**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Parts 357 and 369**

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

# Anthelmintic Drug Products for Over-The-Counter Human Use; Final Monograph

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) anthelmintic drug products (products that destroy pinworms) are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on anthelmintic drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

**EFFECTIVE DATE:** February 2, 1987. For additional information concerning this effective date see "Paperwork Reduction Act of 1980" appearing in the preamble of this document.

**FOR FURTHER INFORMATION CONTACT:** William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

**SUPPLEMENTARY INFORMATION:** In the Federal Register of September 9, 1980 (45 FR 59540), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC anthelmintic drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by December 8, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by January 7, 1981.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for anthelmintic drug products was published in the Federal Register of August 24, 1982 (47 FR 37062). Interested persons were invited to file by October 25, 1982, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by December 22, 1982. Final agency action occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC anthelmintic drug products.

The OTC procedural regulations (21 CFR 330.10) now 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. Accordingly, FDA is no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

As discussed in the proposed regulation for OTC anthelmintic drug products (47 FR 37062), the agency advises that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 6 months after the date of publication in the Federal Register. Therefore, on or after February 2, 1987, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In response to the proposed rule on OTC anthelmintic drug products, a bi-State drug informaiton center, a pediatric association, a consumer, and a physician submitted comments. Several additional comments were received after the close of the comment period from a county department of health services, a university medical center, and three physicians. The issues raised by these comments are the same as those raised by comments submitted during the period the administrative record was open. Copies of the comments received are on public display in the Dockets Management Branch.

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) or the additional information that has come to the agency's attention since publication of the notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

## I. The Agency's Conclusions of the Comments

1. Two comments disagreed with the agency's proposed substitution of the word "doctor" for the "physician" in OTC drug labeling. One comment stated that because "physician" is a term that is recognized by people of all ages and social and economic levels, there is no need for the change, which would be costly and provide no benefit. The comment further contended that physician is a more accurate term, whereas "doctor" is a broad term that could confuse and mislead the lay person into taking advice on medication from persons other than medical doctors, such as optometrists, podiatrists, and chiropractors.

The agency recognizes that the term "doctor" is not a precise synonym for the word "physician," but believes that the terms are frequently used interchangeably by consumers and that the word "doctor" is likely to be more commonly used and better understood by consumers. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs. Based on comments

received on these proposals, the agency has determined that final monographs and any applicable OTC drug regulation will give manufacturers the option of using either the word "physician" or the word "doctor". This final monograph provides that option.

2. Several comments objected to the agency's proposed switch of pyrantel pamoate from prescription to OTC status, arguing that there is a large potential for widespread inappropriate use because the average person is incapable of diagnosing pinworm infestations, and proper diagnosis requires laboratory confirmation. One comment stated that symptoms are not specific in pinworn infestations, and another comment added that parents could incorrectly attribute nonspecific gastrointestinal and other symptoms to worms when the symtomatology may be due to causes other than pinworm infestation.

The agency does not agree that consumers are unable to diagnose pinworm infestations and that reclassification of pyrantel pamoate from prescription to OTC status would result in widespread inappropriate use. As one comment pointed out, the best known symptom of pinworm infestation is pruritis ani (itching in the anal area). Secondary conditions that also occur in pinworm infestation include insomnia, gastrointestinal distress, irritability, enuresis (bedwetting), and secondary infection due to localized scratching. The agency agrees that these symptoms are suggestive of pinworm infestation but are not limited to that condition. When these symptoms occur, the labeling of an OTC anthelmintic drug product will inform consumers having such symptoms that they may have pinworms and will instruct them to make a visual inspection for the worms before using the product.

The agency recognizes that laboratory diagnosis would be required to confirm pinworm eggs, but consumer diagnosis can be made by visual detection of the adult female worm (usually ¼ to ½ inch in length) during the hours of sleep when the worm migrates out of the anus onto the perianal skin. In addition, OTC anthelmintic drug products will not be indicated for the symptoms of pruritus ani, gastrointestinal distress, etc., but instead will be labeled only for the treatment of pinworms. Should a consumer suspect pinworms, the labeling will provide sufficient information on the symptoms, identification, and detection of pinworms to allow consumers to use the product properly.

