DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310 and 357

[Docket No. 79N-0379]

RIN 0905-AA06

Exocrine Pancreatic Insufficiency Drug Products for Over-the-Counter Human Use; Proposed Rulemaking

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would establish that over-the-counter (OTC) exocrine pancreatic insufficiency drug products (drug products used to treat pancreatic enzyme deficiency) are not generally recognized as safe and effective and are misbranded. The agency is also withdrawing the proposed rule (see the **Federal Register** of November 8, 1985; 50 FR 46594), which was issued in the form of a tentative final monograph, that would have established conditions under which OTC exocrine pancreatic insufficiency drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice after considering public comments on the agency's proposed rule of November 8, 1985 and all new data and information on exocrine pancreatic insufficiency drug products that have come to the agency's attention. This proposal is part of the ongoing review of OTC drug products conducted by FDA. Further, FDA is declaring that it considers all exocrine pancreatic insufficiency drug products, whether currently marketed on a prescription or OTC basis, to be new drugs requiring an approved new drug application (NDA) for continued marketing.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by November 12, 1991. Because this notice is significantly different from the previously-proposed rule, the agency is allowing a period of 120 days for comments and objections instead of the normal 60 days. Written comments on the agency's economic impact determination by November 12, 1991. The date of withdrawal of the November 8, 1985 proposed rule is July 15, 1991.

ADDRESSES: 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, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

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 (Miscellaneous Internal Panel), 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 placed on display in the Dockets Management Branch (address above) after deletion of a small amount of trade secret information. Only five comments were submitted in response to the publication of the advance notice of proposed rulemaking.

In the **Federal Register** of November 8, 1985 (50 FR 46594), the agency published a notice of proposed rulemaking to establish a monograph for OTC exocrine pancreatic insufficiency drug products based on the recommendations of the Miscellaneous Internal Panel and the agency's response to comments submitted following the publication of the advance notice of proposed rulemaking. That proposal constituted 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 and information available at that time. In that document, the agency accepted the Panel's recommendation that exocrine pancreatic insufficiency drug products be available as OTC drug products and proposed the conditions under which these drug products would be generally recognized as safe and effective and not misbranded. Interested persons were invited to file by January 7, 1986, 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 March 10, 1986. New data could have been submitted until November 10, 1986, and comments on the new data until January 8, 1987.

In response to the publication of the tentative final monograph on OTC exocrine pancreatic insufficiency drug products, 2 drug manufacturers, 2 foundations, 39 health-care professionals, 2 health departments, 2 Congressmen, 2 advocacy groups, and 147 individuals submitted comments. Copies of the comments received and any additional information that has come to the agency's attention since publication of the tentative final monograph are also on public display in the Dockets Management Branch.

New information submitted in response to the tentative final monograph has caused the agency to reconsider the approach proposed in that document. FDA is now proposing a rule that would classify OTC drug products to treat exocrine pancreatic insufficiency as not generally recognized as safe and effective, as being misbranded, and as new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)). The proposed rule would amend part 310, subpart E by adding new § 310.543 (21 CFR 310.543). Accordingly, the proposed monograph published in the **Federal Register** of November 8, 1985 (50 FR 46594) which would have amended part 357 (21 CFR part 357) by adding new subpart E is being withdrawn on July 15, 1991.

The legal status of this document is that of a proposed rule. Final agency action occurs with the publication at a future date of a final rule relating to these drug products.

The OTC drug 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 rule stage, but will use instead the terms "monograph

conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This proposal retains the concepts of Categories I, II, and III at the tentative final rule stage.

The Miscellaneous Internal Panel stated in its report (44 FR 75666 at 75667 to 75668) that under normal circumstances the pancreas secretes a sufficient amount of enzymes (i.e., lipase for fat digestion, protease for protein digestion, and amylase for starch digestion) into the intestine to aid in the digestion process. When the pancreas is not functioning properly or is partially removed surgically, lesser amounts of pancreatic digestive enzymes are released into the intestine. Because the pancreas has a large functional reserve capacity, malabsorption, due to insufficient digestion, does not occur until the pancreatic enzyme output level is reduced by more than 90 percent. When this level of reduction occurs, the pancreatic insufficiency can usually be suggested by the increased fat content in the stools, and treatment with pancreatic enzymes taken by mouth may be necessary.

The agency recognizes that pancreatic extract drug products have been marketed for a number of years. When properly formulated, these products are effective for the treatment of exocrine pancreatic insufficiency. Some pancreatic enzymes have been marketed as OTC drug products. However, a number of products currently in use, e.g., all encapsulated enteric coated microsphere dosage forms, have been and are being marketed as prescription drug products without an approved NDA. In this document, the agency is proposing that all exocrine pancreatic insufficiency drug products (whether currently marketed on an OTC or prescription basis) are new drugs for which approved applications would be required for marketing.

