Subpart E—Drug Products for the Treatment and/or Prevention of Nocturnal Leg Muscle Cramps

§ 343.100 Scope.

(a) An over-the-counter drug product for the treatment and/or prevention of nocturnal leg muscle cramps 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.

§ 343.103 Definitions.

As used in this part:

Nocturnal leg muscle cramps. A condition of localized pain in the lower extremeties occurring in middle life and beyond with no regular pattern concerning time or severity and variously attributed to:

(1) Arterial insufficiency with resulting anoxic muscle spasm;

(2) Excessive venous dilation secondary to sudden emptying of small venules into larger vessels during recumbency; and

(3) Accumulation of products of muscle metabolism with local pH changes due to lactic acid accumulation.

§ 343.110 Active ingredients for the treatment and/or prevention of nocturnal leg muscle cramps. [Reserved]

§ 343.150 Labeling of products for the treatment and/or prevention of nocturnal leg muscle cramps.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "nocturnal leg muscle cramps treatment," or "nocturnal leg muscle cramps treatment and prevention."

(b) *Indications.* The labeling of the product states, under the heading "Indications", the following: "For the treatment and/or prevention of nocturnal leg muscle cramps." 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) of this chapter, subject to the prohibitions in section 502(a) of the act against misbranding by the use of false or misleading labeling and the prohibition in section 301(d) of the act against the introduction into interstate commerce of unapproved new drugs.

(c) *Warnings.* For products containing quinine: "Discontinue use if ringing in the ears, deafness, skin rash, or visual disturbances occur. Do not take if pregnant, sensitive to quinine, or under 12 years of age."

(d) *Directions.* [Reserved]

Frank E. Young,

Commissioner of Food and Drugs.

Dated: September 10, 1985.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 85-24747 Filed 11-7-85; 8:45 am]

BILLING CODE 4160-01-M

21 CFR Part 357

[Docket No. 79N-0379]

Exocrine Pancreatic Insufficiency 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) exocrine pancreatic insufficiency drug products (drug products used to treat pancreatic enzyme deficiency) 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 public comments on an 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.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by January 7, 1986. New data by November 10, 1986. Comments on the new data by January 8, 1987. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination March 10, 1986.

ADDRESS: Written comments, objections, new data, 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, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 21, 1979 (44 FR 75666) 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 exocrine pancreatic insufficiency 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 April 21, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by May 21, 1980.

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.

In response to the advance notice of proposed rulemaking, two manufacturers, one foundation, and two physicians submitted comments. Copies of the comments received are also on public display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on December 21, 1979 (44 FR 75666), 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) to establish Subpart E of Part 357, FDA states for the first time its position on the establishment of a monograph for OTC exocrine pancreatic insufficiency 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 exocrine pancreatic insufficiency drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC exocrine pancreatic insufficiency drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. 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). These modifications are reflected in the following summary of the comments and FDA's responses to them.

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 will no longer use 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 will use instead 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 agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register.** On or after that date, 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 the advance notice of proposed rulemaking for OTC exocrine pancreatic insufficiency drug products (published in the **Federal Register** of December 21, 1979; 44 FR 75666), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products may have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register.** The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

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

I. The Agency's Tentative Conclusions on the Comments

All comments objected for varying reasons to the Panel's recommendation that pancreatic extracts (pancreatin and pancrelipase) for treating exocrine pancreatic insufficiency be available OTC.

1. Several comments stated that pancreatic extracts should not be available OTC because the disease states that lead to exocrine pancreatic insufficiency, e.g., cystic fibrosis, chronic pancreatitis, post-pancreatectomy, and pancreatic ductal obstruction, require physician diagnosis and treatment. The comments argued that, generally, OTC drug products should be used to treat self-diagnosable conditions and that the public should be able to determine the safe and effective dosage levels from the labeling. The comments contended that none of these criteria are satisfied with respect to pancreatic extracts.

