Guidance for Industry

Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2006
Clinical/Medical

Guidance for Industry

Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs

Additional copies are available from:

Office of Training and Communications
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2006
Clinical/Medical

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1]
Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist manufacturers of exocrine pancreatic insufficiency drug products in preparing and submitting new drug applications (NDAs). On April 28, 2004 (69 FR 23410), the Food and Drug Administration (FDA) announced that all orally administered pancreatic enzyme products (PEPs) are new drugs that will be approved for prescription use only, and explained the conditions for continued marketing of these drug products. This guidance pertains to products that contain the ingredients pancreatin and pancrelipase; these ingredients, which are of animal origin, contain the following enzymes: lipases, proteases, and amylases. These enzymes break down fats (lipases), proteins (proteases), and carbohydrates (amylases) into elementary units of small size that can traverse the intestinal mucosa, incorporate into the blood stream, and work as sources of energy and building blocks of cells.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Pancreatic enzyme preparations of porcine or bovine origin have been available in the United States for the treatment of exocrine pancreatic insufficiency (EPI) in children and adults with cystic fibrosis (CF) and chronic pancreatitis (CP) since before the enactment of the Federal Food, Drug, and Cosmetic Act of 1938 (the Act). Under the Act, beginning in 1938, new drugs were

[1] This guidance has been prepared by the Division of Gastroenterology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

required to be the subject of approved NDAs. With the exception of one PEP approved in 1996, PEPs have been marketed without NDAs.

There are approximately 30,000 pediatric and adult patients with cystic fibrosis in the United States. Pediatric patients affected with cystic fibrosis and patients with chronic pancreatitis who have significant reduction of pancreatic function are unable to digest fats, proteins, and carbohydrates. As a consequence, the absorption of these nutrients is impaired, with the resultant malnutrition and a host of secondary complications, including retarded growth and development, impaired immune response, infections, and bleeding tendencies, among others.

In the *Federal Register* of November 8, 1985 (50 FR 46594), the FDA published a notice of proposed rulemaking to establish a monograph for over-the-counter (OTC) EPI drug products. The Agency accepted the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel) that EPI drug products be considered safe (generally recognized as safe (GRAS)) and effective (generally recognized as effective (GRAE)) and not misbranded.[2] Interested persons were invited to submit new data, written comments, objections, or requests for an oral hearing on the proposed rulemaking. Based on the information received, the FDA reconsidered the approach described in the November 8, 1985, proposed rulemaking and concluded that: (1) an OTC monograph would not be sufficient to adequately regulate these drug products; (2) preclearance of each product to standardize enzyme bioactivity would be necessary; and (3) because continuous physician monitoring of patients would be necessary as a collateral measure to ensure the safe and effective use of these products, such products should be available by prescription only. In the *Federal Register* of July 15, 1991 (56 FR 32282), the FDA withdrew the November 8, 1985, proposed rule and proposed a regulation to declare that OTC drug products used to treat EPI are not GRAS and GRAE and are misbranded. The final rule, which affected only OTC products, published on April 24, 1995 (60 FR 20162).

In the 1991 and 1995 proposed and final rules, the FDA discussed its review of the scientific data that provide the basis for the FDA's decision to require approval of PEPs through the new drug approval process under section 505 of the Act.

At this time, the FDA expects to receive only NDAs, including section 505(b)(2) applications, and not abbreviated new drug applications (ANDAs) for these products. For a pancrelipase or pancreatin product to be approved as an ANDA under section 505(j), the proposed drug product must be shown to contain the same active ingredients as an approved reference listed drug (21 CFR 314.92(a)(1)). 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 pancreatic extract drug products currently are not likely to be appropriate for ANDAs. Nonetheless, manufacturers with further questions about the feasibility of submitting ANDAs for pancreatic extract products are advised to contact the Office of Generic Drugs (HFD-600, Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855).

[2] For a discussion of the conditions for general recognition as safe, effective, and not misbranded, see 21 CFR 330.1.

