

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration**

[Docket No. 2003N-0205]

Exocrine Pancreatic Insufficiency Drug Products**AGENCY:** Food and Drug Administration.**ACTION:** Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that all exocrine pancreatic insufficiency drug products are new drugs and is announcing the conditions for continued marketing of these drug products. Manufacturers who wish to continue to market exocrine pancreatic insufficiency drug products must submit new drug applications (NDAs); manufacturers who contend that a particular drug product is not subject to the new drug requirements of the Federal Food, Drug, and Cosmetic Act (the act) should submit a citizen petition. FDA has determined that prescription exocrine pancreatic insufficiency drug products are medically necessary and, accordingly, is allowing manufacturers 4 years to obtain approved applications.

DATES: This notice is effective April 28, 2004.

A citizen petition claiming that a particular drug product is not subject to the new drug requirements of the act should be submitted no later than June 28, 2004.

After April 28, 2008, any prescription exocrine pancreatic insufficiency drug product introduced or delivered for introduction into interstate commerce without an approved application, unless found by FDA not to be subject to the new drug requirements of the act in response to a citizen petition submitted for that product, will be subject to regulatory action.

ADDRESSES: All communications in response to this notice should be identified with Docket No. 2003N-0205 and directed to the appropriate office listed in section III of this document. References described in section V of this document are available for public examination in the Division of Dockets Management (HFA-305), Food and Drug Administration.

FOR FURTHER INFORMATION CONTACT: Mary E. Catchings, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

This notice covers pancreatic enzyme preparations containing the ingredients pancreatin and pancrelipase. Both ingredients are extracted mainly from hog pancreas and contain principally amylase, protease, and lipase. Pancrelipase differs from pancreatin mainly in that it has a higher lipase concentration than does pancreatin.

Pancreatic extract drug products are indicated as replacement therapy to treat conditions associated with exocrine pancreatic insufficiency, including cystic fibrosis, chronic pancreatitis, pancreatic tumors, or pancreatectomy. Under normal circumstances, the pancreas secretes a sufficient amount of enzymes 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 (i.e., lipase for fat digestion, protease for protein digestion, and amylase for starch digestion) 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 detected by the increased fat content in the stools, and treatment with pancreatic enzymes taken by mouth may be necessary (56 FR 32282 at 32283, July 15, 1991).

Pancreatic extract drug products have been marketed in the United States for many years. Marketing of some of these products predates the 1938 passage of the act. Over the years, other pancreatic extract drug products have entered the market. Until recently, none of these drug products were marketed under approved NDAs.

As part of the OTC drug review, FDA evaluated the safety and effectiveness of drug products used to treat exocrine pancreatic insufficiency. 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. The proposed rulemaking included the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the 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 on the proposed rulemaking.

In the **Federal Register** of November 8, 1985 (50 FR 46594), FDA published a notice of proposed rulemaking to establish a monograph for OTC exocrine pancreatic insufficiency drug products based on the Panel's recommendations and the agency's response to comments submitted following publication of the advance notice of proposed rulemaking (the November 1985 proposed rule). In the November 1985 proposed rule, 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 submit new data, written comments, objections, or requests for oral hearing on the proposed rulemaking.

Based on new information submitted in response to the tentative final monograph and other available information that came to its attention, the agency reconsidered the approach proposed in the November 1985 proposed rule. Mainly because of bioavailability problems associated with use of pancreatic extract drug products and other problems reported with the products manufactured as enteric-coated tablets and encapsulated enteric-coated microspheres, FDA concluded that an OTC drug monograph would not be sufficient to adequately regulate these drug products. FDA concluded that preclearance of each product to standardize enzyme bioactivity would be necessary. FDA also determined that continuous physician monitoring of patients is a collateral measure necessary to the safe and effective use of pancreatic enzyme drug products, requiring such products to be available by prescription only. Thus, in the **Federal Register** of July 15, 1991 (56 FR 32282), FDA proposed a rule (the July 1991 proposed rule) that would declare that OTC drug products used to treat exocrine pancreatic insufficiency are not generally recognized as safe and effective and are misbranded. Accordingly, FDA withdrew the November 8, 1985, proposed rule. In the preamble to the July 1991 proposed rule, FDA also stated that it considers all exocrine pancreatic insufficiency drug products, whether currently marketed on an OTC or a prescription basis, to be new drugs for which approved applications will be required for marketing. The final rule, which affected only OTC products, was published in the **Federal Register** of

April 24, 1995 (60 FR 20162) (the April 1995 final rule).