The Miscellaneous Internal Panel concluded that pancreatic digestive enzymes (i.e., lipase, protease, and amylase) have been safely used to treat the condition of exocrine pancreatic insufficiency for many years. Based on the Panel's recommendation that pancreatic enzymes are generally recognized as safe, and the marketing history and well-established use of these enzymes, the agency concludes that such products are safe for the treatment of exocrine pancreatic insufficiency when properly formulated. Therefore, in most cases, applications for such drugs would not need to include preclinical data but, instead, could refer to the Panel's report as a basis for the safety of the enzymes. However, because of the variation in the formulation and dosage form of some currently available pancreatic extract drugs, e.g., encapsulated enteric coated microsphere dosage forms, preclinical and clinical data to establish the safety of the final formulation may be needed in some cases.

The Department of Health and Human Services has published the "10th Edition of Approved Drug Products with Therapeutic Equivalence Evaluations," commonly called the "Orange Book," which identifies currently marketed products approved by FDA on the basis of safety and effectiveness data. The main criterion for the inclusion of any product in the "Orange Book" is that the product is the subject of an approved application that has not been withdrawn for safety or effectiveness reasons. For a product for which there is no previously approved listed drug in the "Orange Book," an abbreviated new drug application may not be submitted and a new drug application which includes adequate and well-controlled clinical studies of the effectiveness of the specific formulation of the drug must be submitted. There are no pancreatic extract drug products currently listed in the "Orange Book." Therefore, an application for a pancreatic extract drug product must include adequate and well-controlled clinical studies of the product's effectiveness, i.e., the application should contain evidence of human bioactivity in normal volunteers or patients to demonstrate that the enzymes are active in vivo on ingested fats, proteins, and carbohydrates. The bioactivity must be shown to correlate with the stated potency of each proposed product. The studies need to comply with the requirements of 21 CFR part 314. An application would also have to include information on the drug product's formulation, manufacture, and quality control procedures to ensure that the applicant has the ability to manufacture a proper, bioactive formulation. FDA encourages manufacturers to consult with the agency as soon as possible concerning the content of these applications. Inquiries should be directed to the Division of Gastrointestinal and Coagulation Drug Products (HFD–180), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857, 301–443–0479.

Because no applications for pancreatic enzyme drug products are currently approved, an abbreviated application cannot be submitted. However, when one or more applications have been approved, manufacturers should consult with the Office of Generic Drugs (HFD–600), Center of Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857, 301–295–8340 to determine the procedures for obtaining approval of abbreviated new drug applications.

In the advance notice of proposed rulemaking for OTC exocrine pancreatic insufficiency drug products, the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the data of publication of the final monograph in the **Federal Register**. The agency also suggested 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 (44 FR 75666).

If this proposal is adopted as a final rule, the agency advises that the conditions under which the drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions) will be effective 6 months after the date of publication of the final rule in the **Federal Register**. On or after that date, no OTC drug product that is subject to the rule 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 the final rule that is repackaged or relabeled after the effective date of the final rule must be in compliance with the final rule 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 proposed rule at the earliest possible date. Regulatory policy for products containing nonmonograph ingredients is set forth in the **Federal Register** of May 13, 1980 (see 45 FR 31422 at 31424 to 31425).

The agency is aware that drug products containing these ingredients are a daily requirement for sufferers of exocrine pancreatic insufficiency. Most cystic fibrosis patients depend on these products from infancy to digest food properly. Therefore, the agency recognizes a need for consumers with cystic fibrosis to continue to have access to these products and to avoid a disruption of the marketplace. Because the final rule for this class of OTC drug products will be effective 6 months after

its publication in the **Federal Register**, FDA strongly recommends that manufacturers of pancreatic enzyme drug products consult with the agency as soon as possible concerning the content of these applications. Inquiries should be directed to the Division of Gastrointestinal and Coagulation Drug Products (HFD–180), (address above).

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 notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Tentative Conclusions on the Comments and Objections

1. All of the comments submitted in response to the tentative final monograph objected to OTC availability of exocrine pancreatic insufficiency drug products and requested that they be available by prescription only. A number of comments raised the same points that the agency addressed in the tentative final monograph (50 FR 46594 at 46595 to 46597). However, many comments, including those from the health care community involved in the treatment of cystic fibrosis, raised new issues concerning the OTC use of pancreatic extracts.