The agency agrees that, in general, the criteria stated by the comments are important in deciding whether a drug should be prescription or OTC. However, these criteria are not the sole determining factors. Section 503(b)(1)(B) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 353(b)(1)(B)) sets out the principal statutory requirements with respect to the marketing status of a drug. Specifically, it states that a drug shall be dispensed only upon prescription when "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, [it] is not safe for use except under the supervision of a practitioner licensed by law to administer such drug." In the case of pancreatic extracts, the agency does not believe the statutory requirements for prescription restriction are met.

Although the condition of exocrine pancreatic insufficiency requires diagnosis by a physician and the disease states that give rise to exocrine pancreatic insufficiency require close monitoring by a physician, the agency believes that once the insufficiency is diagnosed, a consumer can safely and effectively self-treat the condition with pancreatic extracts.

The recommended OTC dose of pancreatic extracts is virtually free of toxicity. Although doses in considerable excess of the recommended dose have been associated with hyperuricosuria (increased amounts of uric acid in the urine) and hyperuricemia (increased amounts of uric acid in the blood), these problems have not been observed at the recommended OTC dose nor have the increased levels of uric acid been associated with any clinical manifestations. (See comment 2 below.) Also, as discussed in comments 2, 3, and 4 below, other adverse effects that have been associated with these products may be adequately handled through labeling. The agency does not believe that these effects are significant enough to warrant restricting the pancreatic extracts to prescription status.

The agency recognizes that the dose of pancreatic extracts is highly individualized, but believes that the patient is able to self-monitor the presenting symptom (stools with a high fat content) and make any necessary adjustments within the OTC recommended dose. For example, if a person snacks between meals, additional doses of the pancreatic extracts may need to be taken to keep the fatty stools under control. However, the need to adjust dosage is dependent on the amount and content of the diet and will vary from individual to individual. Even if the pancreatic extracts were limited to prescription status, the patient would need to make these same adjustments.

Because the condition of exocrine pancreatic insufficiency can be self-monitored and because pancreatic extracts are not toxic at the recommended OTC dose, the agency sees no need to restrict these drugs to prescription status.

The agency is also aware that a number of pancreatic extract products have been available OTC for many years, whereas others have been available only on prescription. The agency is unaware of any safety problems associated with those products which have been available OTC. There is no reason for perpetuating the dual marketing of these products. Therefore, the agency is proposing that pancreatin and pancrelipase, at the dosages recommended by the Panel, be available OTC.

2. Two comments objected to the OTC availability of pancreatic extracts because hyperuricosuria and hyperuricemia have been associated with their use. The comments supplied several references to support their position (Refs. 1, 2, and 3). One comment also noted that the use of pancreatic extracts may results in obstipation (intractable constipation) or intestinal obstruction (Refs. 4, 5, and 6).

The maximum daily dose recommended by the Panel for pancreatin was 42 grams (g) and 3.5 g for pancrelipase. In each of the references cited by the comments, hyperuricosuria or hyperuricemia was reported to result from daily doses of pancreatic extracts in considerable excess of those recommended by the Panel. However, even when hyperuricosuria or hyperuricemia occurred, the increased uric acid levels are not associated with any clinical manifestations. The agency is unaware of any reports of hyperuricosuria or hyperuricemia when pancreatic extracts are given within the dosage range recommended by the Panel. Likewise, obstipation and intestinal obstruction have been associated with excessive doses of pancreatic extracts, but have not been reported at the recommended OTC dose.

The agency believes that the symptoms of exocrine pancreatic insufficiency can be controlled in most patients within the dosage limits recommended by the Panel. Although recognizing that some patients may require medication in excess of the labeled dose, the agency does not believe the dose should be exceeded without a doctor's knowledge. For this reason, the agency is proposing a warning (§ 357.450(c)(2)) in this tentative final monograph to state clearly that the dose should not be exceeded unless directed by a doctor.