If a sponsor markets or wishes to market more than one PEP, the number of NDAs it needs to submit will depend on the composition of the products. If the products vary by active ingredient (e.g., product 1: amylase and lipase; product 2: amylase and protease), then separate NDAs should be submitted. If the products vary only by potency ratios of the same active ingredients (e.g., product 1: amylase, 15,000 amylase units, lipase, 1,200 lipase units, and protease, 30,000 protease units, and product 2: amylase, 15,000 amylase units, lipase, 1,500 lipase units, and protease, 35,000 protease units), then separate NDAs need not be submitted. Different strengths or concentrations can be submitted in the same NDA.

III. CHEMISTRY, MANUFACTURING, AND CONTROLS SECTION OF THE APPLICATION

To be approved, an NDA must meet the requirements described in 21 CFR 314.50 regarding chemistry, manufacturing, and controls information. We recommend that applicants consult the FDA guideline *Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* and the guidance for industry *Submitting Documentation for the Manufacture of and Controls for Drug Products*.[3] We also recommend that applicants consult relevant International Conference on Harmonisation (ICH) guidance documents (e.g., Q1A, Q2A, Q2B, Q3C, Q5A, Q5C, and Q6B). The following sections describe additional information unique to PEPs that should be provided in NDAs or Drug Master Files.

A. Drug Substance

For the starting material used in the manufacturing process, information on animal species, tissue types, and countries of origin should be provided. Animals used should have been raised with the intent for use as human food. The source documentation should include animal origin, identification, and movement since birth; maintenance animal medical records; surveillance of herds; and documentation of feeds. Feeds should not contain any reprocessed animal products.

The manufacturing process should be validated for its capability to remove and/or inactivate viral agents as recommended in ICH Q5A.[4] A full viral risk assessment should be made and justified.

The drug substance should be adequately characterized using appropriate chemical, physical, and biological testing. Batch-to-batch consistency with respect to chemical identity, biological activity of different classes of enzymes including specific activity, identity, and purity level should be demonstrated. Purity can be evaluated by enzyme-specific activity. Identity can be demonstrated by fingerprint analysis, using (but not limited to) the following methods:

- Chromatography (e.g., ion-exchange or reversed phase high-pressure liquid chromatography (HPLC))

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[4] See ICH guidance for industry *Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin* (http://www.fda.gov/cder/guidance/index/htm).

- Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE)
- Isoelectric focusing (IEF)
- New analytical technologies, when appropriate

Nondrug substance-related impurities such as process-related impurities, inorganic impurities, and residual solvents should be controlled. Estimates of the amounts of inactive cell components and product-related impurities including inactive enzymes present in the drug substance should be made.

Specifications for the drug substance should include tests for identity, biological activity of different classes of enzymes, purity, and other relevant attributes. Appropriate acceptance factors (e.g., limits and ranges) should be established and justified for lipases, amylases, and proteases.

B. Drug Product

Specifications for the drug product should include tests for identity, biological activity of different classes of enzymes, degradants, dissolution, and other relevant attributes. Pancreatic enzymes from natural sources are a mixture of lipases, amylases, and proteases, which are present in varying proportions. Appropriate acceptance criteria should be established and justified for these enzymes. However, for purposes of labeling, product potency should be expressed as lipase activity. When a novel or non-novel, but noncompendial, excipient is included in the formulation of the drug product, manufacturing and control information on the excipient should be provided. Refer to related sections in ICH Q6B.[5]

C. Stability

Due to the inherent lability that has been observed with PEPs, stability data through 12 months at the recommended storage temperature as well as 3 months of accelerated stability data should be provided.

Additional stability data can be submitted as an amendment during the review process, and an expiration date will be determined based on the review of the stability data in the NDA.

Primary stability data should be generated according to the guidance developed in ICH Q1A and Q5C.[6] Primary stability studies should be performed with batches that are formulated to be released at 100 percent of the label-claimed potency for lipase.

