Published in final edited form as:

Am J Gastroenterol. 2014 May ; 109(5): 624–625. doi:10.1038/ajg.2013.430.

The FDA and Prescription Pancreatic Enzyme Product Cost

Timothy B. Gardner, MD MS, Jeffrey C. Munson, MD, and Nancy E. Morden, MD

The Dartmouth Institute for Health Policy and Clinical Practice, Hanover, NH and the Geisel School of Medicine at Dartmouth, Hanover, NH

In 2008, new Food and Drug Administration (FDA) requirements curtailed the marketing of pancreatic enzyme products (PEPs) by establishing new quality standards for their use in the United States; this revision comes at a price. The outcome raises issues about optimal means of retroactively regulating widely-used products predating the FDA.

In 1938, the Food, Drug and Cosmetic Act mandated that new drugs undergo a formal review process to ensure drug quality and standardization; as PEPs were not new, they were not subject to the approval process.¹ PEPs are complex, porcine-derived medications containing mixtures of lipases, proteases and amylases. They are used to treat symptoms of exocrine pancreatic insufficiency resulting from cystic fibrosis, total or partial pancreatectomy, and chronic pancreatitis.² In the early 2000's, prompted by reported product interchange failures, a rise in over-the counter PEPs which were not generally recognized as safe and effective, and pressure from patient advocacy groups, the FDA reviewed PEPs and found wide quality variability.^{3,4} As a result, the FDA mandated that PEPs undergo a formal new drug application (NDA) process. A guide issued in 2006 described the safety, efficacy and quality requirements PEP manufacturers would have to meet for approval by 2009.²

Prior to the NDA requirement, there were approximately 25 different prescription enzyme formulations available with varying dosages of lipase, protease and amylase. However, because the FDA approval process required the conduct of prospective clinical trials to ensure manufacturing standardization and clinical effectiveness, most manufacturers opted not to pursue approval.¹ In May 2013, there were only six FDA approved PEPs.²

Given the expense of conducting the prospective clinical trials and marketing new formulations, in the context of reduced market competition, we hypothesized that an unintended consequence of FDA regulation may have been an increase in prescription costs and a decrease in patient prescription access. We used IMS Health data to calculate the annual total number of prescriptions and sales (U.S. Dollars) for PEPs.⁵ The IMS Health Product Report 5.0 database tracks pharmaceutical sales records in the United States and is a leading source of economic indicators for the pharmaceutical industry. We studied years 2008 through 2012, a timeframe encompassing the FDA action and industry response. The cost per prescription was calculated by dividing total prescriptions by total annual sales.

Since 2008, total PEP prescriptions and the cost per PEP prescription have risen (Figure 1). In 2008, PEP sales from prescriptions totaled \$282 million; by 2012 this had increased to \$675 million (up 240%) while total prescription volume changed little. Figure 2 illustrates

the inverse relationship between the cost per PEP prescription (\$259 in 2008 vs. \$582 in 2012) and the number of marketed PEP products.

With dramatically increased costs per prescription and decreased market competition, did the NDA requirement satisfy the goal of patient advocacy groups in “making enzymes better?”⁶ From the perspective of the FDA, PEP clinical efficacy has been proven and individual products standardized. From the manufacturer’s perspective, the NDA process was either a boon or a loss. Manufacturers that conducted trials have benefited financially due to the universal prescription price increases.

From the individual patient perspective, it is difficult to quantify the effect of this FDA regulation. Certainly, having access to consistent and effective PEP formulations should be beneficial and evoke confidence in the products. However, the clinical efficacy studies upon which the approvals were based were of short duration and had small numbers of participants; each evaluated just one PEP formulation.¹ Because the FDA did not require studies of comparative efficacy between formulations, the NDA process did not directly answer the principal motivating question of PEP therapeutic interchangeability; the individual patient is likely no closer to determining the most effective PEP, and is now paying twice the previous price for the each PEP prescription. Based on national prescription volume, we see no change in the total annual prescriptions fills over this timeframe, suggesting access was not affected – see Figure 1. However, a price-induced shift to smaller dispensings (e.g. a shift from 90 day supply to 30 day supply) would not be noted in this simple count of fills and seems probable for un- and underinsured patients.

Was the NDA PEP approval process worthwhile? Unfortunately, the answer is not clear. While measuring the direct economic impact of this regulatory action is relatively straightforward, there is no simple method to assess the impact of this action on quality and length of life for PEP users. Without such an evaluation, we cannot know the value of the NDA requirement from the patient or societal perspective. If the safeguards, such as patient assistance programs, prove insufficient it seems certain a substantial number of patients will reduce their use of PEPs in response to the increased financial barriers. For some this “cost” may seem acceptable in exchange for predictable products; others will disagree, especially those negatively affected.

Could we have found another path to standardization and quality assurance? Therapeutic interchangeability may have been established without time and cost-intensive prospective randomized trials. Quality and uniformity tests of individual formulations might have been sufficient. By subjecting each product to rigorous content and uniformity analysis, the purity and consistency of each individual PEP may have been determined. The ability of physiochemical and biological analytical tools to demonstrate similarity between active ingredients from two different manufacturers is limited, but individual product testing likely would have sufficed to assure consistency and purity.² Enzyme products not meeting pre-established quality standards could then have been required to complete clinical trials.

Since long term outcomes studies are unlikely to be conducted, we may never have full accounting of the value of this intervention - the balance of benefit and cost. There is

precedent for compromising affordability for known efficacy of drugs long viewed as safe and effective, but that does not mean that such decisions should be repeated.⁷ As the nation continues to wrestle with recognition of finite health care dollars, such tradeoffs deserve careful consideration. Alternative approaches that balance industry incentive and national interest must be pursued.

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What is current knowledge?

- Marketing of pancreatic enzyme products (PEP) required FDA NDA approval in 2009
- The effect of this intervention on PEP cost and access is not known

What is new here?

- The FDA NDA requirement resulted in a dramatic increase in the cost per PEP prescription

Figure 1.
Total U.S. sales and number of prescriptions of pancreatic enzyme products (PEPs) from 2008-2012 in the United States. The FDA requirement for NDA was implemented in 2009.

Figure 2.

Cost per prescription (U.S. Dollars) and number of pancreatic enzyme products (PEPs) marketed in the United States from 2008-12. The FDA requirement for NDA was implemented in 2009. Marketed PEPs were included if total U.S. sales were >100 prescriptions per year.