The agency does not believe that the concerns regarding hyperuricosuria, hyperuricemia, obstipation, or intestinal obstruction from the use of pancreatic extracts warrant restricting these drugs to prescription status.

References

(1) Stapleton, F.B., et al., "Hyperuricosuria Due to High-Dose Pancreatic Extract Therapy in Cystic Fibrosis," *New England Journal of Medicine*, 295:246–248, 1976.

(2) Nousia-Arvanitakis, S., et al., "Therapeutic Approach to Pancreatic Extract-Induced Hyperuricosuria in Cystic Fibrosis," *Journal of Pediatrics*, 90:302–305, 1977.

(3) Davidson, G. P., et al., "Iatrogenic Hyperuricemia in Children with Cystic Fibrosis," *Journal of Pediatrics*, 93:976–978, 1978.

(4) Wood, R. E., T. F. Boat, and C. F. Doershuk, "State of the Art—Cystic Fibrosis," *American Review of Respiratory Diseases*, 113:833–875, 1976.

(5) Letter from C. Denning, St. Vincent's Hospital to R. Vodra, Cystic Fibrosis Foundation, included in Comment No. C00005, Docket No. 79N–0379, Dockets Management Branch.

(6) Letter from H. Shwachman, The Children's Hospital Medical Center to R. J. Beall, Cystic Fibrosis Foundation, included in Comment No. C00005, Docket No. 79N–0379, Dockets Management Branch.

3. One commenter, citing personal experiences in treating patients with pancreatic extracts, reported that serious ulcerations of the mouth, lips, and tongue can occur from chewing tablets of pancreatic extracts. The commenter pointed out that this problem is of particular concern in cystic fibrosis patients because the ulceration provides an ideal portal of entry for the pathogenic bacteria constantly harbored by these patients. The commenter questioned whether pancreatic extracts should be available OTC in light of these adverse effects.

The agency is aware that if the pancreatic extracts are retained in the mouth, the enzymes will begin to digest the mucous membranes and cause ulcerations. However, the agency believes that the labeling of these products can adequately guard against this problem by including the following warning: "Swallow quickly to lessen potential for mouth irritation." In addition, the agency is proposing that tablet dosage forms contain the warning "Do not chew."

4. One comment cited reports of hypersensitivity reactions, including life-threatening asthmatic attacks (anaphylaxis), occurring in parents who administer powdered dosage forms of pancreatic extracts to children (Refs. 1, 2, and 3). The comment stated that these adverse reactions should be considered in deciding whether these drugs are safe for OTC use.

The agency is aware of a number of case reports in the literature of allergic reactions occurring after repeated inhalation of pancreatic extract powder in persons administering the drug (Refs. 3 through 11). The incidence of these reactions is estimated to be between 5 to 11 percent of the population exposed to pancreatic extracts (Ref. 3). For the most part, the reactions are limited to rhinitis, conjunctivitis, and mild asthma symptoms. Although more severe reactions have been reported, they do not appear to be widespread, and restricting the drugs to prescription status would not have prevented them from occurring. However, the agency believes the problems could be minimized by including a warning on these products advising persons not to inhale the powder and is proposing the following warning for pancreatic extracts marketed as powders: "Avoid inhalation of powder. Sensitive individuals may experience allergic

reactions." Also, because parents often open the capsule dosage form and sprinkle the contents on their child's food, the following warning is proposed for capsule dosage forms: "If capsules are opened, avoid inhalation of powder. Sensitive individuals may experience allergic reactions."

References

(1) Letter from C. Denning, St. Vincent's Hospital to R. Vodra, Cystic Fibrosis Foundation, included in Comment No. C00005, Docket No. 79N-0379, Dockets Management Branch.

(2) Letter from H. Shwachman, The Children's Hospital Medical Center to R. J. Beall, Cystic Fibrosis Foundation, included in Comment No. C00005, Docket No. 79N-0379, Dockets Management Branch.