Many comments contended that pancreatic extracts should be restricted to prescription status because the diseases requiring the use of these drug products require a physician's diagnosis and continuous monitoring of the patients. These comments also stated that a physician's interaction/counseling is necessary because the dosage of these drug products must be individualized and because side effects can become significant at higher doses. The comments asserted that the dosage for moderate and severe pancreatic insufficiency will often exceed the daily dosage recommended for OTC marketing and that side effects at these higher doses may become significant.

Several comments stated that pancreatic extracts should be restricted to prescription status because the drugs should not be readily available to the general population. Noting that the general population has no need for pancreatic extracts, these comments pointed out that pancreatic enzymes should only be used by patients with conditions that require a physician's diagnosis. Some of the comments feared that consumers with adequate pancreatic enzyme output would be harmed by misusing the extracts for other conditions, such as indigestion or gallbladder problems. Two other comments maintained that OTC status will lead to abuse, such as use in a diet plan. These comments feared the potential hazards and side effects that might be experienced by uninformed consumers who use the extracts for other than exocrine pancreatic insufficiency.

One comment contended that adequate labeling for the OTC use of pancreatic extracts is impossible and, therefore, objected to the OTC availability of these drugs. Referring to the discussion in comments 3 and 4 of the tentative final monograph (50 FR 46594 at 46596 and 46597), the comment disagreed with the agency's position that added warnings in the labeling will adequately protect the patient or caregiver from ulceration of the mouth, lips, and tongue as well as hypersensitivity reactions that have been reported with pancreatic extracts. Some comments also pointed out that the clinical, dietary, and other considerations which are necessary to select the appropriate product and dosage are too complex for consumers. The comments stated that pancreatin and pancrelipase products do not have comparable enzyme activity and the available dosage forms (tablets, powders, capsules, and enteric coated microspheres in capsules) are not interchangeable on a one-to-one unit basis. These comments feared that lack of computational skills necessary to convert the required dosage from one product to another might lead to underdosing or overdosing with pancreatic extracts. These comments argued that restricting the products to prescription availability would minimize these difficulties and maximize patient care and survival.

Most comments objected to the OTC availability of pancreatic enzymes on the basis that many third party reimbursers do not reimburse for OTC medication. These comments maintained that OTC availability would impose a considerable financial burden on the patients who require these drugs and on their families.

Noting that many manufacturers are phasing out the production of capsules because of concerns about product tampering, many comments stated that pancreatic insufficiency drug products should be restricted to prescription availability to assure that the capsule dosage form of these drug products remains available. Several comments stated that the most useful dosage form for pancreatic enzymes is enteric-coated microspheres in capsules. The enteric coating is designed to dissolve once the microspheres of enzymes are past the stomach and are in the intestine. The comments explained that the enteric coating protects the enzymes from the destructive influence of the stomach acids, and digestion is more complete and efficient, enabling patients to take less medication. One comment felt that before this dosage form became available, the variety of foods that exocrine pancreatic insufficiency sufferers were permitted to eat was extremely restricted and, as a result, babies and children did not grow properly because of a lack of nutrients. Pointing out that the capsules can be opened and the enteric coated microspheres can be safely sprinkled over soft food for infants and toddlers who are otherwise unable to swallow the capsules and can experience damage to the mucosa of the mouth and lips from uncoated enzymes, three comments feared that the removal of this dosage form from the marketplace would adversely affect children suffering from exocrine pancreatic insufficiency. Several comments stated that this dosage form has brought about great improvement in the efficacy of pancreatic enzymes for most patients with cystic fibrosis. These comments expressed concern that if pancreatic enzymes were marketed OTC, the capsule dosage form would no longer be available.

Many comments referred to the use of pancreatic enzymes by patients with cystic fibrosis. Physicians who treat the disease pointed out that cystic fibrosis is the most common fatal genetic disease, estimated to occur in 1 in 2,000 newborns in the U.S. It is a progressive disease which involves changes in multiple organ systems, but whose primary pathophysiology involves the respiratory system and the gastrointestinal tract. In treating cystic fibrosis, replacement pancreatic extracts are used to control the consequences of exocrine pancreatic insufficiency, namely maldigestion and malabsorption and resulting nutritional deficiencies. The physicians estimated that at least 85 percent of cystic fibrosis patients exhibit pancreatic insufficiency, which can result in deficiencies in the intake and absorption of calories, proteins, vitamins, minerals, etc., which, in turn, may lead to nutritional deficiencies and failure to thrive. Some comments noted that the nutritional management of this disease has changed in a manner that promotes the use of higher doses of pancreatic enzymes than are proposed for OTC use. Instead of the historical

practice of prescribing a low fat diet, the current medical approach to the diet of cystic fibrosis patients is to encourage the consumption of a diet of normal to high fat content. Noting that this change in diet for cystic fibrosis patients has necessitated the use of much higher doses of pancreatic enzymes to digest the higher fat diet, the comments maintained that hyperuricosuria (excess uric acid in the urine) and hyperuricosemia (excess uric acid in the blood) have been associated with the consumption of high doses of pancreatic extracts. Therefore, the comments requested that pancreatic enzymes be available by prescription only, under the supervision of a physician, to ensure patient safety with adequate control of the disease.

