used was a single dose of 5 mg/lb of body weight.

Another study, by Sanati and Ghadirian (Ref. 7), determined that pyrantel pamoate was effective in 95 percent of 120 patients. Treatment consisted of a single dose of 10 mg/kg of body weight. One week after the treatment, 114 of the 120 patients had no sign of pinworm infestation. Of 30 patients used as controls, there were no instances of eradication of the pinworm infestation.

(3) *Dosage.* The Panel recommends the usual single dose of pyrantel pamoate in suspension of 5 mg/lb or 11 mg/kg of body weight, not to exceed 1 gram (g) (Refs. 8 and 9). This dose is expressed in terms of the active moiety or pyrantel pamoate and is applicable to both pediatric and adult populations. The Panel recommends that the manufacturer include dosage information in the labeling in such a manner that the user can readily determine how much of the drug product to take in relation to his or her body weight.

(4) *Labeling for pyrantel pamoate.* The Panel recommends that the Category I labeling for OTC anthelmintic drug products be used for pyrantel pamoate. (See part III. paragraph A.2. below—Category I labeling.)

**References**

(1) OTC Volume 170161.

(2) OTC Volume 170033.

(3) Pitts, N. E., and J. R. Migliardi, "Antiminth (Pyrantel Pamoate)—The Clinical Evaluation of a New Broad-Spectrum Anthelmintic," *Clinical Pediatrics,* 13:87–94, 1974.

(4) Summary minutes of the OTC Miscellaneous Internal Drug Products Panel 21st meeting, March 10, 11, and 12, 1978.

(5) OTC Volume 170162.

(6) OTC Volume 170160.

(7) Sanati, S., and E. G. Ghadirian, "Treatment of Enterobiasis with Pyrantel Pamoate in Iran," *Journal of Tropical Medicine and Hygiene,* 74:160–161, 1971.

(8) Tudor, R. B., "Pediatrics—Ridding Children of Common Worm Infections," *Postgraduate Medicine,* 58:115–120, 1975.

(9) Diefenbach, W. C. L., "Intestinal Parasites: Common and Becoming More So," *Consultant,* pp. 47–54, 1976.

2. *Category I labeling.* The Panel recommends the following labeling for the Category I OTC anthelmintic drug products in addition to the specific labeling discussed in the individual ingredient statements.

a. *Indications.* "For the treatment of pinworms."

b. *Warnings.* (i) "If upset stomach, diarrhea, nausea, or vomiting occurs with this medication, discontinue using it and consult a physician."

(ii) "Do not take this product if you are pregnant or ill, without first consulting a physician."

(iii) "Do not give to infants under two years of age or children who weigh less than 25 pounds without first consulting a physician."

c. *Directions.* (i) "When one individual in a household has pinworms, the entire household should be treated. Persons who are ill or pregnant, infants under two years of age, or children who weigh less than 25 pounds should not be treated without first consulting a physician."

(ii) "Take only according to directions."

(iii) "Do not exceed the recommended dosage."

(iv) "If any worms other than pinworms are present before or after treatment, consult a physician."

d. *Package insert.* The Panel recommends that each OTC anthelmintic drug product contains a consumer package insert which includes the following information.

(i) A detailed description of how to find and identify the pinworm.

(ii) A commentary on the life cycle of the pinworm.

(iii) A commentary on the ways in which pinworms may be spread from person to person and hygienic procedures to follow to avoid such spreading.

(iv) All other Category I labeling information contained in the monograph.

*B. Category II Conditions*

The following are Category II conditions under which drug products used as anthelmintics are not generally recognized as safe and effective or are misbranded.

1. *Category II active ingredient.* The Panel has classified piperazine citrate as not generally recognized as safe and effective for OTC use as an anthelmintic.

*Piperazine citrate.* The Panel concludes that piperazine citrate is effective as an anthelmintic for the treatment of pinworms but unsafe for OTC use. The Panel recommends that this drug remain available only on prescription.

(a) *Safety.* Piperazine citrate, the citrate salt of hexahydropiperazine, is widely used as a prescription drug for the treatment of the pinworm (*Enterobius vermicularis*) and the large roundworm (*Ascaris lumbricoides*).

There are many published reports of neurotoxicity characterized by confusion, somnolence, incoordination, and myoclonic or petit mal seizures in persons treated with this product. Nickey (Ref. 1) related the case of a 9-year-old girl who was well-stabilized on trimethadione for petit mal seizures. She was treated with anhydrous piperazine for pinworms and experienced "long, hard" seizures. After discontinuing the piperazine therapy and then rechallenging the patient with additional piperazine citrate, Nickey reported that seizures resumed. This case and others (Refs. 2, 3, and 4) indicate that piperazine citrate can possibly precipitate seizures in patients with neurological disorders.

Miller and Carpenter (Ref. 5) reported that neurotoxic side effects of piperazine citrate were evident in an 8-year-old boy with no history of central nervous system disease. However, the child did have compromised renal function. Thus, it is suggested by this case that transient neurotoxicity may occur in persons with renal dysfunction who are treated with piperazine.

Belloni and Rizzoni (Ref. 6) have described a case of neurotoxicity associated with the dosing of an apparently normal, healthy child. They state that in 10 of 11 patients on piperazine hydrate therapy, electroencephalographic (EEG) changes were noticed over a 5-day period. Schuch et al. (Ref. 2) cite the induction of EEG changes in 11 of 16 children with previously normal tracings.

In view of the reported risk of neurotoxicity, the Panel believes that the benefit-to-risk ratio of piperazine makes it inappropriate for general use as an OTC preparation.

(b) *Effectiveness.* The Panel believes that piperazine citrate is an effective anthelmintic when used under the direct supervision of a physician. This belief is based upon its wide usage as a prescription product for over 20 years since approval of the first new drug application for this ingredient.

