



SOLVAY PHARMACEUTICALS

24 June 2004

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

RE: **Federal Register April 28, 2004 (Volume 69, Number 82)
Docket Number 2003D-0206 "Draft Guidance for Industry on Exocrine
Pancreatic Insufficiency Drug Products- Submitting New Drug
Applications (NDAs)"**

Dear Dockets Management:

Reference is made to the 28 April 2004 Federal Register notice containing Docket No. 2003D-0206 entitled "Draft Guidance for Industry on Exocrine Pancreatic Insufficiency Drug Products- Submitting NDA".

Herein, Solvay Pharmaceuticals, Inc. is submitting comments in response to the above referenced federal register notice. We reserve all rights under the Administration Procedures Act.

Attachment I contains comments pertaining to the Chemistry, Manufacturing, and Controls Section of the draft guidance. Attachment II contains comments pertaining to the Nonclinical Pharmacology and Toxicology Section of the draft guidance. Attachment III contains comments pertaining to the Human Pharmacokinetics and Bioavailability Section of the draft guidance. Attachment IV contains comments pertaining to the Clinical Studies For New PEPs Section of the draft guidance. Attachment V contains comments pertaining to the Pediatric Studies For PEPs Section of the draft guidance. References will be provided to the Agency upon request.

If you have any questions pertaining to the information provided in this correspondence, please contact me at (770) 578-5685 or facsimile (770) 578-5864.

Sincerely,

Edwin O. Billips
Manager, Regulatory Affairs

2003D-0206

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Attachment I

Chemistry, Manufacturing, and Controls Section of the Application

Chemistry, Manufacturing, and Controls Section of the Application

**Re: Section III, Part A. Drug Substance.
Lines 129-130
Similar methods can be used to determine chemical purity**

Comments:

The drug substance is an extract from pancreatic glands; therefore there are process-related impurities that may only be related to the precipitation process such as isopropanol, water, heavy metals, microbiological load or fat (adherent to the pancreatic glands). For product-related impurities all other proteins and peptides come from the pancreatic glands themselves and are therefore defined characteristic compounds of the drug substance or "desired product". Therefore the term "purity" is not clearly defined and needs clarification in detail, based on the characteristic properties of the pancreatic extract.

**Line 116
The manufacturing (extraction and purification) process should be validated for its capability to remove and / or inactivate viral agents**

Comment:

For the manufacturing process of pancreatin other steps than extraction and purification should be considered e.g. hydrolysis, with regard to their capability of viral reduction.

**Re: Section III, Part C. Stability and Part D. Overages.
Lines 154-156
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.**

**Lines 162-165
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.**

Comments:

The term "label claim potency" should be defined in the guidance document. We would propose to refer only on lipase activity as label claim potency.

For lipase activity a certain justified narrow specification range (considering analytical variability and stability losses) should be acceptable close to the 100 % of the labeled activity.

For amylase and protease a broader specification range should be acceptable if justified and unavoidable.

From experiences during production of pancreatin products it is known that it is not feasible to produce a product at 100 % of the labeled activity for all three enzymes. This is mainly due to the natural variability of pancreatin with regard to enzyme activity ratios and due to the losses in enzymatic activities during production process.

Typical enzyme losses of enzymatic activity also occur due to humidity and temperature. Consequently a certain decrease of activity throughout shelf-life is to be expected.

Therefore, either a certain stability overage, or a suitable lower shelf-life limit should be acceptable to guarantee a product complying with the specification during its shelf-life, if justified by stability data.

Attachment II

Nonclinical Pharmacology and Toxicology

Nonclinical Pharmacology and Toxicology Section

Re: Section IV, Part B. Pharmacology.

Lines 195-196

Because of the extensive use of the marketed PEP products, no new pharmacology studies are necessary.

Comments:

While no new pharmacology studies may be necessary because of the long history of usage of pancreatic enzyme products (PEPs), the Federal Register vol. 69, No. 82 dated April 28, 2004 states "Significant variations in bioavailability have been shown both among the various dosage forms and among products from different manufacturers of the same dosage forms. These variations in bioavailability can affect both safety and effectiveness of the products." Moreover, clinically, only lipase for fat digestion is measured, yet the other enzymes (amylase and protease) may be important but the digestibility cannot be measured in clinical settings. It therefore seems important to gain information also on the efficacy of the protease and amylase enzymes from animal studies.