(3) Ganier, M., and P. Lieberman, "IgE Mediated Hypersensitivity to Pancreatic Extract (PE) In Parents of Cystic Fibrosis (CF) Children," *Clinical Allergy*, 9:125-132, 1979.

(4) Nakamura, S., "On Occupational Allergic Asthma of Different Kinds Newly Found in Our Allergy Clinic," *Journal of Asthma Research*, 10:37-47, 1972.

(5) Dolan, T. F., and A. Meyers, "Bronchial Asthma and Allergic Rhinitis Associated With Inhalation of Pancreatic Extracts," *American Review of Respiratory Disease*, 110:812-813, 1974.

(6) Hill, D., "Pancreatic Extract Lung Sensitivity," *Medical Journal of Australia*, 2:553, 1975.

(7) Sakula, A., "Bronchial Asthma Due to Allergy to Pancreatic Extract: A Hazard in the Treatment of Cystic Fibrosis," *British Journal of Diseases of the Chest*, 71:295-299, 1977.

(8) Chignell, R., "External Influences On Nose and Throat," *Proceedings of the Royal Society of Medicine*, 65:679-661, 1972.

(9) Abernathy, R. S., "Why Wasn't Mother Skin Tested?", *Pediatrics*, 56:141, 1975.

(10) Bergner, A., and R. K. Bergner, "Pulmonary Hypersensitivity Associated With Pancreatin Powder Exposure," *Pediatrics*, 55:814-817, 1975.

(11) Twarog, F. G., "Hypersensitivity to Pancreatic Extract In Parents of Patients With Cystic Fibrosis," *Journal of Allergy and Clinical Immunology*, 59:35, 1977.

5. Several comments stated that it is not feasible or possible to describe, in lay terms, the clinical, dietary, and other considerations necessary for consumers to select pancreatic extracts and to determine the dosage levels and modes of administration of these products. The comment contended that although the Panel recommended maximum daily doses for pancreatin and pancrelipase, these levels may be excessive for some individuals and inadequate for others. In addition, because of the wide variation in enzyme activities among products, and, in some cases, variations in enzyme levels between different forms of the same product, a consumer cannot readily make comparisons between products.

As discussed in comment 1 above, the agency recognizes that the dose of pancreatic extracts is highly individualized, but believes that patients are able to self-monitor their condition and make the necessary dosage adjustments as needed. Also, because these drug products would be used only after a diagnosis of exocrine pancreatic insufficiency has been made by a physician, the physician will have the opportunity to give advice on other clinical and dietary considerations.

The agency recognizes that because of the varying amounts of enzyme activities in pancreatic extract products it is important that the labeling of these products state the level of lipase, amylase, and protease activity per dosage unit. Therefore, the agency is proposing in this tentative final monograph that the enzyme activity levels per dosage unit be stated on the labeling of pancreatic extract products.

6. Several comments objected to the OTC availability of pancreatic extracts because persons not suffering from exocrine pancreatic insufficiency would have unlimited access to these drugs. The comments argued that there is no scientific evidence that people who do not have pancreatic insufficiency would benefit by consuming these drugs. In addition, the comment argued that long-term safety of these drugs in persons without pancreatic insufficiency has not been adequately assessed.

Pancreatic extracts have been available on the OTC market for many years in various digestive aid products. The Advisory Review Panel on OTC Miscellaneous Internal Drug Products also reviewed pancreatin and pancrelipase for the use in digestive aid drug products. In its report published in the **Federal Register** of January 5, 1982 (47 FR 454), the Panel concluded that these drugs are safe, but that additional data are needed to determine their effectiveness for testing symptoms of intestinal distress. The agency's position of the use of pancreatic extracts in digestive aid drug products will be stated in a future issue of the **Federal Register.** In addition, the label of pancreatic extracts intended for use in treating exocrine pancreatic insufficiency will carry a warning telling people not to take the product unless directed by a doctor. Nevertheless, these products should cause no harm in individuals who do not have exocrine pancreatic insufficiency if taken according to the labeled directions and other warnings.