Many physicians who treat cystic fibrosis patients expressed the opinion that if the status of pancreatic extracts were changed from prescription to OTC, it would impact negatively on the medical course for these patients. Noting that the life expectancy of cystic fibrosis patients has increased from approximately 5 years in the early 1950's to about 21 years in the 1980's, the comments maintained that the increase in survival rates has resulted from improvement in the overall medical management of the disease and could be correlated to frequent and continuing professional care. The physicians stated that maintenance of adequate nutrition in these patients requires frequent monitoring of their enzyme supplementation requirements which vary dramatically from patient to patient, and from time-to-time (depending on diet and activity) for the same patient. In addition, the physicians reported that too little supplementation may result in impeded growth for these patients. As a result of too little or too much enzyme supplementation, patients suffer from abdominal discomfort ranging from mild symptoms to overt intestinal obstruction, which requires immediate medical and, on occasion, surgical intervention. The physicians also noted that there are indications that nutritional status may affect pulmonary function and the progress of lung disease in these patients. The comments from physicians treating cystic fibrosis patients all requested that exocrine pancreatic extracts be restricted to prescription availability to ensure that the progress being made in the treatment of the disease will continue.

In the tentative final monograph, the agency addressed many of the same objections to the OTC marketing of exocrine pancreatic drug products as have been raised by the above comments (50 FR 46594 at 46595 to 46597). The agency reiterates its position that the requirement for a physician's diagnosis of a condition does not, by itself, necessitate prescription status of a drug as long as the patient can self-monitor the drug's effectiveness and adequate OTC labeling can be developed for the product's safe and effective use. Further, financial considerations (e.g., third party reimbursement) are not among the statutory criteria for limiting a drug product to prescription status.

Also, the agency disagrees with the comments which stated that OTC availability of exocrine pancreatic insufficiency drug products would lead to abuse or cause harm to individuals not suffering from exocrine pancreatic insufficiency who might use the products by mistake or for some other (nonlabeled) use. Many products containing these types of ingredients have been available OTC for decades with no report of abuse or accidental injury to the general public.

The agency shares the comments' concerns about OTC capsule dosage forms and has taken steps to ensure the safety of the two-piece hard gelatin capsule dosage form and its continued availabity in the OTC marketplace. As part of the agency's efforts to improve consumer protection from the threat of product tampering, FDA amended its tamper-resistant packaging regulations for OTC human drug products in 21 CFR 211.132. The original regulation in § 211.132 provided for "an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred." FDA later strengthened this regulation by requiring that manufacturers and packagers who market two-piece hard gelatin capsules utilize packaging that provides a minimum of two tamper-resistant packaging features. Alternatively, tamper-resistant technology, such as gelatin banding, can be used in the manufacturing process to seal capsules. The revised, tamper-resistant packaging requirements were finalized in the **Federal Register** of February 2, 1989 (54 FR 5227) and became effective on February 2, 1990.

However, the information submitted in response to the tentative final monograph and other available information has prompted the agency to reconsider its position on these drug products and to now propose that all pancreatic extract drug products be required to obtain an approved application for marketing. The agency is very concerned with the effects that a pancreatic extract drug product's formulation and dosage form will have on the drug's safe and effective use. These concerns cannot be adequately addressed under the OTC drug monograph system. However, under an approved application, formulation and dosage form issues can be resolved prior to marketing.

This reproposal would also require that all pancreatic extract drug products be marketed by prescription. Based on the numerous comments from physicians that continuous physician monitoring of patients appears to be one of several important factors in the increased survival rates for exocrine pancreatic insufficiency patients, the agency concludes that such collateral measures necessary to the use of these drug products require that these drug products be available by prescription only, as required by section 503(b)(1)(B) of the act (21 U.S.C. 353(b)(1)(B)). The agency also recognizes that some frequently used pancreatic extract drug products are being marketed as prescription drugs, but without approved applications. Some of these products provide higher levels of enzyme than stated in their labeling (Ref. 1). This results in the daily dose being higher than the recommended OTC daily dose of pancreatic enzymes. Also, as stated above, many health professionals involved in the use of these products are concerned about the consequences of exclusive OTC marketing for all pancreatic extract drug products (including the encapsulated enteric-coated microsphere dosage form products which have always been marketed by prescription). Therefore, based upon this new information, the agency has concluded that the previous proposal (50 FR 46594), which would have required all exocrine pancreatic extract drug products to be marketed OTC in compliance with an OTC drug monograph, should be revoked.