This notice reiterates the agency's determination that all pancreatic extract drug products are new drugs under section 201(p) of the act (21 U.S.C. 321(p)), requiring approved NDAs for marketing, and states the conditions for marketing the products.

II. Summary of Data Supporting New Drug Finding

In the July 1991 proposed rule and the April 1995 final rule, the agency discussed its review of the scientific data that provide the basis for the agency's decision to require approval of pancreatic extract drug products through the new drug approval process under section 505 of the act (21 U.S.C. 355).

Those data, including in vitro and in vivo studies, demonstrated variations in bioactivity among pancreatic extract drug products that were labeled as containing the same enzyme activity (Refs. 1 through 9). This notice discusses those data and the most recent data received by the agency.

An early study compared 16 commercially available pancreatic extract products (tablets, capsules, and enteric-coated tablets) in vitro. The study demonstrated a wide range of lipase activity (from 10 to 3,600 United States Pharmacopeia (U.S.P.) units of lipase activity per dosage unit) (Ref. 3). The study also evaluated the effectiveness of an enteric-coated tablet product with and without the enteric coating and observed greater effectiveness for the product lacking the enteric coating.

One in vitro study of various commercial pancreatic enzyme products demonstrated the variations in lipase activity and release rates among the products (Ref. 4). The study tested three main types of dosage forms, 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. The lipase activity of each product was then reanalyzed. The results showed that when subjected to a simulated gastric fluid, the simple dosage form products lost all of the original lipase activity. The enteric-coated tablet dosage form retained all of the original lipase activity under these conditions; the three encapsulated enteric-coated microsphere dosage form products retained 54.0, 90.7, and 99.9 percent, respectively, of their original lipase

activity under these conditions. The study also investigated the release rate of the enzyme and the hydrogen-ion concentration (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 of the enteric-coated microsphere products released their enzymes in the pH range of 5.5 to 6.0.

Variation in effectiveness among various dosage forms also has been observed. Several studies in patients with severe pancreatic insufficiency and with cystic fibrosis indicate that the encapsulated enteric-coated microsphere dosage form of pancreatic enzymes has improved effectiveness over other formulations in treating pancreatic insufficiency (Refs. 5 through 9).

A number of studies that compared the lipase activity and effectiveness of various products also showed variations among encapsulated enteric-coated microsphere products from different manufacturers (Refs. 1, 4, 7, and 9). For example, an in vivo study of 19 cystic fibrosis patients that compared 1 tablet form product and 3 encapsulated enteric-coated microsphere form products showed fewer gastrointestinal symptoms and increased fat absorption with 2 of the encapsulated enteric-coated microsphere products. The tablet 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.

In its review, the agency reported that 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 have resulted in instances of underdosing and overdosing with pancreatic extracts. In one study reviewed by the agency, three patients whose pancreatic insufficiency had been controlled using one encapsulated enteric-coated microsphere dosage form experienced therapeutic failure when a similar product was substituted. The products were labeled as containing the same enzyme activity. Analyses of the products used in the study showed that most of the products contained greater lipase activity than labeled.

Review of the data identified other safety problems associated with the use of high doses of pancreatic extracts, for example, hyperuricosuria, hyperuricemia, obstipation, and intestinal obstruction. FDA has received several reports of intestinal stricture and blockage in cystic fibrosis patients using higher potency pancreatic enzymes in

delayed release microtablets and microspheres (Refs. 10 through 17).

