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; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish 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 notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and the advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATE: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by October 25, 1982. Written comments on the agency's economic impact determination by December 22, 1982

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

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, National Center for Drugs and Biologics (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In 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 intital 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 (address above), after deletion of a small amount of trade secret information.

The advance notice of proposed rulemaking, which was published in the Federal Register on September 9, 1980 (45 FR 59540), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) the FDA states for the first time its position on the establishment of a monograph for OTC anthelmintic drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC anthelmintic drug products.

No comments were received in response to the advance notice of proposed rulemaking. This proposal to establish Part 357 (21 CFR Part 357) constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC anthelmintic drug products, as modified on the basis of the agency's independent evaluation of the Panel's report. (This tentative final monograph constitutes Subpart B of Part 357. Subpart A is reserved for publication at a later date.) Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above).

FDA published in the Federal Register of September 29, 1981 (46 FR 47730) a final rule revising 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 review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations 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 (46 FR 47738).

Although it was not required to do so under *Cutler*, FDA will no longer use 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). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The revised regulations provide in § 330.10(a)(7)(ii) for the Commissioner to publish a separate tentative final order containing a statement of those active ingredients reviewed and proposed to be excluded from the monograph on the basis of the Commissioner's determination that they would result in a drug product not being generally recognized as safe and effective or would result in misbranding, and for which no substantive comments in opposition to the Panel report or new data and information were received by the FDA pursuant to § 330.10(a)(6)(iv). In the case of anthelmintic drug products, the only active ingredient which the Panel excluded from the monograph (as Category II) is piperazine citrate. In the preamble to the Panel's report, the agency stated that, because it considered the potential risks from the use of gentian violet (which the Panel had placed in Category I) to outweigh its benefits, it intended to classify this ingredient in Category II in the tentative final monograph. The agency explained in detail the reasons it intended to classify gentian violet in Category II and confirms this classification later in this document. Because no comments were received in response to the Panel's report and the recommended classification of these ingredients as not being generally recognized as safe and effective, the regulations authorize the Commissioner to issue a separate tentative final order for these ingredients.

The revised regulations also provide in § 330.10(a)(7)(iii) for a 12-month period to submit data and information to support a condition excluded from the monograph in the tentative final order. Other than gentian violet and piperazine citrate, as described above, the only ingredient remaining to be considered is pyrantel pamoate, which has been included in the monograph. Thus, the agency concludes that there is no need for a 12-month period following publication of this tentative final monograph for the submission of new

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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" (45 FR 59546). The Panel, while noting this effect, did not address the issue of including a warning against the use of pyrantel pamoate in patients with preexisting liver disease. The agency has required a precautionary statement in the current prescription labeling for pyrantel pamoate as follows: "Minor transient elevations of SGOT have occurred in a small percentage of patients. Therefore, this drug should be used with caution in patients with pre-existing liver dysfunction" (Ref. 1).

The agency feels that it is in the best interest of consumers to include a similar warning in the OTC labeling for pyrantel pamoate. Therefore, in this tentative final monograph the agency is proposing the following warning as § 357.150(c)(2):

"If you have liver disease, do not take this product unless directed by a doctor."

Reference

(1) FDA-approved labeling from NDA 16-883, included in OTC Volume 16BTFM, Docket No. 79N-0378, Dockets Management Branch.

3. The Panel recommended the inclusion of a pregnancy warning as part of the general labeling for all OTC anthelmintic drug products in § 357.150(c)(1)(ii). In the preamble to the Panel's report (45 FR 59541), the agency advised that the Panel's recommendations for a pregnancy warning was inconsistent with the required labeling for pyrantel pamoate which previously had been available only by prescription. The agency stated that the data were insufficient at that time to require a pregnancy warning. However, because the directions for use state that "when one individual in a household has pinworms, the entire household should be treated," the agency believes the label should articulate the circumstances under which a pregnant woman should take the drug. Although there are no new data available demonstrating that pyrantel pamoate is unsafe for use by pregnant women, the agency does not believe the drug should be taken by pregnant women unless they themselves have pinworms and a doctor has directed them to do so. If a pregnant woman does not have pinworms, then a risk from the drug, however slight, is not justified. Consulting a physician would enable the physician to determine whether the woman had pinworms or whether the liklihood of her having pinworms was sufficiently great to justify the use of the drug. Thus, the agency is proposing the following warning in § 357.150)c)(3): "If you are pregnant, do not take this product unless you have pinworms yourself and are directed to take it by your doctor."