The agency's proposed requirement for an approved application is based primarily on the nature of these drug products. Pancreatic extract drug products are composed of three types of digestive enzymes: Amylase, trypsin (protease), and lipase (Ref. 2). Their effectiveness in treating exocrine pancreatic insufficiency is dependent on the specific formulation, the dosage form, and the procedures employed in the manufacture of each product, e.g., the integrity of the enteric coating. Successful use of these drugs as enzyme replacement therapy in exocrine pancreatic insufficiency relieves the symptoms of steatorrhea (diarrhea, abdominal fullness or bloating, and

cramps) and prevents further weight loss or produces a gain in weight (Ref. 3). The success of replacement enzyme therapy with pancreatic extract drug products is proportional to the amount of bioactive enzymes that reach the duodenum of the patient (Ref. 4). It has been shown experimentally that trypsin is inactivated by gastric juices and that lipase is inactivated by pH less than 4 (Ref. 5). In patients with exocrine pancreatic insufficiency, as little as 22 percent of the trypsin and 8 percent of the lipase ingested in pancreatin may survive the gastric environment of the stomach and reach the duodenum (Ref. 6).

The survival of the enzymes in the body is dependent on the dosage form of the drug product. Pancreatic extracts were originally marketed as powders, powders in capsules, and tablets. Because of inactivation of the enzymes by stomach juices, some pancreatic extracts have been manufactured in tablets with enteric coatings and as encapsulated enteric-coated microspheres. The enteric coating should, theoretically, allow the enzymes to pass through the acid environment of the stomach without being denatured and be delivered to the alkaline environment of the small intestine, where the enteric coating should dissolve (Ref. 7). It has been shown that some patients with pancreatic insufficiency have a lower than normal pH in the upper small intestine (Refs. 8 and 9). Because of this, the pH at which the enteric coating dissolves and the preparations release their enzymes becomes critical to the product's effectiveness. The enzymes should not be released at a pH that is too low, i.e., in the stomach where deactivation of enzymes can occur, or too high, in which case the coating may not dissolve in the small intestine and the enzymes would not be released. To fit these requirements, the enzymes should ideally be released between pH 5.5 and pH 6.0 (Ref. 10). Therefore, the character of the enteric coating of tablets and microspheres of pancreatic extracts becomes extremely important in protecting and delivering the drug product to its site of activity.

In vivo and in vitro studies have demonstrated the variations among pancreatic extract drug products (Refs. 1, 4, 7, and 10 through 15).

An early study compared 16 available preparations in vitro and revealed a wide range of enzyme activities, e.g., from 10 to 3,600 United States Pharmacopeia (U.S.P.) units of lipase activity per dosage unit (Ref. 7). The same study also compared the effectiveness of an enteric-coated tablet product with and without the enteric coating in six patients and found greater effectiveness for the product lacking the enteric coating (Ref. 7). Many studies of the encapsulated enteric-coated microsphere dosage form of pancreatic enzymes in patients with severe pancreatic insufficiency and with cystic fibrosis indicate that these products have improved effectiveness over other formulations in treating pancreatic insufficiency (Refs. 11 through 15).

In addition to variations in effectiveness between various dosage forms, comparisons of the lipase activity and effectiveness of various products also show variations among encapsulated enteric-coated microsphere products from different manufacturers (Refs. 1, 10, 13, and 15). An in vivo random crossover study undertaken in 19 cystic fibrosis patients compared the efficacy of 4 pancreatic extract products, 1 tablet dosage form, and 3 encapsulated enteric-coated microsphere products (Ref. 15). The results of the study showed fewer gastrointestinal symptoms and increased fat absorption with two of the encapsulated enteric coated microsphere products. Patients using those two products were able to enjoy a normal diet without fat restrictions. The tablet product and the third encapsulated enteric-coated microsphere product gave less satisfactory results, although the enzyme content of the latter was similar to the two more successful encapsulated enteric-coated microsphere products.