In February 2001, FDA received correspondence from the Cystic Fibrosis Foundation reporting apparent therapeutic failures associated with the use of pancreatic enzymes when "generic" versions of the drug products were substituted for "brand name" products. The adverse events reported included abdominal pain, intestinal obstruction, increased incidence of steatorrhea, increased episodes of rectal prolapse, and increased number of stools. In view of the information provided, however, no direct link between the 14 cases of insufficient therapeutic effect and the substitution of pancrelipase products reported here can be established. No information on adherence to dose and dose regimen has been provided. Also lacking are data on the clinical severity of cystic fibrosis in these patients, which is known to vary widely. Even with good compliance, some patients may not respond promptly or well to the suggested low starting doses of the pancreatic enzymes. Further, no information was provided to demonstrate that the patients with an inadequate therapeutic effect of the substituted "generic" version were administered equivalent units of the "brand name" product. Nonetheless, the substitution of pancrelipase appears to be somehow involved and raises additional concerns that should be addressed by FDA's requirement for new drug approval (Ref. 18).

Based on a review of all available data, including the studies and adverse reports referenced above, FDA concluded that the safe and effective use of pancreatic enzyme drug products requires that the products be marketed by prescription only and that the products be approved through the new drug approval process to standardize enzyme activity. FDA determined that bioactivity must be shown to correlate with the stated potency of each product, particularly for newer formulations that include microspheres and high-potency levels of pancreatic enzymes.

III. Office Contacts

All communications in response to this notice should be directed to the appropriate office as follows:

Applications under section 505 of the act: Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266.

Citizen petitions (see § 10.30 (21 CFR 10.30)) contending that a particular drug product is not subject to the new drug

requirements of the act: Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Requests for an opinion on the applicability of this notice to a specific product: Division of New Drugs and Labeling Compliance (HFD-310), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Inquiries regarding procedures for obtaining approval of NDAs: Division of Gastrointestinal and Coagulation Drug Products (HFD-180), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7310.

Inquiries regarding procedures for obtaining approval of abbreviated new drug applications (ANDAs): Office of Generic Drugs (HFD-600), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

IV. Legal Status

Pancreatic enzyme drug products containing the ingredients pancreatin and pancrelipase are used as replacement therapy in conditions in which the exocrine secretions of the pancreas (principally, amylase, lipase, and protease) are either absent or deficient. The goal of therapy in pancreatic enzyme replacement is to control the consequences of exocrine pancreatic insufficiency, namely maldigestion and malabsorption of fats, protein, and carbohydrates and resulting nutritional deficiencies. Individualization of treatment is needed for optimal therapeutic effect (50 FR 46594 at 46597, November 8, 1985).

Various dosage forms of pancreatic enzyme drug products are currently marketed: Uncoated tablets, powders, capsules, enteric-coated tablets, and encapsulated enteric-coated microspheres. Significant variations in bioavailability have been shown both among the various dosage forms and among products from different manufacturers of the same dosage form. These variations in bioavailability can affect both safety and effectiveness of the products. Subpotent doses of pancreatic enzyme products may result in patients experiencing steatorrhea, malnutrition, and consequent nutritional deficiencies. High doses of these products have been associated with hyperuricosuria, hyperuricemia, and other severe complications such as colonic strictures and intestinal blockage in patients using high-potency dosage preparations.

Available data have shown that the formulation, dosage, and manufacturing process of pancreatic enzyme drug products have a critical effect on the safe and effective use of these drugs. The bioavailability of the enzymes present in these products depends on the process used to manufacture the drug products. Standardization of the enzyme bioactivity is necessary to avoid serious safety problems resulting from too little or too much supplementation.

FDA has approved an NDA for one pancreatic enzyme product (Cotazym, manufactured by Organon, Inc.). This product is not currently being marketed. No currently marketed pancreatic enzyme product has been shown to demonstrate consistent enzyme bioactivity that results in predictable safety and effectiveness. The approval of the NDA for Cotazym does not equate to general recognition of safety and effectiveness for pancreatic enzyme products as a class. Because bioactivity relates to product-specific formulation and manufacturing issues, each pancreatic enzyme product must be shown to be safe and effective based upon the specific characteristics of the drug product. Therefore, no currently marketed unapproved pancreatic enzyme drug product is generally recognized as safe and effective. Accordingly, pancreatic extract drug products used to treat exocrine pancreatic insufficiency are new drugs under section 201(p) of the act and are subject to the requirements of section 505 of the act. The submission of an NDA is necessary to provide FDA with information on the product's formulation, manufacture, quality control procedures, and the effectiveness of the marketed formulation to ensure, among other things, that a company has the ability to manufacture a consistently bioactive pancreatic enzyme formulation.