7. Several comments contended that if pancreatic extract preparations were available OTC, cystic fibrosis patients would avoid checkups with their physician, thus allowing other complications (e.g., pulmonary infection or deterioration of pulmonary function) to go untreated.

The agency shares the comments' concern, but disagrees that the OTC availability of pancreatic extracts will cause cystic fibrosis patients to avoid checkups with their physician. Exocrine pancreatic insufficiency is only one component of the cystic fibrosis syndrome. Chronic obstructive pulmonary disease occurs in almost all cases of cystic fibrosis and is the major cause of morbidity and mortality in these patients. The pulmonary involvement tends to be progressive and to become severe enough that physician intervention is necessary. The pancreatic extracts have no effect on the progression of the lung involvement. In addition, the agency believes that patients with cystic fibrosis recognize the seriousness of their condition and will make frequent physician visits whether or not the pancreatic extracts are available OTC.

8. Several comments objected to the OTC availability of pancreatic extracts because many third-party reimbursers do not reimburse for OTC medications. The comments argued that making the pancreatic extracts available OTC would impose an insurmountable financial burden on patients who require these drugs.

In comment 1 above, the agency discusses the statutory provisions regarding prescription or OTC status of a drug. Financial considerations are not among the statutory criteria and, therefore, cannot be used in deciding whether pancreatic extracts should be available OTC. FDA is aware of variability in third-party reimbursements for OTC drugs. Because pancreatic extracts, for the most part, are also maintenance drugs, third-party reimbursers might wish to consider the need for any changes in current reimbursement policies for these drugs.

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. Summary of Ingredient Categories

The agency has reviewed the claimed active ingredients submitted to the Panel as well as other data and information available at this time and concurs with the Panel's categorization of pancreatin and pancrelipase in Category I and hemicellulase in Category II for use in exocrine pancreatic insufficiency.

2. Testing of Category II and Category III Conditions

Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any exocrine pancreatic insufficiency ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified in the **Federal Register** of April 1, 1983 (48 FR 14050). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made in the Panel's conclusions and recommendations follows.

1. The Panel did not recomend a specific statement of identity. The agency is proposing "pancreatic enzyme replacement" as the statement of identity for OTC pancreatic extract drug products.

2. The agency is proposing a warning to guard against the potential for mouth irritation. (See comment 3 above.)

3. The agency is proposing a warning advising against inhalation of pancreatic extract powder. (See comment 4 above.)

4. The agency is proposing that the enzyme activity levels per dosage unit be stated on the labeling of pancreatic extract products. (See comment 5 above.)

5. In an effort to further clarify the labeling of pancreatic extract products, the agency is proposing that the indications be limited to the following: "For the treatment of exocrine pancreatic insufficiency." In addition, the following warning is being proposed: "Do not take this product unless directed by a doctor." The agency believes that these two statements will be more meaningful and less confusing to consumers than the indication statement recommended by the Panel in § 357.450(b).

b. Because pancreatin is available from beef or pork (Ref. 1), the agency is proposing in this tentative final monograph that the pork-allergenicity warning recommended by the Panel in § 357.450(c) be included only on the labeling of pork-derived pancreatic extract products. For consistency in style between this and other similar warnings in other OTC drug monographs, the agency is proposing that the warning read as follows: "Do not take this product if you are allergic to pork."

7. Although the Panel recommended that the dose of pancreatic extracts be "as recommended by a physician," the agency does not believe that these directions are adequate for OTC labeling. The Panel did not specify whether the recommended maximum daily dose of pancreatic extracts was for adults or children, but the agency has determined that the dose applies to children as well as to adults. The agency is also aware that there is little difference in effectiveness between giving pancreatic extracts in divided doses with meals or giving them in evenly spaced intervals (1 to 2 hours) throughout the day (Ref. 2). Therefore, the agency is proposing that the labeling indicate that the maxium daily recommended dose of pancreatic extracts be administered to adults or children either in divided doses with meals (with an extra dose taken with food eaten between meals) *or* at 1- to 2-hour intervals throughout the day *or* as directed by a doctor.