4. In its recommended labeling for OTC anthelmintic drug products, the Panel included several similar statements in both the *"Warnings,"* § 357.150(c), and *"Directions,"* § 357.150(d).

The agency can find no reason to include these statements under both headings, and proposes, therefore, to delete from the *"Warnings"* in § 357.150(c)(1) (ii) and (iii) those statements that also appear in the *"Directions"* in § 357.150(d)(1). The agency proposes to delete the words "discontinue using it" from the warning statement in § 357.150(c)(1)(i) because the directions for use for pyrantel pamoate provide for a single (one-time) dose of medication. The agency proposes also revising this warning slightly for clarity. The agency has deleted the "age" definition from § 357.103(a) of the Panel's recommended monograph because these age limits are adequately defined in the directions for use.

5. In several of its warnings, the Panel recommeded use of the phrase "consult a physician." This phrase has often been used in OTC labeling as advice to the consumer in case of symptoms that indicate a condition that cannot be self-treated. Believing that the word "doctor" is more commonly used and better understood by consumers, the agency proposes to substitute "doctor" for "physician" in the warnings appearing in the tentative final monograph. The Panel also used the phrases "* * * without first consulting a physician" and "* * * except under the advice and supervision of a physician." The agency proposes to change these phrases to read "* * * consult a doctor" or "* * * except under the supervision of a doctor." These changes are part of a continuing effort to achieve OTC labeling language that is simple, clear, and accurate, in keeping with § 330.10(a)(4)(v) (21 CFR § 330.10(a)(4)(v)), which states in part, "Labeling * * * shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use." If the word "doctor" and the shortened phrases described above are adopted in the final monograph, the agency will use this language in other final monographs and other applicable OTC drug regulations and will propose amendments to those regulations accordingly. Public comment on these proposed changes in labeling language is invited.

6. In § 357.150(a) of its recommended monograph, the Panel suggested a statement of identity that describes the product as an "anthelmintic." The Panel defined an anthelmintic in § 357.130(b) as "an agent that is destructive to pinworms." An anthelmintic is defined in "Dorland's Medical Dictionary" (Ref. 1) as "an agent that is destructive to worms" and could, therefore, be used for treatment of worms other than pinworms. The agency concludes that the word "anthelmintic" is not specific to pinworms and is not well understood by consumers. Use of the words "pinworm treatment" in the statement of identity should result in a better understanding by consumers of the nature of the product. The agency is revising the statement of identity in § 357.150(a) accordingly. In addition, with the inclusion of a professional labeling claim for the treatment of common roundworm infection in the tentative final monograph (see paragraph 8 below), the agency has changed the Panel's recommended definition of anthelmintic in § 357.103 to "an agent that is destructive to worms."

Reference

(1) "Dorland's Illustrated Medical Dictionary," W. B. Saunders Co., Philadelphia, 1974, s.v. "anthelmintic."

7. The Panel recommended a pyrantel pamoate dosage in § 357.150(d)(3) of 11 milligrams per kilogram of body weight. Believing that consumers are more familiar with weight measurements in pounds, the agency proposes to convert this dosage to its equivalend dosage of 5 mg/lb, clarify that this dosage relates to the pyrantel base, and include this information in § 357.150(d)(1) of this tentative final monograph. The agency concludes that this dosage information must be provided to consumers with directions that are easily understood. Therefore, the agency also proposes to include a requirement in § 357.150(d)(1) of this tentative final monograph 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 agency has provided a dosage schedule in § 357.150(d)(1).

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Where appropriate, it is recommended that a graduated measuring cup be provided with the product. The agency believes that certain information on how to take the drug, which appears in the labeling of a currently approved prescription product containing pyrantel pamoate (Ref. 1), would be useful to consumers in self-medicating with this drug. Accordingly, the following statement has been added to the tentative final monograph in § 357.150(d)(3) to read as follows: "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."

Reference

(1) FDA-approved labeling from NDA 16–883, included in OTC Volume 16BTFM, Docket No. 79N–0378, Dockets Management Branch.