A recent in vitro study of various commercial pancreatic enzyme preparations demonstrated the variations in lipase activity and release rates among the products (Ref. 10). Three main types of dosage forms were tested, i.e., simple pancreatic enzyme preparations (uncoated tablets and powder filled capsules), enteric-coated tablets, and encapsulated enteric-coated microspheres. The products were analyzed for amylase, lipase, and protease activity before being subjected to a simulated gastric fluid (0.1 N HCl) at 37 degrees for 2 hours in a disintegration apparatus. The lipase activity of each product was then reanalyzed. It was found that the simple dosage form products had lost all of the original lipase activity. The enteric-coated tablet dosage form retained all of the original lipase activity; the three encapsulated enteric-coated microsphere dosage form products retained the following percentages of their original lipase activity: 54.0, 90.7, and 99.9 percent, respectively. The study also investigated the release rate of enzyme and the pH level at which release begins. The enteric-coated tablets showed negligible release of enzymes in the pH range of 4.0 to 6.0. All the enteric-coated microsphere products released their enzymes in the pH range of 5.5 to 6.0. Although, as noted above, not all the original lipase content remained for all the preparations.

These studies demonstrate the variation in pancreatic extract drug products, both among various dosage forms and among products from different manufacturers of the same dosage form. Because of this, the agency recognizes that a monograph based only on the labeled activity of the enzymes contained in the product would not provide enough information on the activity of the enzymes after the product is ingested. Therefore, a monograph would not be sufficient to adequately regulate the drug products or to provide labeling for consumers to use the products safely and effectively. In addition, the United States Pharmacopeia XXII/National Formulary XVII monographs for pancreatic extracts (Ref. 16) do not contain dissolution standards and do not have quantitative drug release standards for dosage forms that are enteric coated. The United States Pharmacopeial Convention (U.S.P.C.) is aware of these problems and is presently evaluating what changes in the compendial standards are needed to effectively address them (Refs. 17 through 21).

As a result of the wide range of enzyme activity, the variety of dosage forms, and the apparent uneven quality of the enteric coatings among pancreatic extract drug products, there have been instances of underdosing and overdosing with pancreatic extracts. A recent paper reports on three patients whose pancreatic insufficiency had been controlled using one encapsulated enteric-coated microsphere dosage form pancreatic extract drug product. These patients experienced therapeutic failure when a similar product that was labeled as containing the same enzyme activity was substituted for the first product (Ref. 1). The therapeutic failure in these cases was characterized by various symptoms, e.g., stomach cramps, intestinal gas, abdominal distention, greasy stools, and constant hunger. The products involved in these cases, both original "brand name" products and substituted "generic" products, were analyzed for lipase activity before and after exposure to simulated gastric fluid. The two "brand name" products actually contained much greater lipase activity than labeled (almost twice as much). Of the three "generic" products,

two contained more than the labeled activity of lipase per capsule (one about 30 percent more and one 20 percent more), and one contained 25 percent less. After exposure to gastric conditions, the two "brand name" products retained 91 and 98 percent of their original lipase activities, respectively (still much more than their labeled lipase activity). The three generic brands lost essentially all their lipase activity, retaining only 2 to 4 percent.

The above study also demonstrates that the two "brand name" products have been delivering much more enzyme than is indicated in their labeling. One of the reported cases had been stabilized on 20 capsules per day of a "brand name" product. This product was labeled to contain 4,000 U.S.P. units of lipase activity per capsule but actually contained 7,480 U.S.P. units of lipase activity. This would be a daily dose of 149,600 U.S.P. units of lipase activity, which is almost twice the daily dose of 84,000 U.S.P. units recommended by the agency as safe for OTC use (50 FR 46600). This particular product was used by many of the cystic fibrosis patients who submitted comments to the rulemaking. The number of capsules used by these patients was in line with that reported in this study. It appears, therefore, that users of pancreatic enzymes are routinely ingesting higher than the recommended OTC dose of pancreatic enzymes even when the amounts on the labels of the products would appear to be within the OTC limits. This is consistent with claims made by many comments that high doses of pancreatic extracts are routinely being used currently, especially in the management of cystic fibrosis.

The published literature on the management of cystic fibrosis also emphasizes that higher fat diets, which require higher dosages of the encapsulated enteric-coated microsphere dosage form of pancreatic extracts individualized to the particular patient and diet, are recommended for the control of nutritional problems (Ref. 22). A recent 6-year study of 37 cystic fibrosis patients who consumed a high-energy diet with no fat restriction reported a significant weight gain (Ref. 23). These patients were given individualized nutritional counseling, and the dosage of pancreatic extract drug product was adjusted according to the fat content of meals and snacks. The agency notes that, according to the reports, the patients were being closely monitored by health professionals.