The comments did not present, and the agency is unaware of, any evidence that drugs previously marketed OTC for pinworm treatment have been inappropriately used. Likewise, the comments did not present, and the agency is unaware of, any evidence that the OTC availability of pyrantel pamoate will result in misuse of the drug. However, because pyrantel pamoate is a single-dose (one time) medication and should not be repeated without consulting a doctor, the agency is amending the directions for use in § 357.150(d)(2) by adding the following: "Medication should only be taken one time as a single dose; do not repeat treatment unless directed by a doctor," and "If any symptoms of pinworms are still present after treatment, consult a doctor."

3. Several comments argued that pyrantel pamoate is not safe for OTC use because of the side effects sometimes associated with use of the drug. The comments further contended that the lay person cannot differentiate between the side effects that might occur with use of the drug and potentially serious pathologic conditions. One comment stated that pyrantel pamoate-related increases in serum glutamic-oxaloacetic transaminase (SGOT) occurred in 0 to 4 percent of individuals who took the drug and included three references purporting to show that the incidence of side effects after taking pyrantel pamoate varied from 0 to 20 percent, depending on geographic area and observer (Refs. 1,2, and 3). The comment also included a report alleging that pyrantel pamoate was responsible for causing two deaths in Egypt (Ref. 4).

The agency has reviewed the references included by the comment and other available data and believes that they do not support the contention that the drug pyrantel pamoate is unsafe for OTC use because of the side effects which might occur with use of the drug. In fact, the references (Refs. 1, 2, and 3) suggest the pyrantel pamoate is a safe and effective single-dose anthelmintic with a low incidence of side effects. Additionally, the agency notes that when side effects do occur (i.e., abdominal cramps, nausea, vomiting, or diarrhea, and, less frequently, headaches and dizziness) they are mild and transient. Therefore, the agency believes the concern over side effects can be adequately handled through the OTC drug labeling. The agency is expanding the monograph warnings to include the side effects most frequently mentioned in the references, as follows: "Abdominal cramps, nausea, vomiting, diarrhea, headache, or dizziness sometimes occur after taking this drug. If any of these conditions persist, consult a doctor." The agency recognizes that the lay person cannot differentiate between side effects that might occur with the use of pyrantel pamoate, or any other OTC drug, and serious pathologic conditions. However, in view of the fact that pyrantel pamoate is a single-dose medication, the agency believes it is sufficient for the labeling of the product to advise consumers to consult a doctor if side effects persist or become bothersome.

Although no significant changes in or impairment to hepatic function attributable to the use of pyrantel pamoate have been reported, the agency proposed in the tentative final monograph (47 FR 37064) to include a warning against the use of pyrantel pamoate in patients with preexisting liver disease because minor transient elevations of SGOT have occurred, as the comment pointed out, in a small percentage of patients. The agency reaffirms that decision by including the warning in this final rule.

The agency notes that the Panel was aware of, reviewed, and evaluated the information available to it regarding the incident in Egypt (Refs. 5 and 6) and concluded that the deaths were not due to pyrantel pamoate (45 FR 59546). The agency concurs with the Panel's findings that pyrantel pamoate can be generally recognized as safe for OTC use as an anthelmintic.

*References*

(1) Gilles, H. M., "Diseases of the Alimentary System—Treatment of Intestinal Worms," *British Medical Journal*, 2:1314–1315, 1977.

(2) Piekarski, G., "Die Askariasis (Spulwurmbefall)," *Deutsche Medizinische Wochenschrift*, 105:1406–1408, 1980.

(3) Stahel E., "Therapie der Darmparasitosen," *Deutsche Medizinische Wochenschrift*, 102:133–135, 1977.

(4) Comment No. C00003, Docket No. 79N–0378, Dockets Management Branch.

(5) OTC volume 170160, Docket No. 79N–0378, Dockets Management Branch.

(6) OTC volume 170162, Docket No. 79N–0378, Dockets Management Branch.

4. One comment objected to the OTC availability of pyrantel pamoate because its safety has not been demonstrated for use by pregnant women.

The agency recognizes that there are no data demonstrating that pyrantel pamoate is safe for use by pregnant women. Conversely, as stated in the tentative final monograph (47 FR 37064), there are no data available demonstrating that pyrantel pamoate is unsafe for use by pregnant women. The directions for use for treating pinworms state that when one individual in a

household has pinworms, the entire household should be treated unless otherwise advised. In the case of a pregnant woman, the agency believes that the decision to use an anthelmintic drug product would best be made through consultation with a doctor and, therefore, has included the following warning in the proposed liver disease warning: "If you are pregnant or have liver disease, do not take this product unless directed by a doctor."

