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June 28th, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry – Exocrine Pancreatic Insufficiency Drug
Products – Submitting NDAs: Docket N. 2003D – 0206

Dear Sir/Madam:

In accordance with Docket N. 2003D-0206, KV Pharmaceutical Company is herein providing comments related to the above referenced draft guidance document. We hope these comments will be helpful in designing the final guidance.

The proposed guidance document is intended to provide guidance to industry on the requirements for submission of an NDA in support of exocrine pancreatic drug products. While the guidance clearly lays out the rationale requiring industry to submit a new drug application for exocrine pancreatic products, KV Pharmaceutical Company believes that the origin of the active ingredient may prevent many of the guidance's requirements from being met.

Animal derived pancreatic enzyme concentrate is extracted from porcine pancreatic tissue. The material contains many different compounds of which the enzymes amylase, protease and lipase are considered the principal pancreatic compounds for therapeutic use. Lipase is considered the most important enzyme in the extract because lipase deficiency is the most significant clinical factor in patients with exocrine pancreatic insufficiency.¹ Consequently, the activity grade of the raw pancreatic extract is based primarily on the lipase potency followed by the relative amounts of amylase and protease activities.

Out of the 3 main enzymes, protease is the most stable and is subject to very little (if any) degradation and lipase is the most sensitive to denaturing, followed by amylase. There have been various published reports describing the degree of lipase degradation and loss of activity, whether by physical property changes like

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freezing, or because of the proteolytic effect of proteases or other factors that destabilize lipase. These rates of loss of activity vary between 20 and 80%.^{2,3} In addition, lipase undergoes destabilization in the gastrointestinal tract^{4,5}

Lines 154 through 156 of the draft guidance document state ***“Primary stability studies should be performed with batches that are formulated to be released at 100 percent of the label-claimed potency. The proposed shelf life should not depend on the existence of a stability overage”.***

Modern therapeutic concepts recommend administration of 25,000 to 40,000 IU lipase per meal⁶. With the loss of activity expected during the extraction and purification process, manufacturers supply pancreatic enzyme with specifications to ensure that minimum label claims are met, especially for lipase, which is the most clinically relevant but also the most susceptible to degradation.

Manufacturers set their potency claims according to what the minimum effective clinical dose expectation is and through tests of degradation percentage, have been able to determine what overage is necessary to guarantee a raw material that the industry can rely on to meet 100% of the minimum label claim.

Lines 162 through 165 of the draft guidance document state ***“The finished product should be formulated to be released at 100 percent of the label-claimed potency to reflect accurate labeling, to reduce batch-to-batch variability in potency and to reduce the amount of accumulated degradants in the product. As a result, patients will at no time receive a much higher or lower dose than intended, a possible safety concern.”*** Degradation of lipase activity does not stop immediately after extraction and purification and in fact has been shown to continue for many weeks.^{3,4} Hence, formulation at 100% of the label claim could result in products having below label doses of lipase.

Furthermore, trying to analyze all biologic materials (and particularly the subject of this guidance) with the same tools used to measure synthetic chemical compounds, and then to hold them to the same standards of precise reproducibility is confusing biologic variability with manufacturing quality control. The variability in the USP assay methodology alone for lipase, amylase and protease in a formulation that meets 100% of the label claim might fail batches.

Lines 164 through 165 of the draft guidance document state in part ***“As a result, patients will at no time receive a much higher or lower dose than intended, a possible safety concern.”*** KV Pharmaceutical Company has taken steps to ensure that the fullest possible therapeutic benefit is offered to patients with exocrine pancreatic insufficiency to reduce or eliminate symptoms by producing a product that it can confidently guarantee a minimum lipase potency. The only way to make that guarantee to the prescribing physicians and patients, is to formulate with an overage.

Simulated physiologic lipase concentrations triple from about 600,000 IU/L to 1.8m IU/L following a cholecystokinin stimulation test⁷. Typical doses of pancreatic enzyme products for exocrine insufficiency are between 2 and 4

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capsules per meal or 40,000 to 80,000 IU lipase per meal. For cystic fibrosis patients, it has been recommended to take 1500 to 3000 IU per kg per meal.

For a 70 kg male, this would translate into about 200,000 IU/meal – still substantially below the stimulated physiologic level in a healthy volunteer.

The draft guidance notice describes isolated case reports of colonic strictures as well as 15 cases of colonopathy from 114 cystic fibrosis centers in the United States⁸. All had taken between 6,700 and 29,100 IU per kg per meal and another study published two years later was able to demonstrate in nine cystic fibrosis patients with fibrosing colonopathy, taking at least 6000 IU/kg per meal, were able to reduce their lipase intake to 2000 IU/kg per meal and maintain satisfactory nutrient absorption⁹. Furthermore, a study from the Research Institute, Hospital for Sick Children in Toronto¹⁰ demonstrated antibodies to porcine trypsin associated with very high dose pancreatic enzyme supplementation in 14 children, suggesting that an immune mediated mechanism may be responsible for this severe complication of very high dose therapy.

Whatever the pathogenesis of fibrosing colonopathy is, it is clear that it appears to only be associated with individuals in whom very high doses of the pancreatic enzyme was used, and that the safety concern related to overages of 3200 IU to 8000 IU per capsule to ensure a minimum 8000 IU to 20,000 lipase content are extremely unlikely to pose any safety concerns for this serious complication raised by the agency. In the approximately 70 million capsules of our pancreatic enzyme product, to the best of our information and belief we have not received any reports of fibrosing colonopathy.

While we recognize the need for the agency to require all companies who wish to continue to market their pancreatic enzyme products to submit a new drug application, KV is very concerned about many of the provisions of the guidance document that would in effect result in the undeserved removal of these products from the market that serve the needs of a very challenging medical condition.

We therefore respectfully request that the FDA reconsider its position with respect to formulation methodologies that are created to ensure minimum label claim doses by the use of consistent overages that are in accordance with internal and published data supporting lipase activity and safety of the products.

Sincerely,



Herbert G. Luther, Ph.D.

Vice President, Clinical and Regulatory Affairs
KV Pharmaceutical Company

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