Existing stability data not obtained under ICH conditions can be submitted as supporting data.

---

[5] See ICH guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (http://www.fda.gov/cder/guidance/index/htm).

[6] See ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* and ICH guideline for industry *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (http://www.fda.gov/cder/guidance/index/htm).

D. Overages

Since high doses of pancreatic enzymes have been associated with safety problems (see 69 FR 23411), the finished product should be formulated to 100 percent of the label-claimed lipase enzyme activity. With suitable justification (e.g., manufacturing losses), however, overages may be acceptable. Amylase and protease activity in the formulation should remain within justified limits.

E. Dissolution Method

An appropriate in vitro release test method should be developed.

IV. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SECTION

To be approved, an NDA must meet the requirements described in 21 CFR 314.50 for nonclinical and toxicology data.

A. Toxicology

No toxicology studies are needed if excipients are classified as GRAS for oral administration or are USP/NF compendial excipients and are present at levels previously found acceptable.[7] If the excipients are not classified as GRAS or have not been previously approved for the same route of administration, amount, or therapeutic use, safety should be established through toxicology studies. For new excipients without previous clinical data, clinical trials of the drug product containing the new excipients should also be performed. If the new excipients are classified as GRAS but are present in quantities in excess of the allowed levels, their safety should be established at the higher levels through toxicological studies of the excipients or the drug product containing the higher levels of the excipients. To determine their safety, the toxicology program for new excipients or for excipients with higher levels than listed for GRAS should supply data from long-term studies in both rodent and nonrodent mammalian species plus standard reproductive toxicity and genotoxicity information (Steinberg et al. 1996).[8] Information from published reports of toxicology studies should also be included in the NDA.

B. Pharmacology

Because of the extensive use of the currently marketed PEP products, no new pharmacology studies for such products are necessary. The FDA recommends that applicants summarize the published literature about the pharmacology of their particular PEP and submit this summary with the bibliography as part of a 505(b)(2) application. In addition, we encourage submission of all available nonclinical information including any pharmacological data generated with the drug substance and/or drug product.

---

[7] GRAS listings are included in 21 CFR parts 182 and 582 and are updated each year.

[8] See also the guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*. (http://www.fda.gov/cder/guidance/index.htm)

V. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION

To be approved, an NDA must meet the requirements in 21 CFR 314.50 for human pharmacokinetic and bioavailability information. The bioactivity and/or bioavailability of the active ingredients should be determined at the site of action (gastrointestinal tract). The lipase, amylase, and protease activities should be determined from aspirates from the stomach and duodenum. The data should be obtained under fasting conditions as well as after a standard meal stimulation.

The use of any inactive ingredient in the formulation to prevent or minimize the hydrolysis of the enzymes in the stomach should be supported with in vitro and/or in vivo release data. An appropriate in vitro release test method should be developed.

VI. CLINICAL STUDIES FOR PEP NDAS (SECTION 505(b))

To be approved, a PEP NDA must meet the requirements for clinical studies described in 21 CFR 314.50. The Agency has determined that there is a considerable body of evidence that replacement of pancreatic enzymes has clinical benefit for patients with cystic fibrosis and chronic pancreatitis (69 FR 23410). This section summarizes general approaches to the design of clinical studies intended to provide such evidence of effectiveness and safety in support of an NDA for currently marketed PEPs of animal origin. The discussion includes guidance on patient populations that should be studied, endpoints (outcome measures) to evaluate efficacy and safety, and suggestions for the design of clinical studies.

A. Considerations for Clinical Trial Development

Currently marketed PEPs differ in their composition, enzymatic activities, formulation, method of manufacture, stringency of quality control during manufacturing, stability, and bioavailability (i.e., bioactivity in the small intestine). These differences have led to highly variable PEP quality and therapeutic performance among manufacturers. For any given manufacturer, such differences over time can lead to batch-to-batch inconsistency and to unacceptable variability in PEP quality and therapeutic performance. With improvements in quality as outlined in the guidance, therapeutic performance may be better predicted from in vitro studies or from in situ measurements of PEP bioactivity in the small intestine.