5. Two comments stated that determination of the required dose of pyrantel pamoate based on the weight of the patient could be confusing to the lay person.

Because the agency shares the concern expressed by the comments, it concluded in the tentative final monograph that the dosage information for pyrantel pamoate must be provided to consumers with directions that are easily understood (47 FR 37064). The agency provided a dosage schedule and proposed that the label should state the quantity of drug (liquid measurement or the number of dosage units) to be taken for varying body weights. The dosage chart is further clarified in this final monograph to include weight ranges.

6. One comment stated that none of the Panel members was knowledgeable in the field of medical parasitology and that expertise in this field was essential to the development of the Panel's report on OTC anthelmintic drug products.

Although the Miscellaneous Internal Drug Products Panel did not include a medical parasitologist, experts in the fields of parasitology and pediatrics appeared before the Panel to express their views and present data for the Panel's consideration. Additionally, data submitted to the Panel were reviewed by three pediatricians knowledgeable in the diagnosis and treatment of pinworms (Ref. 1). Thus the Panel was not denied expertise in these areas in developing its report.

The agency points out that data on which the Panel based its conclusions, including published and unpublished references, are available to interested persons through the Dockets Management Branch (address above).

*Reference*

(1) Summary Minutes of the OTC Panel on Miscellaneous Internal Drug Products, Ninth Meeting, March 7–8, 1976, Docket No. 79N–0378, Dockets Management Branch.

7. The directions for use for pyrantel pamoate in proposed § 357.150(d)(2) stated that when one individual in a household has pinworms, the entire household should be treated. To avoid a contradiction between this statement and the warnings which advise persons who are pregnant or have liver disease not to take the drug unless directed by a doctor, the agency has revised the directions statement to read as follows: "When one individual in a household has pinworms, the entire household should be treated unless otherwise advised. See Warnings."

## II. The Agency's Final Conclusions on OTC Anthelmintic Drug Products

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC anthelmintic drug products are generally recognized as safe and effective and not misbranded. Specifically, the agency has determined that the only monograph ingredient is pyrantel pamoate. All other ingredients, including gentian violet and piperazine citrate, are considered nonmonograph ingredients. Hexylresorcinol, which was not submitted for review by the Panel or the agency, but which has been the subject of a recommended warning in § 369.20, is also a nonmonograph ingredient. Any drug product marketed for use as an OTC anthelmintic that is not in conformance with the monograph (21 CFR Part 357, Subpart B) will be considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) and may not be marketed for this use unless it is the subject of an approved new drug application. Accordingly, the agency is removing from § 369.20 the entry "GENTIAN VIOLET (METHYLROSANILINE) TABLETS" and its caution statement; and the entry "HEXYLRESORCINOL ANTHELMINTICS" and its warning statement.

In the Federal Register of April 22, 1985 (50 FR 15810), the agency proposed to change its "exclusivity" policy for the labeling of OTC drug products that has existed during the course of the OTC drug review. Under that policy, the agency had maintained that the terms used in an OTC drug product's labeling were limited to those terms included in a final OTC drug monograph.

In the Federal Register of May 1, 1986 (51 FR 16258), the agency published a final rule changing the exclusivity policy and establishing three alternatives for stating the indications for use in OTC drug labeling. Under the final rule, the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All required OTC drug labeling other than indications for use (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under an OTC drug monograph. The final rule in this document is subject to the final rule revising the exclusivity policy.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (47 FR 37065). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final rule for OTC anthelmintic drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Public Law 96–354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC anthelmintic drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

## Paperwork Reduction Act of 1980

In accordance with the Paperwork Reduction Act of 1980 (44 U.S.C. Chapter 35), the collection of information requirement in § 357.152 in this regulation will be submitted for approval to the Office of Management

and Budget (OMB). This requirement will not be effective until FDA obtains OMB approval. FDA will publish a notice concerning OMB approval of this requirement in the Federal Register prior to February 2, 1987. Any comments on this provision should be submitted to the Office of Information and Regulatory Affairs, Office of Management and Budget, Rm. 3002, New Executive Office Building, Washington, DC 20503, Attn: Desk Officer for FDA.