The agency believes that physician monitoring is imperative when large doses of pancreatic extracts are being consumed. In comment 2 of the tentative final monograph, the agency discussed reports (50 FR 46594 at 46596) (Refs. 24 through 29) of hyperuricosuria, hyperuricemia, obstipation, and intestinal obstruction resulting from daily doses of pancreatic extracts in excess of the amounts proposed in the tentative final monograph. The occurrence of cramps, bloating, and abdominal discomfort resulting from excessive doses of pancreatic enzymes has also been reported (Ref. 30).

The agency has become aware of another problem resulting from overdosing with another pancreatic enzyme drug product. In the last few years, encapsulated enteric-coated microsphere pancreatic extract drug products labeled with very high enzyme activity per capsule have entered the marketplace as prescription drugs without approved applications. The most potent of these products is labeled 16,000 U.S.P. units of lipase activity and 48,000 U.S.P. units each of amylase and protease activity per capsule. The agency is aware of a report of a 17-year old male who experienced a small bowel obstruction after 3 days of treatment with the above formulation (Ref. 31). This situation resulted in hospitalization but was resolved when the treatment was withdrawn and the patient given a lower potency pancreatic extract drug product.

Based on the above information, the agency recognizes that it is not possible for a consumer to safely use pancreatic enzyme drug products based only on the labeled enzyme content of the drug product. The products require (1) professional intervention to establish individual specifications and (2) agency preclearance of each product to standardize bioactivity to avoid serious safety problems resulting from too little or too much enzyme supplementation. Further, the above information shows the need for the agency to require approved NDA's for all exocrine pancreatic insufficiency drug products.

In addition, the agency recognizes that advances in the treatment of cystic fibrosis patients have been accomplished largely, although not exclusively, with the use of prescription pancreatic extracts in the encapsulated enteric-coated microsphere dosage form. Although changes in other factors in the treatment of cystic fibrosis over the years have certainly contributed to the improved prognosis in the disease, e.g., use of antibiotics and vitamin supplements, the agency does not believe it would be prudent to jeopardize the successes of this treatment by allowing pancreatic enzymes to be marketed only as OTC drug products, which would occur if they were generally recognized as safe and effective in an OTC drug monograph. Therefore, because of the above considerations, the agency is proposing to withdraw proposed 21 CFR part 357 subpart E (proposed OTC drug monograph) and to amend 21 CFR part 310 (new drugs) by adding new § 310.543 (21 CFR 310.543).

If this proposal becomes final, approved drug applications will be required for the marketing of these drug products. The requirements (procedures and content) for submitting an application are discussed above.

References

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2. One comment contended that manufacturers of prescription pancrelipase products were not given ample opportunity to participate in the rulemaking for OTC exocrine pancreatic insufficiency drug products. The comment stated that neither the call-for-data notices nor the advance notice of proposed rulemaking for OTC exocrine pancreatic insufficiency drug products stated that the review of these drug products would also include prescription pancrelipase. The comment requested that the administrative record be reopened to allow for comment and data for pancrelipase preparations.

The comment is correct that the November 16, 1973, and August 27, 1975, call-for-data notices did not specifically state that pancrelipase would be subject to the OTC drug review of ingredients in exocrine pancreatic insufficiency drug products. However, the advance notice of proposed rulemaking, published on December 21, 1979 (44 FR 75666), addressed pancrelipase. The Panel discussed pancrelipase in its discussion of Category I conditions (44 FR 75668). The Panel included this ingredient in § 357.410(b) of its recommended monograph and provided the recommended OTC dosage in § 357.450(d)(2) (44 FR 75669). In addition, in response to the advance notice of proposed rulemaking, two manufacturers of prescription pancrelipase products submitted comments to the rulemaking. These comments have been on public display in the Dockets Management Branch since they were submitted in 1980. Further, the agency also discussed these comments in the tentative final monograph (50 FR 46594 at 46595 to 46597).

The agency believes that manufacturers of prescription pancrelipase drug products have had ample opportunity to comment and submit data to the rulemaking for OTC exocrine pancreatic insufficiency drug products. However, this reproposal provides another opportunity (a 120-day period) for manufacturers to submit comments and data to this rulemaking.