For NDA approval of any particular PEP, clinical studies should demonstrate a relationship between the extent of clinical benefit and the amount of PEP administered (e.g., empirical demonstration of dose-response relationships in clinical trials).

NDAs filed under section 505(b)(2) of the Act may include published articles along with a bibliography of clinical trials in lieu of clinical data.

B. Patient Populations in Clinical Studies

Two distinct populations have the largest clinical need in practice for PEPs: (1) pediatric and adult patients with cystic fibrosis; and (2) adult patients with chronic pancreatitis. Both conditions can cause pancreatic insufficiency and maldigestion, leading to malabsorption of dietary nutrients and subsequent malnutrition. Different dosages of PEPs may be recommended to treat these two populations. ***At a minimum, because cystic fibrosis is primarily a pediatric disease, the efficacy studies in the NDA should include clinical studies in pediatric patients with cystic fibrosis.***

C. Endpoints (Outcome Measures) Efficacy

Although demonstrating a beneficial effect on clinical outcomes is desirable in clinical trials (e.g., weight gain or nutritional status), efficacy can also be demonstrated by showing a meaningful beneficial effect on appropriate pharmacodynamic measures such as steatorrhea. Some examples are provided here:

- Demonstration that administration of the PEP to patients with exocrine pancreatic insufficiency causes a meaningful decrease in stool fat as evaluated in a 72-hour quantitative stool collection

- Demonstration that administration of the PEP to patients with exocrine pancreatic insufficiency causes significantly more responders than in a comparison group (e.g., stool fat originally higher than 14 g/day decreased to less than 7 g/day)

- Demonstration that administration of the PEP to patients with exocrine pancreatic insufficiency causes significantly fewer patients to withdraw from blinded therapy because of steatorrhea than in a comparison group

- Other quantitative endpoints can be considered

D. Safety

Safety variables that should be assessed in clinical trials with PEPs include symptoms and signs of malabsorption, such as manifestations of steatorrhea; complaints of bloating; flatus; abdominal pain; loose and frequent stools; overt diarrhea; blood in the stool; and uric acid elevations.

With regard to safety, we note that the etiology of fibrosing colonopathy has not been completely elucidated. In an effort to minimize development of fibrosing colonopathy that has been assumed to be related to high doses of PEPS, the FDA, in conjunction with the Cystic Fibrosis Foundation (CFF), recommends a starting dose of 500 to 1,000 lipase units /Kg/meal with titration to less than 2,500 units/Kg/meal or less than 4,000 lipase units/g fat/day (FitzSimmons et al., 1997; Borowitz et al., 2002). Doses in excess of 2,500 USP lipase units/Kg/meal should be used with caution and only if their benefit is documented by 3-day fecal fat. Doses in excess of 6,000 USP lipase units/Kg/meal have been associated with fibrosing colonopathy. This

dosing recommendation, applicable to any formulation, was made on the basis of concern over dose-related colonic strictures in cystic fibrosis and the likelihood that maximal efficacy is achieved at the recommended ceiling dose of 2,500 USP lipase units/Kg/meal.

E. Design

The clinical studies confirming efficacy of the specific PEP can be: (1) parallel; (2) randomized withdrawal; or (3) crossover designs. The designs of these studies for PEP products are discussed below. Other designs, such as those in which patients are challenged with increases in dietary fat, can also be considered.

The clinical studies confirming efficacy of the specific PEP should include appropriate controls, such as dose-comparison controls, or active treatment controls. Placebo may be appropriate with a rescue protocol to protect patients. As noted in the following sections, if a placebo is not used (such as in a comparison of two doses of a PEP, or in a comparison of one PEP with another (e.g., an active control)), differences between treatments should be demonstrated to help interpret results. If desired, the efficacy and dose response of the PEP can be demonstrated in the same study.