If a manufacturer of a pancreatic enzyme drug product contends that the particular drug product is not subject to the new drug requirements of the act, this claim should be submitted in the form of a citizen petition under § 10.30 and should be filed to Docket No. 2003N-0205 no later than June 28, 2004. Sixty days is the time allowed for such submissions in similar proceedings. (See § 314.200(c) and (e) (21 CFR 314.200(c) and (e).) Under § 10.30(e)(2), the agency will provide a response to each petitioner within 180 days of receipt of the petition. A citizen petition that contends that a particular drug product is not subject to the new drug requirements of the act should contain the quality and quantity of data and information set forth in § 314.200(e).

Note especially that a contention that a drug product is generally recognized as safe and effective within the meaning of section 201(p) of the act is to be supported by the same quantity and quality of scientific evidence that is required to obtain approval of an application for the product. (See § 314.200(e)(1).)

Conditions for Approval and Marketing

Manufacturers who wish to continue marketing pancreatin or pancrelipase drug products must submit applications as required by section 505 of the act and part 314 (21 CFR part 314). At this time, FDA expects to receive only NDAs, including section 505(b)(2) applications, for these products. For the reasons described below, the agency has determined that pancreatic extract drug products currently are not likely to be appropriate subjects for ANDAs.

For a pancrelipase or pancreatin product to be submitted as an ANDA, the proposed drug product would have to be shown to contain the same active ingredient(s) as an approved reference listed drug. Because of the complexity of pancreatic extract products, it is unlikely that currently available physiochemical and biological analytical tools would be able to demonstrate that the active ingredients in pancreatic extract products from two different manufacturers are the same. Therefore, the agency has concluded that manufacturers currently are unlikely to obtain approval of pancreatic extract products under section 505(j) of the act.

Manufacturers interested in submitting ANDAs for pancreatic extract products are strongly advised to contact the Office of Generic Drugs (HFD-600) (see section III of this document) to discuss the feasibility of such an application.

FDA discussed the requirements for approval of a full NDA in the July 1991 proposed rule (56 FR 32282 at 32283). An NDA must include adequate and well-controlled clinical studies of the product's effectiveness, i.e., 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 product. The studies need to comply with the requirements of part 314. An application must also include information on the drug product's formulation, manufacture, and quality control procedures to ensure that the applicant has the ability to manufacture a consistently bioactive formulation. Elsewhere in this issue of the **Federal**

Register, FDA is announcing the availability of a draft guidance for industry entitled "Exocrine Pancreatic Insufficiency Drug Products—Submitting NDAs." This draft guidance, when finalized, will aid sponsors of exocrine insufficiency drug products in submitting NDAs for the drug products.

Inquiries regarding procedures for obtaining approval of NDAs should be directed to the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) (see section III of this document).

Pancreatic enzyme products are medically necessary because they are used to treat exocrine pancreatic insufficiency, a condition in which symptoms are due to deficient secretion of pancreatic enzymes (i.e., lipase, protease, amylase) essential for normal digestion and absorption. Exocrine pancreatic insufficiency associated with cystic fibrosis, chronic pancreatitis, and other pancreatic diseases causes malabsorption and malabsorption of fats, protein, and carbohydrates, and poor absorption of fat-soluble vitamins, iron, folic acid, and other micronutrients. These nutritional deficiencies lead to steatorrhea, diarrhea, and malnutrition in cystic fibrosis and chronic pancreatitis, and also growth retardation in children, adolescents, and adults with cystic fibrosis. The severity of the conditions varies from patient to patient as does the dosage requirement of pancreatic enzyme replacement therapy needed to relieve the symptoms of pancreatic insufficiency. The dosage, including the relative amounts of enzymes (lipase for fat digestion, protease for protein digestion, and amylase for starch digestion), should be individualized for each patient and adjusted when clinically indicated. In recommended doses, pancreatic extracts are virtually free of adverse effects.