(c) *Evaluation.* Based on its review of the neurotoxic side effects of piperazine citrate, the Panel concludes that piperazine citrate is not safe for OTC use and should remain a prescription drug product.

**References**

(1) Nickey, L. N., "Possible Precipitation of Petit Mal Seizures with Piperazine Citrate," *Journal of the American Medical Association,* 195:1069–1070, 1966.

(2) Schuch, P., U. Stephan, and G. Jacobi, "Neurotoxic Side Effects of Piperazine," *The Lancet,* 1:1218, 1966.

(3) Neff, L., "Another Severe Psychological Reaction of Side Effects of Medication in an Adolescent," *Journal of the American Medical Association,* 197:150–151, 1966.

(4) Savage, D. C. L., "Neurotoxic Effects of Piperazine," *British Medical Journal,* 2:840–841, 1967.

(5) Miller, C. G., and R. Carpenter, "Neurotoxic Side-Effects of Piperazine," *The Lancet,* 1:895–896, 1967.

(6) Belloni, C., and G. Rizzoni, "Neurotoxic Side-Effects of Piperazine," *The Lancet,* 2:369, 1967.

2. *Category II labeling.* Of the products reviewed, the Panel found no claims which are inappropriate, unreasonable, or incorrect. However, OTC anthelmintic labeling should not, in any way, suggest that anthelmintic drug products intended to treat pinworm infestations can be used successfully to treat other intestinal worms. Such information would be not only misleading, but also would present a direct, serious health hazard to the patient.

The Panel also believes that any statement suggesting the prophylactic use of anthelmintic drug products is entirely unwarranted and should not appear on any OTC anthelmintic labeling.

The agency has carefully considered the potential environmental effects of this proposal and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement therefore will not be prepared. The agency's finding of no significant effect and the evidence supporting this finding, contained in an environmental assessment under 21 CFR 25.31 (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742), may be seen in the Hearing Clerk's Office, Food and Drug Administration.

Therefore, 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 by adding to Part 357 a new Subpart B to read as follows:

## PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

### Subpart B—Anthelmintic Drug Products

Sec.

Sec.

357.152 Package inserts for anthelmintic drug products.

**Authority:** 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); (5 U.S.C. 553, 554, 702, 703, 704).

## Subpart B—Anthelmintic Drug Products

### § 357.101 Scope.

(a) An over-the-counter anthelmintic drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart in addition to each of the general conditions established in § 330.1 of this chapter.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

### § 357.103 Definitions.

As used in this part:

(a) *Age.* "Infant" means a person under 2 years of age, "child" means a person 2 years to under 12 years of age, and "adult" means a person 12 years of age and older.

(b) *Anthelmintic.* An agent that is destructive to pinworms.

### § 357.110 Anthelmintic active ingredients.

The active ingredients of the product consist of the following when used within the dosage limits and dosage forms established for each ingredient:

(a) *Gentian violet* (enteric-coated tablets).

(b) *Pyrantel pamoate.*

### § 357.150 Labeling of anthelmintic drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "anthelmintic."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "For the treatment of pinworms."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing any ingredient identified in § 357.110.* (i) "If upset stomach, diarrhea, nausea, or vomiting occurs with this medication, discontinue using it and consult a physician."

(ii) "Do not take this product if you are pregnant or ill, without first consulting a physician."

(iii) "Do give to infants under two years of age or children who weigh less than 25 pounds, without first consulting a physician.

(2) *For products containing gentain violet identified in § 357.110(a).* "Because of the staining properties of this preparation, do not bite, chew, or suck the tablets.

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions," followed by "or as directed by a physician."

(1) *For products containing any ingredient identified in § 357.110.* (i) "When one individual in a household has pinworms, the entire household should be treated. Persons who are ill or pregnant, infants under two years of age, or children who weigh less than 25 pounds should not be treated without first consulting a physician."

(ii) "Take only according to directions."

(iii) "Do not exceed the recommended dosage."

(iv) "If any worms other than pinworms are present before of after treatment, consult a physician."

(2) *For products containing gentian violet identified in § 357.110(a).* (i) Oral dosage for adults and children is 2 milligrams/kilogram daily, divided into two or three administrations as enteric-coated tablets. Treatment continues for a complete 10-day course with a maximum of 150 milligrams/day. For infants under two years of age or children who weigh less than 25 pounds, there is no recommended dosage except under the advice and supervision of a physician.

(ii) "Tablets should be swallowed whole and taken with water."

(3) *For products containing pyrantel pamoate identified in § 357.110(b).* Oral dosage for adults and children is 11 milligrams/kilogram. The total single dose does not exceed 1 gram. For infants under two years of age and children who weigh less than 25 pounds, there is no recommended dosage except under the advice and supervision of a physician.

(e) *Other information.* The labeling of gentian violet, identified in § 357.110(a), contains the following additional information:

(1) "If vomiting occurs with this medication, the vomitus may be colored purple."

(2) "This medication will cause your stools to be colored purple. This is harmless."

### § 357.152 Package inserts for anthelmintic drug products.

The labeling of the product containing any ingredient identified in § 357.110 contains a consumer package insert which includes the following information:

(a) A detailed description of how to find and identify the pinworm.

(b) A commentary on the life cycle of the pinworm.

(c) A commentary on the ways in which pinworms may be spread from person to person and hygenic procedures to follow to avoid such spreading.

(d) All labeling information contained in the § 357.150.

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 December 8, 1980. Comments should be addressed to the office of the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replying to comments may also be submitted on or before January 7, 1981. Comments may be seen in the above-named 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 supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: August 27, 1980.

**Jere E. Goyan,**

*Commissioner of Food and Drugs.*

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