The healthy human pancreas secretes a large number of enzymes including: lipases, proteases, α -amylase, phospholipase A2, RNase and DNase (Rinderknecht; 1993). In enzyme supplementation therapy for digestive disturbances and malnutrition resulting from pancreatic exocrine insufficiency, it is customary to regulate only the replacement of lipase, protease and amylase enzymes. When these groups of enzymes are deficient, malabsorption is the result requiring enzyme substitution.

Protein absorption is estimated less frequently than fat absorption and by virtue of the influence of the hindgut flora, the fecal nitrogen content can at best give only a very rough estimate of the extent of dietary protein absorption. It is not possible to differentiate between bacterial nitrogen and non-digested, non-absorbed proteins (Stephen & Cummings 1980), moreover considerable amounts of nitrogen will be released during hindgut fermentation and absorbed as ammonia. Direct studies in a minipig model of pancreatic exocrine insufficiency (PEI) (Gregory et al. 1999) showed protein digestibility measured in the feces only fell from 90% to 57%, whereas when measured at the ileum, protein digestibility fell from 79% in controls to 27% in PEI minipigs, i.e. protein malabsorption was actually as severe as fat malabsorption (30-40% in ileum and feces) in PEI, but this would not be noted if determined only at the level of the feces.

Diagnosis and especially quantification of starch malabsorption (indicator for amylase activity) is difficult in clinical settings. Malabsorption cannot be determined via stool analyses, due to the avid hindgut fermentation of undigested starch and other residual carbohydrates (Layer and Holtmann 1994). However, it was shown that there is a load-dependent small intestinal malabsorption of starch in patients with PEI (DiMagno 1993). Although hindgut fermentation results in some energy being salvaged and absorbed as SCFA (short chain fatty acids) there is, nevertheless, a loss of some 60% metabolizable energy could seriously affect the nutritional status, especially in cystic fibrosis patients. In addition, increased fermentation may cause flatulence and loss of appetite (Fernandes et al. 1985) and the breakdown products may contribute to diarrhea. In direct studies in a minipig model (Gregory et al. 1999) it was confirmed that PEI resulted in a load-dependent malabsorption of starch,

although less severe than fat or protein. Moreover, it was noted that the starch malabsorption could only be determined at the level of the ileum and not in the feces, due to hindgut fermentation of the unabsorbed starch.

In conclusion, animal models are available to investigate the effect of amylase and proteases as well as of lipase of PEPs. Data from those studies should be mandatory.

References:

- DiMagno 1993; Gastroenterol 104; 1255-62
Fernandes et al. 1985; Acta Paediatrica Scandinavica, Supplement 317: 5-8
Gregory et al 1999; In "Biology of the Pancreas in Growing Animals" (eds: SG Pierzynowski & R. Zabielski); Elsevier, Amsterdam; pp 381- 93
Layer and Holtmann. 1994; International Journal of Pancreatology 15 (1): 1-11
Rinderknecht 1993 In "The Pancreas: Biology, Pathobiology, and Disease" 2nd Edition (Eds: VLW Go et al) Raven Press, New York; pp 219-51.
Stephen and Cummings 1980; J Med Microbiol 13: 45-56

Attachment III

Human Pharmacokinetics and Bioavailability

Human Pharmacokinetics and Bioavailability Section

**Re: Section V
Lines 204-205
The bioactivity and/or bioavailability of the active ingredient should be determined at the site of action (gastrointestinal tract).**

Comments:

To determine the bioactivity and/or bioavailability of the active ingredients at the site of action (gastrointestinal tract), the subjects must be duodenally intubated. Diseases like cystic fibrosis (CF) and chronic pancreatitis (CP) cause pancreatic exocrine insufficiency. The pathophysiology of the pancreas of CF patients, who are mainly children, and CP patients, who may have a residual function of the pancreas, are different. It is considered that the risk of the performance of duodenal intubation studies in pediatric patients exceeds the potential benefit for the patients. Therefore, children with CF cannot be involved in duodenal intubation studies used to determine the bioactivity of pancreatic enzymes. In healthy volunteers without pancreatic exocrine insufficiency (PEI), the bioactivity of the enzymes in the gastrointestinal tract may be different from PEI patients and therefore would not be an option for determining the bioactivity of the enzymes.