8. A number of investigators have reported the effectiveness of pyrantel pamoate in the treatment of common roundworm infection, ascariasis (Refs. 1 through 6), and the agency has approved pyrantel pamoate as a prescription drug for the treatment of both pinworm and common roundworm infection. Under the general discussion in its report, the Panel stated that the diagnosis and treatment of common roundworm should be under the supervision of a physician and placed such a claim in Category II for OTC use (45 FR 59543). The agency agrees with the Panel, but believes that this information on the use of pyrantel pamoate should be provided to health professionals. Therefore, the agency has expanded the tentative final monograph to include professional labeling as proposed new § 357.180 which includes the following indication: "For the treatment of common roundworm infection."

References

(1) Desowitz, R. S., et al., "Anthelmintic Activity of Pyrantel Pamoate," *The American Journal of Tropical Medicine and Hygiene*, 19:775–778, 1970.

(2) Bell, W. J., and S. Nassif, "Comparison of Pyrantel Pamoate and Piperazine Phosphate in the Treatment of Ascariasis," *The American Journal of Tropical Medicine and Hygiene*, 20:584–588, 1971.

(3) Cervoni, W. A., and J. Oliver-Gonzales, "Clinical Evaluation of Pyrantel Pamoate in Helminthiasis," *The American Journal of Tropical Medicine and Hygiene*, 20:589–591, 1971.

(4) Villarejos, V. M., et al., "Experience with the Anthelmintic Pyrantel Pamoate," *The American Journal of Tropical Medicine and Hygiene*, 20:842–845, 1971.

(5) Rim, H. J., and J. K. Lim, "Treatment of Enterobiasis and Ascariasis with Combantrin (Pyrantel Pamoate)," *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 66:170–175, 1972.

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

9. The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other available data and information, and has changed the categorization of one ingredient. For the convenience of the reader, the following table is included as a summary of the categorization of anthelmintic active ingredients:

Ingredient	Panel categorization	Agency categorization
Gentian violet	I	II.
Piperazine citrate	II	II.
Pyrantel pamoate	I	I.

10. The agency points out that the Panel did not place any ingredients or claims for the teatment of pinworm infection in Category III, and the agency has added none.

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a Regulatory Impact Analysis, as specified in Executive Order 12291, or a Regulatory Flexibility Analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96–354). Specifically, the proposal allows the drug pyrantel pamoate to switch from prescription to OTC status. Under the OTC drug review procedures, manufacturers have been allowed to market this ingredient OTC since the advance notice of proposed rulemaking was published in the Federal Register of September 9, 1980 (45 FR 59540). The agency has made some minor revisions in the Panel's recommended labeling. Therefore, some relabeling will be necessary. Manufacturers will have up to 6 months to revise their product labeling. In most cases, this will be done at the next printing so that minimal costs should be incurred. Issuance of the final monograph as proposed will result in the removal of anthelmintic products containing gentian violet from the OTC market. Some products containing this ingredient have already been voluntarily removed from the market. Thus, the impact of the final regulation appears to be minimal. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities, as defined in the Regulatory Flexibility Act.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC anthelmintic drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC anthelmintic drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on anthelmintic drug products, a period of 120 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has 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 impact 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 Dockets Management Branch, Food and Drug Administration.

List of Subjects in 21 CFR Part 357

OTC drugs: Anthelmintics, Cholecystokinetics.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 357, to read as follows:

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

Subpart A [Reserved]

Subpart B—Anthelmintic Drug Products

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); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (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.

(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 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) *Indications.* The labeling of the product contains a statement of the indication under the heading "Indication" 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) "If upset stomach, diarrhea, nausea, or vomiting occurs with use of this product, consult a doctor."

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

(3) "If you are pregnant, do not take this product unless you have pinworms yourself and are directed to take it by your 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, or 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 pounds	125 milligrams.
50 pounds	250 milligrams.
75 pounds	375 milligrams.
100 pounds	500 milligrams.
125 pounds	625 milligrams.
150 pounds	750 milligrams.
175 pounds	875 milligrams.
200 pounds	1,000 milligrams.
More than 200 pounds	1,000 milligrams.
For in-between weights, use closest weight on chart.	

[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) "Take only according to directions and do not exceed the recommended dosage unless directed by a doctor. When one individual in a household has pinworms, the entire household should be treated. If any worms other than pinworms are present before or 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."

§ 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 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 hygienic procedures to follow to avoid such spreading.

(d) 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 infection."

Interested persons may, on or before October 25, 1982 submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before December 22, 1980. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the Federal Register.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on October 25, 1982. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the Federal Register unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: June 15, 1982.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: July 21, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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