



THE SUPPLEMENT

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ENZYME REPLACEMENT THERAPY AND CYSTIC FIBROSIS

Pancreatic enzyme replacement therapy (PERT) has played a pivotal role in the care of persons with CF since the disease was first identified. The original pancreatic enzyme products (PEPs) were developed to treat all types of exocrine pancreatic insufficiency, including pancreatitis, pancreatic tumors, or CF. Enteric-coated enzymes were launched in 1978 and were an important breakthrough in PERT. Other than developing enteric-coating, few changes have been made in the form of PEPs. Until recently PEPs did not require FDA approval, thus leading to the development of many name brand, over-the-counter, and generic forms of PEPs. In 1995, the FDA first announced that it would require manufacturers to obtain approval prior to marketing PEPs. [1] This issue of The Supplement focuses on the FDA guidance for industry for new drug applications (NDA's) for PEPs. [2]

FEATURED PAPERS:

Overfilling in current pancreatic enzyme preparations (PEPs): Still an unresolved issue. Anelli M, Foresti R, Peloso L, Orteni G. *Pediatr Pulm (Suppl 30)*. Oct; 2007. Objective: To compare actual vs. label-claim of 16 commercial PEPs. **Methods:** Using United States Pharmacopeia (USP) methodology, lipase activity was determined in 16 commercially available PEPs. Average age of tested products was 10 to 12 months old. **Results:** 1.) No finished product was formulated to 100% of the label-claimed lipase enzyme activity; 2.) Overfill ranged from 7% to 47%, with a median of 32%. **Conclusions:** There is wide variability in actual vs. label-claimed lipase activity in PEPs.

Enzyme content and acid stability of enteric-coated pancreatic enzyme products in vitro. Case CL, Henniges F, Barkin JS. *Pancreas*. Mar;30(2):180-3, 2005. Objective: To evaluate the enzyme content and dissolution of various PEPs. **Methods:** Using USP methodology, the enzyme content and dissolution of 9 commercially available PEPs was tested.

Results: The lipase, protease, and amylase content was within USP guidelines, but the total content of the three enzymes did not meet label claim. Amylase content ranged from 129% to 216%; protease content 102% to 192%; and lipase 97% to 139% of label claim. Lipase activity following dissolution varied among products from not dissolving to 138% of label claim. **Conclusions:** Differences in enzyme content vs label claim and dissolution activity may be clinically relevant.

Pancreatin preparations used in the treatment of cystic fibrosis-lipase content and in vitro release.

Walters MP, Littlewood JM. *Aliment Pharmacol Ther*. Jun;10(3):433-40, 1996. Objective: To identify factors leading to variable clinical response to PERT.

Methods: The lipase content and resistance to simulated gastric emptying were investigated in 6 commercially available PEPs. **Results:** Lipase content of all PEPs exceeded amount declared on the labels. All PEPs were acid resistant. Enzyme release rates were variable and dependent on pH. **Conclusions:** Results indicate reasons for variable clinical response among patients. A trial of a different PEP may show improvement in patients symptomatic on their current product.

SPECIAL POINTS OF INTEREST:

- Until recently pancreatic enzyme products (PEPs) did not require FDA approval . . .
- In 1995, the FDA first announced that it would require manufacturers to obtain approval prior to marketing PEPs.
- There is wide variability in actual versus label claimed activity in PEPs.

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REVIEW

Pancreatic extracts have been available since the early 1930's. [3] Andersen described the need for diet modification and the use of pancreatin in her early papers. [4] The form of PEP available for persons who had CF was not very effective and in an attempt to reduce the symptoms of fat malabsorption patients were maintained on fat-restricted diets. [5] Although Harris et al. [6] published one of the first papers describing the importance of nutrition and PERT in CF, patients continued to be prescribed low fat diets well into the 1970s. In the 1970's patients at the Hospital for Sick Children in Toronto were encouraged to eat diets containing liberal amounts of fat. They also were instructed to take sufficient PEP to reduce symptoms of malabsorption, which was often up to 100 pills daily. [7] The impact of the liberal fat diet was monumental and described in the landmark paper by Corey et al. [8]

As noted by Littlewood [9] "Pancreatic enzymes up to the end of the seventies were crude, impure and inefficient and were regarded more as a food supplement than a drug." It was in the late seventies that acid resistant microspheres (Pancrease®) became available. Their marked superiority, when compared to nonenteric-coated enzymes was noted in several papers. [10,11] Since the 1970's, other than the addition of bicarbonate to one brand (Pancreacarb®), there has been little change in PEP formulation. A number of papers provide data describing the enzyme content and solubility of various PEPs. [12, Anelli, Case, Walter] The overall evidence is that the actual enzyme content (lipase, protease, and amylase) of the products does not reflect label claims and that solubility varies among products. Currently, PEPs must contain 90% of the label claim at the time of expiration, but there is no upper limit for enzyme content. Therefore, to meet the mandate, manufacturers overfill their products so that with deterioration over time the product will contain 90% of the label claim at expiration. A newly manufactured PEP may contain more lipase, amylase, and protease per dose than the label states. Older PEPs, near the expiration date, may contain any amount of enzyme activity from overage down to 90% of label claim. [13]