There are safety issues associated with the continued marketing of unapproved pancreatic enzyme products. As discussed previously in this document, there are safety problems associated with high doses of pancreatic extracts. The most common adverse effects are gastrointestinal in nature, specifically diarrhea, nausea, stomach cramps, or pain. Excessive doses of pancreatic extracts have been associated with hyperuricosuria, hyperuricemia, obstipation, and intestinal obstruction. It appears that these side effects have been addressed to some extent in the labeling for a number of the currently marketed products. Continuous physician monitoring is also recommended to help minimize these problems. Cases of intestinal stricture and obstruction have been observed in

one adult and one child without cystic fibrosis treated for prolonged periods with high concentrations of pancreatic enzymes. Intestinal stricture and obstruction have also been observed in children with cystic fibrosis treated with various concentrations of pancreatic enzymes or with pancreatic enzyme preparations containing high lipase concentrations. Whether there is a relationship between the use of these products and intestinal stricture needs further investigation.

Despite the risks associated with use of unapproved pancreatic enzyme products, no alternative drug is relied upon by the medical community to treat the lack of lipase, protease, and amylase caused by exocrine pancreatic insufficiency. Pancreatic enzyme supplements are a daily requirement for patients with exocrine pancreatic insufficiency and are needed for survival for many of these patients, e.g., cystic fibrosis patients.

To meet the needs of patients requiring pancreatic enzyme replacement therapy, pancreatic extract drug products in varying dosage forms, enzyme content, and activity are currently being marketed. According to FDA records, there are 23 manufacturers and 26 repackers/private label distributors marketing 38 formulations. Pancreatic enzyme products, including some of the currently marketed products, have been marketed for years. Only one product, Cotazym, sponsored by Organon, Inc., is the subject of an approved NDA and that product is not currently being marketed. However, there is a need for a range of products to remain available for patient use. The dosage requirements of patients vary, and the appropriate daily dose of pancreatic enzyme supplements must be individualized and adjusted when clinically indicated. Furthermore, physicians have identified and stabilized their patients on currently available products with different ratios of lipase, protease, and amylase that meet the patients' needs. Thus, to meet the dosing requirements and to maintain compliance with treatment, pancreatic supplements are needed with varied concentrations of lipase, protease, and amylase.

Accordingly, FDA will permit currently marketed pancreatic enzyme products to be marketed without approved applications until April 28, 2008, to give manufacturers time to conduct the required studies and to prepare and submit applications, and to allow time for review of and action on these applications. This provision for continuation of marketing, which applies only to pancreatic enzyme

products marketed on or before the publication of this document, is consistent with the order in *Hoffmann-LaRoche, Inc. v. Weinberger*, 425 F. Supp. 890 (D.D.C. 1975), as amended, reprinted in the **Federal Register** of September 22, 1975 (40 FR 43531), and March 2, 1976 (41 FR 9001), because pancreatic enzyme products are medically necessary drug products.

After April 28, 2008, any pancreatic enzyme drug product that is introduced or delivered for introduction into interstate commerce without an approved application will be subject to regulatory action, unless there has been a finding by FDA, under a citizen petition submitted for that product as described above, that the product is not subject to the new drug requirements of the act.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505 (21 U.S.C. 352, 355)) and under authority delegated to the Associate Commissioner for Policy and Planning (21 CFR 5.20).

V. References

The following references have been placed on display in the Division of Dockets Management (see the **ADDRESSES** section of this document) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Hendeles, L. et al., "Treatment Failure After Substitution of Generic Pancrelipase Capsules: Correlation with In Vitro Lipase Activity," *Journal of the American Medical Association*, 263:2459-2461, 1990.
2. Regan, P. T. et al., "Comparative Effects of Antacids, Cimetidine and Enteric Coating on the Therapeutic Response to Oral Enzymes in Severe Pancreatic Insufficiency," *New England Journal of Medicine*, 297:854-858, 1977.
3. Graham, D. Y., "Enzyme Replacement Therapy of Exocrine Pancreatic Insufficiency in Man: Relation Between In Vitro Enzyme Activities and In Vivo Potency in Commercial Pancreatic Extracts," *New England Journal of Medicine*, 296:1314-1317, 1977.
4. Fatmi, A. A. and J. A. Johnson, "An In Vitro Comparative Evaluation of Pancreatic Enzyme Preparations," *Drug Development and Industrial Pharmacy*, 14:1429-1438, 1988.
5. Graham, D. Y., "An Enteric-Coated Pancreatic Enzyme Preparation that Works," *Digestive Diseases and Sciences*, 24:906-909, 1979.
6. Mischler, E. H. et al., "Comparison of Effectiveness of Pancreatic Enzyme Preparations in Cystic Fibrosis," *American Journal of Diseases of Children*, 136:1060-1063, 1982.
7. Littlewood, J. M. et al., "In Vivo and In Vitro Studies of Microsphere Pancreatic Supplements," *Journal of Pediatric Gastroenterology and Nutrition*, 7 (Supplement 1):S22-S29, 1988.