Duodenal intubation is an invasive procedure done to recover aspirates from the stomach and especially from the duodenum. The subjects are intubated with a double-lumen duodenal tube and a separate single-lumen naso-gastric tube. The positions of the tubes are checked fluoroscopically. Aspiration is done over time while the enzyme activity and other parameters are measured. Because of intubation, the physiological or pathophysiological conditions may be altered. Specifically, the duodenal pH can be influenced by the irritation of the tube. Therefore, the measured parameters taken while the subject is intubated may not always reflect the true bioactivity of the product. Additionally, it is not possible to differentiate between endogenous and exogenous enzymes in the aspirates when enzyme activities are determined. Physiological aspects like dietary habits, including fatty diets, and a highly variable pancreatic secretion due to a complex regulatory mechanism, may influence the activity pattern of the enzymes.

Duodenal intubation mainly determines the pancreatic secretory capacity as a direct pancreatic function test¹. Presently, direct pancreatic function tests are mostly replaced with indirect pancreatic function tests which have been shown to be simpler and more reliable in reflecting the status of the pancreas. Indirect pancreatic function tests are also less bothersome to the subjects.

A non-invasive test used to determine the bioactivity of the lipase in the duodenum is the ¹³C mixed triglyceride (MTG) breath test which measures the activity of the lipase at the site of action². This test can be done in CF children³ as well as in CP patients and healthy volunteers without restrictions and better reflects the activity of lipase under pathophysiological situations of a PEI subject. However, a reliable ¹³C breath test is only established for pancreatic lipase. Therefore, the ¹³C-MTG test could be an alternative test for the bioactivity measurement of the lipase.

The ¹³C starch/H₂ breath test measures starch maldigestion and is therefore not specific for duodenal activity of amylase. No ¹³C breath tests are available for proteases.

References:

- 1) Chowdhury R.S., and Forsmark C.E., Review article: pancreatic function testing, Aliment Pharmacol Ther 2003; 17: 733-750
- 2) Vantrappen, G.R., Rutgeerts, P.J., Ghooos, Y.F., Hiele, M.,: Mixed Triglyceride Breath test: An non-invasive Test of Pancreatic Lipase Activity in the Duodenum, Gstroenterology, 1998, 96, 1126-34
- 3) Amarri, S., Hardin, M., Coward, W.A.: ¹³C mixed triglyceride breath test: a non-invasive measure of exocrine pancreatic function in children with cystic fibrosis, Journal of Pediatric Gastroenterology and Nutrition, 1995, 20, 457

Attachment IV

Clinical Studies for New PEPs

Clinical Studies for New PEPS Section

**RE: Section VI, Part C. Endpoints (Outcome Measures) Efficacy.
Lines 259-261
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.**

Comments:

Stool fat is influenced by fat intake; therefore, stool fat excretion without adequate fat intake evaluation (96 hour diet record) is not reliable. We suggest using the coefficient of fat absorption [(CFA), fat balance] as a parameter for measuring the efficacy of pancreatic exocrine products (PEP). A standardized diet is insufficient without recording and evaluating fat intake.

**RE: Section VI, Part E. Design.
Lines 306-307
The total number of patients in the study can be between 10 and 25,
depending on study design. Two studies are desirable. A single, larger
study may also be appropriate.**

Comments:

The number of patients in a study should be based on adequate statistical planning including a sample size estimate depending on the study design. Therefore, no specific patient numbers should be described in the guidance unless a rationale is provided for the figures.

Attachment V

Pediatric Studies for PEPs

Pediatric Studies for PEPs

**RE: Section VII,
Lines 377-378
Solid dosage forms of PEPs cannot be swallowed by very young
pediatric patients. Therefore sponsors are encouraged to develop age-
appropriate formulations for this patient population.**

Comments:

There is a possibility to administer solid dosage forms of PEPs to very young pediatric patients. As an example, the enteric-coated mini-microspheres from a capsule formulation may be added to a small amount of soft food or fluid with a pH less than 5.5. The soft food or fluid including the enteric-coated mini-microspheres should be swallowed immediately without chewing and followed with a glass of water or juice to insure swallowing. Therefore, solid dosage forms should not be excluded from the list of age-appropriate formulations.