Duration of the entire trial could be days to 2 to 3 weeks, depending on the design chosen. Blinding and randomization are recommended to reduce bias. Diets may need to be standardized. The total number of patients in the study can be between 10 and 25, depending on study design. Either two studies or one adequate and well-controlled clinical investigation and confirmatory evidence may be appropriate.

1. Parallel Studies

Parallel studies can be used to demonstrate efficacy of a PEP, such as when the effects of the PEP are compared to other doses of a PEP and/or to another active product (such as another PEP) or placebo.

2. Randomized Withdrawal

A randomized withdrawal study should have two phases: a run-in phase and a randomized withdrawal phase. In the run-in phase, patients should be administered the PEP under study and the dose should be adjusted (e.g., titrated) to achieve and stabilize at the desired clinical outcome (e.g., control of stool fat excretion). An open-label design is appropriate for this phase. In the next phase (the withdrawal phase), patients who have apparently responded to the PEP should then be randomized in a double-blind fashion to either continued treatment with the PEP or, as is typical, to placebo. At the end of the withdrawal phase the effects of the two treatments should be compared. For example, the primary efficacy endpoint could be a quantitative measure of stool fat over 72 hours (e.g., the mean change in stool fat or the number of nonresponders who have recurrent steatorrhea). In some cases at the outset of the randomized withdrawal period, it may be desirable to discontinue treatment gradually to avoid sudden onset of symptoms of pancreatic insufficiency.

Patients should be monitored even during the withdrawal phase to allow discontinuation from randomized study treatment if clinically appropriate (e.g., for clinically worrisome diarrhea). Patients who discontinue study treatment can then be given appropriate medical therapies. If prespecified in the protocol, a count of these treatment failures (nonresponders) can be incorporated into the primary efficacy analysis. In such cases, the protocol should define specific discontinuation criteria for patients who fail treatment.

A randomized withdrawal design also can be adapted to incorporate a dose-response evaluation of a PEP. At the outset of the withdrawal phase, for example, patients can be randomized to placebo and to two or more dosage levels of a PEP. The response of patients at the different dosage levels (including placebo) can then be compared. Although inclusion of a placebo arm is often the most usual and straightforward way of demonstrating efficacy, this arm can sometimes be excluded.

3. Crossover Studies

In a crossover study, each patient in the study is treated with all or most of the treatments under investigation, usually in a randomized sequence.

A crossover study allows for a paired statistical analysis of the data (i.e., each patient serves as his or her own control), thereby decreasing the effects of interpatient variability, which otherwise might obscure true drug effects. In general, fewer patients are needed to perform a crossover study than a parallel study. However, because each patient is administered several treatments, each patient's study involvement is longer than in a parallel study. Moreover, sponsors are strongly cautioned that if baseline conditions are not reestablished between treatment periods, or if treatment in one period carries over into the subsequent period or periods, the results likely will not be interpretable using a paired statistical analysis. Although data from the first period could still be analyzed as in a parallel study (unpaired statistical analysis), the main advantage of using a crossover design would have been lost.

In a randomized, two-period, placebo-controlled, crossover study of a PEP, for example, patients should first be stabilized on existing therapy to establish baseline conditions. Patients should then be randomized to receive one of two treatment sequences: placebo-PEP versus PEP-placebo. If quantitative determination of stool fat is used as the primary endpoint, each period should last at least 72 hours to allow for adequate collection of stool specimens. Reestablishment of baseline conditions should be documented between periods.

VII. PEDIATRIC STUDIES FOR PEPS

A significant portion of the target population for PEPs includes pediatric patients with cystic fibrosis, a congenital genetic disease in which there is chronic exocrine pancreatic insufficiency dating from birth. These patients represent the majority of pediatric patients with exocrine pancreatic insufficiency. At the time of publication of this guidance, the only PEP approved for use in pediatric cystic fibrosis patients is an immediate-release formulation, and that product is not currently marketed.