## List of Subjects

*21 CFR Part 357*

OTC drugs, Anthelmintic drug products, Cholecystokinetic drug products.

*21 CFR Part 369*

Labeling, OTC drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

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

1. In Part 357 by adding new Subpart B to read as follows:

### Subpart B—Anthelmintic Drug Products

Sec.



Authority: 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); 5 U.S.C. 553; 21 CFR 5.11.

### 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 condition in this subpart and each general condition established in § 330.1.

(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 Definition.

As used in this subpart:

*Anthelmintic.* An agent that is destructive to worms.

#### § 357.110 Anthelmintic active ingredient.

The active ingredient of the product is pyrantel pamoate when used within the dosage limits established in § 357.150(d)(1).

#### § 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 a "pinworm treatment."

(b) *Indication.* The labeling of the product states, under the heading "Indication," the following: "For the treatment of pinworms." Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed above, may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

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

(1) "Abdominal cramps, nausea, vomiting, diarrhea, headache, or dizziness sometimes occur after taking this drug. If any of these conditions persist consult a doctor."

(2) "If you are pregnant or have liver disease, do not take this product unless directed by a doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) Adults and children 2 years to under 12 years of age: oral dosage is a single dose of 5 milligrams of pyrantel base per pound, or 11 milligrams per kilogram, of body weight not to exceed 1 gram. Dosing information should be converted to easily understood directions for the consumer using the following dosage schedule:

| Weight | Dosage (taken as a single dose) [1] |
|---|---|
| Less than 25 pounds or under 2 years old. | Do not use unless directed by a doctor. |
| 25 to 37 pounds | 125 milligrams. |
| 38 to 62 pounds | 250 milligrams. |
| 63 to 87 pounds | 375 milligrams. |
| 88 to 112 pounds | 500 milligrams. |
| 113 to 137 pounds | 625 milligrams. |
| 138 to 162 pounds | 750 milligrams. |
| 163 to 187 pounds | 875 milligrams. |
| 188 pounds and over | 1,000 milligrams. |

[1] Depending on the product, the label should state the quantity of drug as a liquid measurement (e.g., teaspoonsful) or as the number of dosage units (e.g., tablets) to be taken for the varying body weights. (If appropriate, it is recommended that a measuring cup graduated by body weight and/or liquid measurement be provided with the product.) Manufacturers should present this information as appropriate for their product and may vary the format of this chart as necessary.

(2) "Read package insert carefully before taking this medication. Take only according to directions and do not exceed the recommended dosage unless directed by a doctor. Medication should only be taken on time as a single dose; do not repeat treatment unless directed by a doctor. When one individual in a household has pinworms, the entire household should be treated unless otherwise advised. See Warnings. If any worms other than pinworms are present before or after treatment, consult a doctor. If any symptoms or pinworms are still present after treatment, consult a doctor."

(3) "This product can be taken any time of day, with or without meals. It may be taken alone or with milk or fruit juice. Use of a laxative is not necessary prior to, during, or after medication."

(e) *Optional wording.* The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

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

The labeling of the product contains a consumer package insert which includes the following information:

(a) A discussion of the symptoms suggestive of pinworm infestation, including a statement that pinworms must be visually identified before taking this medication.

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

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

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

(e) The appropriate labeling information contained in § 357.150

#### § 357.180 Professional labeling.

The labeling provided to health professionals (but not to the general public) may contain an additional indication: "For the treatment of common roundworm infestation."

## PART 396—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

2. The authority citation for 21 CFR Part 369 is revised to read as follows:

Authority: Secs. 502, 503, 506, 507, 701, 52 Stat. 1050–1052 as amended, 55 Stat. 851, 59 Stat. 463 as amended, 52 Stat. 1055–1056 as amended (21 U.S.C. 352, 353, 356, 357, 371); 21 CFR 5.11.

**§ 369.20 [Amended]**

3. In § 369.20 *Drugs; recommended warnings and caution statements* by removing the entry "GENTIAN VIOLET (METHYLROSANILINE CHLORIDE) TABLETS" and its caution statement and by removing the entry "HEXYLRESORCINOL ANTHELMINTICS" and its warnings statement.

Dated: May 3, 1986.

**Frank E. Young,**

*Commissioner of Food and Drugs.*

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