8. The agency is aware that the United States Pharmaceopeia (U.S.P.) monographs for pancreatin and pancrelipase specify only the minimum amounts of enzyme activity per milligram (mg) and do not specify any upper limit of enzyme activity (Ref. 1). In addition, marketed products contain varying levels of enzyme activity per mg. The agency believes it would be confusing to specify the maximum daily recommended dose only in terms of a gram amount because there is no standard correlation between that amount and enzyme activity.

Also, it is not clear from the U.S.P. monographs whether the ratios of activity level (2 U.S.P. units lipase:25 U.S.P. units protease:25 U.S.P. units amylase for pancreatin; and 24 U.S.P. units lipase:100 U.S.P. units protease:100 U.S.P. units amylase for pancrelipase) are to be maintained in all products. The U.S.P. is also aware of these problems and presently has a revision committee looking into them (Ref. 3).

For these reasons, the agency is proposing in this tentative final monograph to include the maximum daily recommended enzyme activity levels based on the minimum levels established in the U.S.P. in addition to the gram amounts as follows: For pancreatin the maximum daily recommended dose is 42 g, equivalent to 84,000 U.S.P. units lipase activity, 1,050,000 U.S.P. units protease activity and 1,050,000 U.S.P. units amylase activity. For pancrelipase the maximum daily recommended dose is 3.5 g, equivalent to 84,000 U.S.P. units lipase activity, 350,000 U.S.P. units protease activity, and 350,000 U.S.P. units amylase activity. The agency invites specific comment on these proposed dosage limits.

References

(1) "United States Pharmacopeia XXI—National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 777–781, 1985.

(2) DiMagno, E. P., et al., "Fate of Orally Ingested Enzymes in Pancreatic Insufficiency—Comparison of Two Dosage Schedules," *New England Journal of Medicine*, 296:1318–1322, 1977.

(3) Memorandum of telephone conversation between J. Short, FDA, and E. Theimer, U.S.P., concerning interpretation of the U.S.P. Pancreatin and Pancrelipase monographs, August 22, 1983, copy included in OTC Volume 17BTFM.

9. 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 on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor". This tentative final monograph proposes that option.

The agency has examined the economic consequences of this proposed rulemaking 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 proposed rule for OTC exocrine pancreatic insufficiency 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, Pub. L. 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 exocrine pancreatic insufficiency drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC exocrine pancreatic insufficiency 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 exocrine pancreatic insufficiency 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 exocrine pancreatic insufficiency 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 action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact, and the evidence supporting that finding may be seen in the Dockets Management Branch, Food and Drug Administration (address above) between 9 a.m. and 4 p.m., Monday through Friday. FDA's regulations implementing the National Environmental Policy Act (21 CFR Part 25) have been replaced by a rule published in the **Federal Register** of April 26, 1985 (50 FR 16636). Under the new rule, an action of this type would require an environmental assessment under 21 CFR 25.31a(a).

Sections 357.450(d) (1) and (2) of this proposed rule contain collection of information requirements. As required by section 3504(h) of the Paperwork Reduction Act of 1980, FDA has submitted a copy of this proposed rule to the Office of Management and Budget (OMB) for its review of these collection of information requirements. Other organizations and individuals desiring to submit comments on these collections of information requirements should direct them to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, Rm. 3208, New Executive Office Bldg., Washington, DC 20503, Attn: Bruce Artim.

Exclusivity of Labeling. 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 this policy, the agency has maintained that the terms that may be used in an OTC drug product's labeling are limited to those terms included in a final OTC drug monograph.