To comply with the Pediatric Research Equity Act of 2003 (PREA) (21 U.S.C. 355c), the application must contain data that are adequate to assess the safety and effectiveness of the PEP for the claimed indications in each of the appropriate pediatric subgroups (newborns, infants, children, and adolescents). The data should be adequate to support dosing and administration in each pediatric subpopulation for which the drug has been assessed to be safe and effective. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Whether or not pediatric studies in more than one age group are necessary depends on expected therapeutic benefit and use in each age group, and on whether safety and effectiveness data from one age group can be extrapolated to other age groups. As with the use of adult data, the extrapolation can be supplemented with data to define dosing and safety for the relevant age groups. Because solid dosage forms of PEPs cannot be swallowed by young pediatric patients (i.e., generally six years of age or younger), under PREA, sponsors must attempt to develop age-appropriate formulations for this patient population.

REFERENCES

Beverley, DW, J Kelleher, A MacDonald, JM Littlewood, T Robinson, and MP Walters, 1987, Comparison of Four Pancreatic Extracts in Cystic Fibrosis, *Archives of Disease in Childhood*, 62:564-568.

Borowitz, D, RD Baker, and V Stallings, 2002, Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis, *Journal of Pediatric Gastroenterology and Nutrition*, 35:246-259.

Briars, GL, DM Griffiths, IE Moore, PH Williams, K Johnson, and CJ Rolles, 1994, Letter to the Editor, *Lancet*, 343:600.

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

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

Dutta, SK, VS Hubbard, and M Appler, 1988, 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.

Fatmi, AA and JA Johnson, 1988, An In Vitro Comparative Evaluation of Pancreatic Enzyme Preparations, *Drug Development and Industrial Pharmacy*, 14:1429-1438.

FitzSimmons, SC, GA Burkhart, D Borowitz et al., 1997, High-Dose Pancreatic Enzyme Supplements and Fibrosing Colonopathy in Children with Cystic Fibrosis, *New England Journal of Medicine*, 336:1283-1289.

Graham, DY, 1979, An Enteric-Coated Pancreatic Enzyme Preparation that Works, *Digestive Diseases and Sciences*, 24:906-909.

Graham, DY, 1977, 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.

Hendeles, L, A Dorf, A Stecenko, and M Weinberger, 1990, Treatment Failure After Substitution of Generic Pancrelipase Capsules: Correlation with In Vitro Lipase Activity, *Journal of the American Medical Association*, 263:2459-2461.

Knabe, N, M Zak, A Hansen, J Moesgaard, N Kvist et al., 1994, Letter to the Editor, *Lancet*, 343:1230.

Littlewood, JM, J Kelleher, MP Walters, and AW Johnson, 1988, In Vivo and In Vitro Studies of Microsphere Pancreatic Supplements, *Journal of Pediatric Gastroenterology and Nutrition*, 7 (Supplement 1):S22-S29.

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

Mischler, EH, S Parrell, PM Farrell, and GB Odell, 1982, Comparison of Effectiveness of Pancreatic Enzyme Preparations in Cystic Fibrosis, *American Journal of Diseases of Children*, 136:1060-1063.

Oades, PJ, A Bush, PS Ong, and RJ Brereton, 1994, Letter to the Editor, *Lancet*, 343:109.

Regan, PT, JR Malagelada, EP DiMagno, SL Glanzman, and VL Go, 1977, 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.

Smyth, RL, D van Velzen, A Smyth, DA Lloyd, and DP Heaf, 1994, Strictures of Ascending Colon in Cystic Fibrosis and High-Strength Pancreatic Enzymes, *Lancet*, 343:85-86.

Steinberg, M, JF Borzelleca, EK Enters, FK Kinoshita, A Loper, et al., 1996, A New Approach to the Safety Assessment of Pharmaceutical Excipients, *Regul. Toxicol. Pharmacol.*, 24:149-154.

Taylor, CJ, 1994, Colonic Strictures in Cystic Fibrosis, *Lancet*, 343:615-616.