3. One comment requested that the daily dosage limits of pancrelipase be increased to at least 350,000 U.S.P. units of lipase activity, 1,050,000 U.S.P. units of protease activity, and 1,050,000 U.S.P. units of amylase activity. The comment stated that the agency's proposal in the tentative final monograph (limits of 84,000 U.S.P. units of lipase activity, 350,000 U.S.P. units of protease activity, and 350,000 U.S.P. units of amylase activity) appears to be based upon the minimum activity per milligram (mg) of pancrelipase as described in the United States Pharmacopeia XXI/National Formulary XVI (U.S.P. XXI/N.F. XVI) (Ref. 1). The comment alleged that the proposed upper limit for lipase activity for pancrelipase preparations appears to have been arbitrarily set by using pancreatin as the reference standard. The comment stated that pancrelipase differs from pancreatin principally in lipase activity (1 mg of pancrelipase contains 12 times the lipase activity of pancreatin and only 4 times the protease and amylase activity). The comment argued that because the daily recommended dose proposed in the tentative final monograph appears to standardize pancreatin and pancrelipase preparations on the basis of lipase activity, the advantage of the greater lipase activity in pancrelipase is negated, and the protease and amylase activity are substantially decreased on a weight basis in the pancrelipase preparations. The comment recommended that if the two preparations were to be standardized, it should be on the basis of protease and amylase activity, which would allow for better control of steatorrhea at smaller doses. In addition, the comment expressed the opinion that preparations with much higher specific activity are urgently needed.

As discussed above in comment 1, the agency is withdrawing the proposed monograph on OTC exocrine pancreatic insufficiency drug products published in the **Federal Register** of November 8, 1985 (50 FR 46594). Therefore, OTC dosage strengths for any pancrelipase drug products are not being addressed in this document. If the proposal to require all exocrine pancreatic insufficiency drug products to acquire an approved application for marketing becomes final, each manufacturer who submits an application for an exocrine pancreatic insufficiency drug product will have the opportunity to include data in support of

a particular daily dosage limit for that product.

eference

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

II. The Agency's Tentative Conclusions on Exocrine Pancreatic Insufficiency Drug Products

Pancreatin and pancrelipase have been present as ingredients in exocrine pancreatic insufficiency drug products. Both ingredients are composed of three types of digestive enzymes: Amylase, trypsin (protease), and lipase. Some exocrine pancreatic insufficiency drug products have been marketed OTC and others have been marketed by prescription, all without approved applications. Based on available evidence, the agency has determined that the bioavailability of these enzymes is dependent on the process used to manufacture the drug products. Therefore, the agency has determined that the safe and effective use of these enzymes for exocrine pancreatic insufficiency cannot be regulated adequately by an OTC drug monograph. The agency proposes that any pancreatic extract drug product that is labeled, represented, or promoted for se in exocrine pancreatic insufficiency ill be considered a new drug within he meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)), for which an approved application under section 505 of the act (21 U.S.C. 355) and Part 314 of the regulations (21 CFR part 314) is required for marketing. In the absence of an approved application, such a product would also be misbranded under section 502 of the act (21 U.S.C. 352).

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 ncluded that the overall OTC drug eview 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 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 this proposal on OTC exocrine pancreatic insufficiency drug products is significantly different from the previously-proposed rule, a period of 120 days from the date of publication of this proposed rule in the **Federal Register** is being provided for comments and data 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 determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before November 12, 1991 submit to the Dockets Management Branch 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 November 12, 1991. 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.**

In establishing a final rule, the agency will ordinarily consider only comments and data submitted prior to the closing of the administrative record on November 12, 1991. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final rule 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 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, it is proposed that subchapter D of chapter I of title 21 of the Code of Federal Regulations be amended in part 310 as set forth below; and the proposed amendment to subpart E of part 357 (November 8, 1985; 50 FR 46594) is withdrawn.

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 376); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Section 310.543 is added to subpart E to read as follows:

§ 310.543 Drug products containing active ingredients offered over-the-counter (OTC) for human use in exocrine pancreatic insufficiency.

(a) Pancreatin and pancrelipase have been present as ingredients in exocrine pancreatic insufficiency drug products. Both ingredients are composed of enzymes: amylase, trypsin (protease), and lipase. Some exocrine pancreatic insufficiency drug products have been marketed OTC and others have been marketed by prescription, all without approved new drug applications. Significant differences have been shown in the bioavailability of marketed exocrine pancreatic insufficiency drug products produced by different manufacturers. These differences raise a potential for serious risk to patients using these drug products. In addition,

continuous physician monitoring of patients who take these drug products is a collateral measure necessary to the safe and effective use of these enzymes, causing such products to be available by prescription only. Therefore, the safe and effective use of these enzymes for exocrine pancreatic insufficiency cannot be regulated adequately by an OTC drug monograph.

(b) Any drug product that is labeled, represented, or promoted for OTC use in exocrine pancreatic insufficiency is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted as an OTC exocrine pancreatic insufficiency drug product is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter

(d) After (*insert date 6 months after date of publication of the Final Rule in the* **Federal Register**), any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

Dated: May 31, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

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