The proposed rule would establish three alternatives for stating the indications for use in OTC drug labeling while all other aspects of OTC drug labeling (i.e., statement of identity, warnings, and directions for use) would continue to be subject to the existing exclusivity policy. The proposed rule for OTC exocrine pancreatic insufficiency drug products included in this document incorporates the exclusivity proposal by providing for the use of other truthful or nonmisleading statements in the product's labeling to describe the indications for use. After considering all comments submitted on the proposed revision to the exclusivity rule, the agency will announce its final decision on this matter in a future issue of the **Federal Register.** The final rule for OTC exocrine pancreatic insufficiency drug products will incorporate the final decision on exclusivity of labeling.

Interested persons may, on or before January 7, 1986 submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–64, 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 March 10, 1986. 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 office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before November 10, 1986, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before January 8, 1987. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on January 8, 1987. 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.

List of Subjects in 21 CFR Part 357

OTC drugs; anthelmintic drug products, cholecystokinetic drug products, deodorant drug products for internal use, exocrine pancreatic insufficiency drug products, orally administered drug products for fever blisters, poison treatment drug products, and smoking deterrent drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 357 by adding new Subpart E as follows:

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

Subpart E—Exocrine Pancreatic Insufficiency 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); 5 U.S.C. 553; 21 CFR 5.11.

Subpart E—Exocrine Pancreatic Insufficiency Drug Products

§ 357.401 Scope.

(a) An over-the-counter exocrine pancreatic insufficiency 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.

§ 357.403 Definition.

As used in this subpart:

Exocrine pancreatic insufficiency. A condition in which the symptoms are due to inadequate exocrine pancreatic secretion as diagnosed by a physician.

§ 357.410 Exocrine pancreatic insufficiency active ingredients.

The active ingredient of the product consists of either one of the following when used within the dosage limits established for each ingredient:

(a) Pancreatin.

(b) Pancrelipase.

§ 357.450 Labeling of exocrine pancreatic insufficiency 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 "pancreatic enzyme replacement."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "For the treatment of exocrine pancreatic insufficiency." 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) of this chapter, subject to the prohibitions in section 502(a) of the act against misbranding by the use of false or misleading labeling and the prohibition in section 301(d) of the act against the introduction into interstate commerce of unapproved new drugs.

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

(1) "Do not take this product unless directed by a doctor."

(2) "Do not exceed the labeled dose unless directed by a doctor."

(3) "Swallow quickly to lessen potential for mouth irritation."

(4) *For tablet dosage forms.* "Do not chew."

(5) *For powder dosage forms.* "Avoid inhalation of powder. Sensitive individuals may experience allergic reactions."

(6) *For capsule dosage forms.* "If capsules are opened, avoid inhalation of powder. Sensitive individuals may experience allergic reactions."

(7) *For pork-derived pancreatic products.* "Do not take this product if you are allergic to pork."

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

(1) *For products containing pancreatin.* The daily dose of pancreatin is up to 42 grams (equivalent to 84,000 U.S.P. units lipase activity, 1,050,000 U.S.P. units protease activity, and 1,050,000 U.S.P. units amylase activity) either in divided doses at 1- or 2-hour interval *or* with meals and an extra dose taken with food eaten between meals *or* as directed by a doctor. The label must state the amount of enzyme activity per dosage unit in terms of U.S.P. units of lipase, amylase, and proteases activity.

(2) *For products containing pancrelipase.* The daily dose of pancrelipase is up to 3.5 grams (equivalent to 84,000 U.S.P. units lipase activity, 350,000 U.S.P. units protease activity, and 350,000 U.S.P. units amylase activity) either in divided doses at 1- or 2-hour intervals *or* with meals and an extra dose taken with food eaten between meals *or* as directed by a doctor. The label must state the amount of enzyme activity per dosage unit in terms of U.S.P. units of lipase, amylase, and protease activity.

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

Dated: October 8, 1985.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

[FR Doc. 85–26687 Filed 11–7–85; 8:45 am]

BILLING CODE 4160–01–M