



June 28, 2004

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket No. 2003D-0206

To whom it may concern:

Meristem Therapeutics is a corporation based in Clermont-Ferrand, France, which is engaged in the development of pharmaceutical products from transgenic plants, including Merispase®, a recombinant gastric lipase manufactured by recombinant DNA technology and expressed in maize seeds. This product is currently under clinical development (Phase II in Europe) and is used for the treatment of lipid malabsorption in patients with Exocrine Pancreatic Insufficiency (EPI).

1. The main comment that Meristem Therapeutics has with regard to the aforementioned document is that its title is misleading. This is because the title refers to all drug products for the treatment of EPI, while the Guideline is not, in fact applicable to all products for the treatment of EPI because it refers only to Pancreatic Enzyme Products (PEPs).

Meristem is currently well advanced in developing a recombinant form of lipase to be used for the treatment of the same indication, EPI. This product is currently in Phase II clinical trials in Europe. Historically, all products for the treatment of EPI were PEPs, which are extracted from bovine or porcine pancreases. However, the Guideline, as written, is not applicable to Meristem's product. For example, it refers specifically to products which are extracted, and furthermore, which contain three pancreatic enzymes (amylase, protease and lipase); whereas, Meristem's product contains only lipase as an active ingredient. As such, if this guidance is intended specifically for extracted PEPs, then Meristem proposes that the title of this guidance be modified to reflect its actual content, to read as follows,

“Guidance for Industry. Extracted Pancreatic Enzyme Products for Exocrine Pancreatic Insufficiency – Submitting NDAs.”

2. Section VI C “Endpoint Efficacy (outcome measures) for new PEPs”, as currently written, only contains endpoints reflective of the efficacy of the lipase component of the extracted PEPs, (steatorrhea), whereas, the guideline is silent with regard to the demonstration of clinical efficacy of the other two active ingredients of extracted PEPs, amylase and protease. The demonstration of safety and efficacy should be required for all active ingredients present in the preparation (lipase, protease and amylase).

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Such a demonstration would be particularly relevant for protease, due to the fact that a recognised complication of the treatment with high doses of PEPs is fibrosing colonopathy. This condition is characterized by the development of fibrotic strictures in the colon, and is, among other factors, related to the local activity of proteases. As such, the efficacy of the protease should be specifically demonstrated to justify a positive risk/benefit ratio.

It is of particular note that the commercialised PEPs are characterised and labelled by their lipase content, and not by the content of protease or amylase. There is neither rationale nor data to support the hypothesis that lipase is the causal factor for fibrosing colonopathy. Rather, it is logical to assume that protease is one causal factor. In any event, with high doses of PEPs, the safety concern is that fibrosing colonopathy will occur. This safety concern is addressed in two guidelines suggesting an upper limit dose of 10 000 IU lipase /kg/day¹ (or 6 000 IU lipase/kg/meal²) and a maximum daily dose of 250 000 IU of lipase in adults. This is misleading, due to the fact that the protease, and not the lipase, is likely to be the salient issue.

3. If this guidance is intended to all products intended for the treatment of Exocrine Pancreatic Insufficiency, as is currently stated in the title, then there should either be a new guidance document specifically addressing the new generation of compounds currently in development, or the content of this guidance should be modified to reflect the state of the art of the manufacture of products for the treatment of EPI.

Looking forward to hearing from you, we remain

Yours Sincerely,



Jean-Paul Rohmer
President and CEO

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¹ Anthony H, Collins CE, Davidson G et al. Pancreatic enzyme replacement therapy in cystic fibrosis: Australian guidelines. J Paediatr Child Health 1999;35:125-29.

² Borowitz,D.S.; Grand,R.J.; Durie,P.R. et al. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. J.Pediatr. 1995; 127:681-684.