In the 1990's, pharmaceutical companies launched "high lipase enzymes." [14] The complication of fibrosing colonopathy, rarely seen prior to the availability of the high lipase products, was reported. As a result, the CF Foundation (CFF) convened a consensus committee to address the new complication and provide recommendations for PERT. [15] High lipase enzymes are no longer available in the United States.

The combination of unreliable product content and fibrosing colonopathy led the FDA to reconsider how it manages PEPs. PEPs have been available in the US prior to the enactment of the Federal Food, Drug, and Cosmetic Act of 1938. The "Act" required that all drugs developed after its enactment submit to the New Drug Application process. Because PEPs were available prior to 1938, they received "grandfathered" approval and were included in the GRAS (generally accepted as safe) and GRAE (generally recognized as effective) listing. Enteric-coated products developed in the late 1970s fell under the same "grandfathering."

In 1995 the FDA announced that PEPs are new drugs and companies manufacturing the products must submit NDAs. [1] The guidance for industry became available in 2006. The guidance is available for review at the FDA website. [2] In 1996, prior to the guidance publication, one company received NDA approval. [16] The approved products no longer are available in the United States. The original NDA submission deadline of April 2008, using the guidance for industry, recently was extended to April 2010. [17] The FDA guidance for NDA is specific and detailed, in general it stipulates: **1. Chemistry, manufacturing, and controls.** Manufacturers must maintain documentation as to the source materials used in production, including the animal source of enzyme. The drug substance must contain batch-to-batch consistency. PEPs must be formulated to be stable at 100% of label claim for lipase for at least 12 months from the date of manufacture. **2. Nonclinical pharmacology and toxicology.** New pharmacology studies will not be required. Toxicology studies are not required if excipients are classified as GRAS. **3. Human pharmacokinetics and bioavailability.** Human studies are required to test the bioactivity and bioavailability of the active ingredients in the gastrointestinal track. **4. Clinical studies.** Manufacturers must undertake clinical studies which demonstrate the relationship of clinical benefit to the amount of PEP administered, include pediatric patients in the studies, have meaningful measures of outcome, assess safety variables, and use clinical design that is scientifically sound. **5. Pediatric studies.** The study design must comply with the Pediatric Equity Act of 2003 [18] and include children. All pediatric ages need not be included if there is sufficient evidence to indicate that results from one age group can be extrapolated to another age group. The guidance also includes recommendation for the development of an appropriate in vitro release test methodology for a better understanding of dissolution and the role of inactive ingredients, which prevent or minimize hydrolysis of the enzymes.

CLINICAL APPLICATIONS

As we strive to provide evidence-based care, the review of past and current research describing efficacy of PERT becomes important. In its guidance to industry the FDA [2] identified areas of PERT lacking sufficient scientific evidence. The pharmaceutical industry was directed to undertake specific research related to PEPs. The results of the research will provide evidence that should lead to better care for pancreatic insufficient CF patients.

CF patients and healthcare providers have assumed that the content of PEPs is reliable. Variations in enzyme content can alter therapeutic effect and impact overall health status. Current manufacturing techniques regarding dose content makes optimal dosing difficult since the enzyme content of the dose may not match the label claim. PEPs fresh from the manufacturer may contain significantly more active enzyme compared to a product close to its expiration date. To date none of the PEPs currently available in the US meet FDA standards. The extension of the FDA deadline to 2010 indicates that PEPs may not be standardized for some time.

As new products do start to become available the RD may find it necessary to readjust patients' enzyme product and dose. In the meantime the RD must: 1. Be aware of the FDA regulations; 2. Understand the impact of product age, handling, and storage on overall enzyme content; 3. Consider these variables if patient reports change in enzyme effectiveness; 4. Know

**PEPS FRESH FROM THE MANUFACTURER
MAY CONTAIN SIGNIFICANTLY MORE
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CLOSE TO ITS EXPIRATION DATE.**

when currently available PEPs are replaced with FDA approved products. 5. Consider patient's genetic profile, age, medical status, usual diet, and adherence in prescribing PERT; 6. Utilize PERT educational materials available through PORTCF and/or pharmaceutical companies; 7. Encourage patients to participate in PERT research designed to meet FDA standards.

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