8. Dutta, S. K., V. S. Hubbard, and M. Appler, "Critical Examination of Therapeutic Efficacy of a pH-Sensitive Enteric-Coated Pancreatic Enzyme Preparation in Treatment of Exocrine Pancreatic Insufficiency Secondary to Cystic Fibrosis," *Digestive Diseases and Sciences*, 33:1237-1244, 1988.

9. Beverley, D. W. et al., "Comparison of Four Pancreatic Extracts in Cystic Fibrosis," *Archives of Disease in Childhood*, 62:564-568, 1987.

10. Cystic Fibrosis Foundation Results of a Survey of 114 Cystic Fibrosis Care Centers in the United States, Patient Registry 1992 Annual Data Report, Bethesda, MD, October 1993, in OTC Vol. 17BFR, Docket No. 79N-0379, Division of Dockets Management.

11. Smyth, R. L. et al., "Strictures of Ascending Colon in Cystic Fibrosis and High-Strength Pancreatic Enzymes," *Lancet*, 343:85-86, 1994.

12. Oades, P. J. et al., "Letter to the Editor," *Lancet*, 343:109, 1994.

13. Campbell, C. A., J. Forrest, and C. Musgrove, "Letter to the Editor," *Lancet*, 343:109, 1994.

14. Briars, G. L. et al., "Letter to the Editor," *Lancet*, 343:600, 1994.

15. Mahony, M. J. and M. Corcoran, "Letter to the Editor," *Lancet*, 343:599-600, 1994.

16. Knabe, N. et al., "Letter to the Editor," *Lancet*, 343:1230, 1994.

17. Taylor, C. J., "Colonic Strictures in Cystic Fibrosis," *Lancet*, 343:615-616, 1994.

18. Letter dated February 14, 2001, from P. W. Campbell, III, Cystic Fibrosis Foundation, to L. Talarico, FDA.

Dated: April 5, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2003D-0206]

Draft Guidance for Industry on Exocrine Pancreatic Insufficiency Drug Products—Submitting New Drug Applications; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for

industry entitled "Exocrine Pancreatic Insufficiency Drug Products—Submitting NDAs." Elsewhere in this issue of the **Federal Register**, FDA is announcing that all exocrine pancreatic insufficiency drug products are new drugs requiring approved new drug applications (NDAs) for marketing. This draft guidance is intended to aid sponsors of exocrine insufficiency drug products in submitting NDAs for the drug products.

DATES: Submit written or electronic comments on the draft guidance by June 28, 2004. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the draft guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Monika Houstoun, Center for Drug Evaluation and Research (HFD-180), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7310.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Exocrine Pancreatic Insufficiency Drug Products—Submitting NDAs." Elsewhere in this issue of the **Federal Register**, FDA is announcing that all exocrine pancreatic insufficiency drug products are new drugs. The document states that manufacturers who wish to continue to market these products must submit applications as required by section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C.

355) and 21 CFR part 314. The document states that FDA is prepared to accept NDAs for these products, including applications submitted under section 505(b)(2) of the act. This draft guidance is intended to assist manufacturers of exocrine pancreatic insufficiency drug products in preparing and submitting documentation to meet NDA requirements for the drug products.

This level 1 draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the agency's current thinking on issues concerning applications, including applications under section 505(b)(2) of the act, for exocrine pancreatic insufficiency drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments on the draft guidance. Submit a single copy of electronic comments to <http://www.fda.gov/dockets/ecomments> or two paper copies of any written comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

III. Electronic Access

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/cder/guidance/index.htm> or <http://www.fda.gov/ohrms/dockets/default.htm>.

Dated: April 15, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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